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POTENTIAL MECHANISMS UNDERLYING THE EFFECT OF BARIATRIC SURGERY ON EATING BEHAVIOUR

Roxanna Zakeri[1-3] and Rachel L. Batterham[1-3]

Author Affiliations

[1]Centre for Obesity Research, Rayne Institute, Department of Medicine, University College London (UCL), London WC1E 6JF, United Kingdom (UK).

[2]University College London Hospital (UCLH) Bariatric Centre for Weight Management and Metabolic Surgery, UCLH, Ground Floor West Wing, 250 Euston Road, London NW1 2PG, United Kingdom (UK).

[3]National Institute of Health Research, UCLH Biomedical Research Centre, London W1T 7DN, United Kingdom (UK).

Corresponding author:

Rachel L Batterham

Telephone; +44 2076790991

Email: r.batterham@ucl.ac.uk

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Conflicts of interest

None declared.

ABSTRACT

Purpose of the review: Reduced energy intake, resulting from favourable changes in eating behaviour, is the predominant driver of weight-loss following bariatric surgery. Here we review the most recent studies examining the impact of Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG), the two most common bariatric procedures, upon eating behaviour and the suggested underlying biological mechanisms.

Recent findings: Following RYGB or SG most people report subjective changes in appetite, taste and food preference, with decreased high-fat preference most commonly reported. Objective post-surgery changes in taste and olfactory acuity occur. A new phenomenon, 'meal-size aversion', may contribute to reduced post-operative energy intake. Recent studies provide evidence for peptide YY3-36, glucagon-like peptide-1, ghrelin, neurotensin and oleoylethanolamide as mediators of post-operative eating behaviour changes. Factors modulating these changes include sex, type 2 diabetes status, genetics and bariatric procedure. New studies implicate central dopaminergic and opioid receptor signalling as key neural mediators driving altered eating behaviour. Brain neuroimaging studies show that obesity-associated changes in food-cue responses, brain connectivity and structural abnormalities are normalised following bariatric surgery.

Summary: Understanding the biological mechanisms mediating the eating behaviour changes engendered by bariatric surgery may lead to the development of novel therapeutic strategies for people with obesity.

Keywords

Taste, olfaction, food reward, sleeve gastrectomy, gastric bypass

Key points

- Reduced preference for high-fat foods is the most common self-reported change in food preference following RYGB or SG. This finding is corroborated by objective assessment of food preference changes in RYGB-operated rats with evidence for a learnt response that is inconsistent with the development of conditioned taste aversion.

- Gender, type 2 diabetes status, genetics and bariatric procedure type impact upon eating behaviour changes following surgery.

- New mechanistic studies implicate PYY, GLP-1, ghrelin, NT and OEA as key gut-derived factors that mediate changes in eating behaviour following RYGB or SG.

- Brain neuroimaging studies suggest that neuroplastic structural recovery and restoration of functional connectivity as well as changes in neural responses to food cues are normalised following bariatric surgery.

INTRODUCTION

Bariatric surgery is the most effective treatment for people with severe obesity, leading to marked sustained weight-loss together with reduced morbidity and mortality. Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) are the most commonly performed bariatric procedures undertaken globally(1). Weight-loss induced by lifestyle modification engenders powerful compensatory biological changes leading to increased hunger, enhanced neural responses to food-cues and heightened drive to consume energy-dense foods. Together these changes contribute to the high rate of weight recidivism observed following lifestyle intervention weight management programmes(2)*. In contrast following RYGB or SG, despite marked weight-loss, hunger is reduced, neural responses to food-cues diminish, food becomes less rewarding and a shift in preference away from high-fat, high-sugar foods is reported enabling patients to adopt and maintain favourable changes in eating behaviour(3). Post-operative changes in gut-derived factors such as gut hormones, nutrients, bile acids, microbiome and neural signals acting peripherally and centrally upon homeostatic and hedonic brain regions are suggested to mediate these post-surgical eating behaviour changes.

Weight-loss following RYGB or SG is highly variable with up to 20% of people experiencing poor initial weight-loss or weight regain(4). Emerging evidence suggests a causal link between favourable post-operative eating behaviour changes and subsequent weight-loss(5)*. Importantly, whilst weight-loss independent metabolic improvements occur immediately post-surgery, longer-term health improvements are related to the degree of sustained weight-loss achieved, thus highlighting the need to maximise post-surgery weight-loss(6,7). A greater understanding of the impact of RYGB and SG upon key determinants of eating behaviour, namely appetite, taste, olfaction, food preference or aversion, food-reward and

more importantly the biological mechanisms mediating these changes, may lead to the development of novel therapeutic strategies for people with overweight or obesity.

This review summarises recent data examining the impact of RYGB and SG upon the key determinants of eating behaviour, the differences in response following these two procedures, and the purported underlying biological mechanisms involved.

NEW STUDIES EXAMINING THE IMPACT OF BARIATRIC SURGERY UPON SUBJECTIVE AND OBJECTIVE DETERMINANTS OF EATING BEHAVIOUR

Reduced energy intake due to a decreased consumption of energy-dense food and beverages is suggested to contribute to long-term weight reduction following RYGB(3) and SG(8)*. The factors determining nutrient selection and subsequent ingestion are complex and include taste, olfaction, subjective pleasure, adverse post-ingestive gastrointestinal effects and higher executive function.

Most studies examining food preference changes relate to RYGB and have utilised self-report questionnaires. Collectively these studies suggest that post-RYGB intake of high-fat, high-sugar, unhealthy foods is reduced whilst intake of healthy food items is increased(9)*. Recently, however, studies have begun to examine food preference changes post-SG. Van Vuuren et al., in a prospective study of 106 individuals undergoing SG, reported that most participants experienced a change in the taste, desire and enjoyment of flavours in the first 6 months post-SG(10)*. Increased intensity of sweet and fatty tastes coupled with decreased enjoyment and desire for these were the most consistent findings. Gero and colleagues also

prospectively assessed the desire to consume different tastes (sweet, sour, bitter, spicy, salt, fatty and umami) in 100 participants pre-SG and 6 days and 6 months post-SG using food photographs. Preference for all tastes decreased early post-SG with greatest decline observed for sweet and fatty foods(11)*. However, a 2-year prospective study in 30 SG patients suggests these changes in sweet preference may be short-lived; whilst the majority of patients reported changes for sweet and fat tastes at 6 months post-surgery, by 2 years only 23% reported reduced interest in sweet(8)*. The accuracy of self-reported food preferences has, however, been questioned. A recent study directly measured food intake during an *ad libutum* buffet and food preferences using photographs in 31 RYGB and 10 SG patients pre-operatively and 6 months post-operatively(12)**. Energy intake following surgery was halved but the relative intake from high/low fat, sweet and savoury groups remained unchanged, suggesting that reduced meal size drives reduced energy intake at this time. Interestingly, in the accompanying picture preference test individuals preferentially choose low-fat savoury food post-surgery. The reason for this disparity between self-reported preference and direct measurement is unclear but highlights the need for objective eating behaviour assessments.

Objective changes in food preference post-RYGB have been shown in rodents using nutritive stimuli such as sucrose solution and intra-lipid. These findings have now been extended to more complex diets. After an 18-day recovery period from sham or RYGB surgery, rats were studied with 8-days free access to 4 semisolid foods of differing fat and sugar concentrations, alongside standard chow and water(13)**. Post-RYGB rats consumed fewer total calories than sham-operated rats, whilst a significant decrease in the percentage of calories from sugar-fat whip (high-fat/high-sugar) led to an overall reduction in relative fat intake, increase in non-sugar carbohydrate and a marginal increase in protein. Interestingly these changes were progressive, reaching significance from day 4 onwards, thus suggesting a learned

response to the post-ingestive consequences of different diets. However, RYGB rats, like sham rats, continued to consume the majority of their calories from the high-fat/high-sugar option. Evidently, RYGB rats still found this food item palatable, a finding which is inconsistent with the development of a conditioned taste aversion. Moreover, new evidence from a study in rats without bariatric surgery, in which meal intake exceeding a pre-defined size threshold was coupled with lithium chloride-induced gastric illness, suggested the existence of a novel phenomenon, 'conditioned meal-size', as opposed to conditioned taste aversion. Here, the adverse consequence of consuming large meals was also learnt(14)**. This phenomenon may be one of the mechanisms by which bariatric surgery leads to reduced meal size and induces weight-loss.

Two new cross-sectional studies, one focused predominately on patients in the first post-operative year(15)* (104 RYGB, 50 SG) and the other examining patients 6 months to 5 years post-surgery(16)* (98 RYGB, 155 SG), utilised the same questionnaire to compare the impact of RYGB and SG upon self-reported changes in appetite, taste, olfaction and food aversion post-operatively and examined potential association with weight-loss. Both studies found the majority of patients following both procedures reported reduced appetite, new food aversions and changes in taste, most commonly for sweet and fat with no differences between RYGB and SG groups. These studies differed in their findings relating to self-reported olfactory changes, being more prevalent post-SG (52%) compared to post-RYGB (34%) in the early post-operative period(15)* but less common post-SG (28%) than post-RYGB (41%) in the long-term(16)*. Of note, the prevalence of appetite changes also decreased with time post-SG but not post-RYGB. Interestingly, gender differences were noted in the SG group, with taste and smell changes being more prevalent in female patients than male. Furthermore,

men post-SG lost significantly less weight compared to men post-RYGB whereas weight loss was similar in women(16)*.

Recently two longitudinal studies, albeit with small numbers, have objectively examined early post-operative changes in gustatory sensitivity as compared to pre-surgery(17*,18*). Sensitivity to all tastants evaluated (sweet, sour, bitter and salty) increased post-surgery(17)*. Comparison between RYGB and SG groups revealed a higher sourness threshold post-RYGB compared to post-SG, with no differences in either the other taste thresholds or sweetness acceptability(18)*. Objective, longitudinal assessments of olfactory function alone also report improved function in the early post-surgery stage(19,20).

Taken together these new studies suggest that post-surgery change in appetite, taste and smell may contribute to food preference changes following RYGB and SG, whilst conditioned meal-size aversion may contribute to reduced meal-size. However, large longitudinal studies combining subjective and objective measures of energy intake, food preference, taste and olfaction, with a focus on gender and procedural differences are warranted. Furthermore, in order to evaluate the role of adiposity and weight-loss *per se* in mediating taste and olfactory changes, additional control groups of normal-weight subjects, obese weight-stable subjects and weight-matched participants who lose weight through dietary restriction also need to be evaluated.

NEW INSIGHTS INTO BIOLOGICAL MECHANISMS UNDERLYING EATING BEHAVIOUR FOLLOWING RYGB AND SG

The biological mediators underlying the marked and sustained weight-loss observed following RYGB and SG remain incompletely understood. However, there is general agreement that altered nutrient and/or biliary flow engenders changes in a multitude of gut-derived signals. In concert, these modulate brain regions regulating food intake, reward-processing and executive function, ultimately leading to favourable changes in eating behaviour and reduced energy intake.

New evidence supporting a causal role for the anorectic gut hormones glucagon-like peptide-1 (GLP-1) and peptide YY3-36 (PYY) in reducing energy intake post-RYGB has emerged. In individuals post-RYGB, combined GLP-1 receptor antagonism and di-peptidyl-peptidase-4 (DPP-4) inhibition, the enzyme required to generate PYY, led to a 20% increase in energy intake(21)**. Isolated GLP-1 receptor antagonism or DPP-4 inhibition had no demonstrable effect, conceivably due to a compensatory rise in the unblocked hormone. Functional neuroimaging studies have shown that altering circulating gut hormone levels and/or receptor activation modulates neural response within homeostatic, hedonic and executive function regions in humans(22). Similarly, brain regions exhibit changes in neural activity post-RYGB coupled with reduced appetitive behaviour for energy-dense foods leading to the suggestion that gut hormones mediate these changes. Evidence in support of this hypothesis comes from a study of RYGB-operated individuals that coupled a functional magnetic resonance (fMRI) imaging food picture evaluation task with blockage of gut hormone release via administration of a somatostatin analogue. Reduction in circulating PYY levels positively correlated with increase in brain reward system activity, with a similar trend observed for GLP-1(23)**.** Moreover, a prospective, longitudinal fMRI study in RYGB and SG candidates

with weight-stable controls implicated post-operative suppression of the orexigenic hormone, ghrelin, as a key mediator of changes in liking for highly-palatable foods post-surgery. Proposed mechanisms include ghrelin-mediated modulation of dopaminergic neuron activity in the ventral tegmental area (VTA) (Table 1), a central site for reward processing(24)*. Interestingly, a study in RYGB-operated rats suggests that changes in ghrelin-mediated signalling in VTA dopaminergic reward neurons may underlie the increased incidence of alcohol-dependence observed following RYGB(25)*.

Neurotensin (NT), which is co-expressed in enteroendocrine cells with GLP-1 and PYY(26), has also been proposed to contribute to eating behaviour changes post-RYGB. Peripheral NT administration reduces food and sucrose intake in rodents with hypothalamic, brainstem and vagal sites of action being implicated from mechanistic studies(27)**. Circulating NT levels increase after RYGB and NT receptor blockade in post-RYGB rats transiently increased food intake. Importantly, combined peripheral administration of NT with GLP-1 or PYY synergistically reduced intake of palatable food and inhibited gastric emptying(28)**. These findings argue that a therapeutic approach targeting two or more gut hormones is likely to be more efficacious. Indeed, Tan and colleagues have recently shown that acute continuous subcutaneous infusion of GLP-1, PYY and oxyntomodulin, replicating the postprandial levels observed following RYGB, reduced mean energy intake of obese volunteers by approximately one third(29)**. An alternative approach is to stimulate endogenous hormone secretion akin to the physiological response post-RYGB where L-cell stimulation through bile acids is proposed to contribute to increased circulating gut hormone levels. Further evidence in support of this notion comes from the recent finding that oral administration of primary bile acid chenodeoxycholic acid (CDCA) to RYGB-operated participants increased plasma concentrations of GLP-1, PYY and NT in the absence of nutrients(30)*. Moreover, these

findings suggest that oral CDCA may represent a therapeutic strategy to enhance gut hormone levels in people with poor weight loss post-RYGB.

A complex interaction exists between bile acids, the gut microbiome and gut hormone secretion from enteroendocrine cells(31). A new study has identified a novel link between intestinal microbiota and circulating levels of metabolites purported to regulate energy homeostasis(32). Moreover, following SG, weight loss was associated with altered microbiota and circulating metabolite levels. Additional studies are needed to establish the directionality of this relationship.

A reduced preference for and intake of high-fat foods is a consistent finding following RYGB and SG. Understanding the post-surgery drivers underlying these changes is therefore a key priority. New studies undertaken in RYGB-operated rats by Hankir et al., provide novel insights into the gut-brain pathways mediating this reduced fat preference(33*,34*). In RYGB-operated rats they found circulating levels of oleoylethanolamide (OEA), an anorectic lipid mediator synthesised by enterocytes from dietary oleic, were increased post-meal with high-fat feeding(33)*. In subsequent mechanistic studies they identified that OEA acts via vagal afferents to modulate striatal dopaminergic signalling and reduce postoperative high-fat consumption (Table 1). Next, in light of the fact that the brain μ-opioid receptor (MOR) system is implicated in regulating fat consumption, they examined fat preference, MOR availability and MOR protein expression in RYGB-operated rats who were in the weight-loss maintenance phase compared to sham-operated, calorically-restricted weight-matched rats(34)*. High-fat intake was reduced in RYGB-operated rats and associated with widespread reduction in MOR availability particularly in the striatum (Table 1). Levels of MOR protein were also reduced in

the striatum and prefrontal cortex compared to weight-matched rats. The authors concluded that the reduced fat preference following RYGB may be due to reduced brain MOR signalling.

Brain neuroimaging studies have identified that obesity is not only associated with altered food-cue responses but also structural abnormalities(35,36) and changes in resting-state connectivity in brain regions involved in energy regulation, reward and motivation(37). Neuroimaging studies have shown that these obesity-associated neural responses to food cues are 'normalised' following bariatric surgery(23**,38–40). More excitingly, emerging data suggest that both neuroplastic structural recovery and restoration of functional connectivity occur following RYGB and SG(41**,42**). Table 2 summarises key findings from recent neuroimaging studies.

EVIDENCE FOR INTERPLAY BETWEEN GENETICS, EATING BEHAVIOUR AND WEIGHT-LOSS

Weight-loss following RYGB and SG is highly variable with genetics estimated to contribute up to 70% of this variability(43)**.** Candidate-gene based approaches and hypothesis-free genome-wide association studies (GWAS) have been used to identify the genes underlying this variability with limited success, in part due to low sample sizes(44–48). Poor post-surgery weight loss can ensue from high-allelic burden of such SNPs(47). However, even the marked hyperphagia seen in the complex genetic condition Prader-Willi syndrome might be effectively altered by bariatric surgery; Magel2 knockout mice, an animal model of this condition, have shown comparable fat-mass loss and reduced fat intake to wild-type carriers after SG(49)**. Future large GWAS coupled with detailed eating behaviour phenotyping will hopefully allow informed selection of both surgical candidates and surgical procedures but also identify novel pathways that can be targeted non-surgically to modulate eating behaviour.

CONCLUSION

Changes in taste, olfaction, food preference and food reward following RYGB and SG, drive favourable changes in eating behaviour and reduced energy intake. Moreover, obesity-associated neural changes are normalised post-operatively. Changes in gut-derived factors altered as a consequence of anatomical gastrointestinal tract rearrangement acting in concert underlie these changes (Figure 1). Emerging data suggest nuanced differences in the impact of RYGB and SG upon the determinants of eating behaviour that most likely reflect their differential impact upon gut-derived hormones. Future longitudinal studies, in people undergoing RYGB or SG compared to people losing weight through non-surgical means, with subjective and objective assessments of appetite, taste, olfaction, food preference and food reward together with mechanistic studies are needed to fully elucidate how bariatric surgery alters eating behaviour. A greater understanding of the mechanisms involved and interaction with a person's genetics and pre-surgery phenotype will allow surgical procedure choice to be tailored to the individual and facilitate discovery of novel non-surgical treatments for people with obesity.

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Through a series of mechanistic rodent studies, this study identifies a novel gut-brain signalling pathway that may mediate the reduced preference and intake of high-fat food

commonly found after RYGB surgery. Further investigating this pathway could help development of novel pharmacological approaches to weight loss.

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Neuroimaging study using positron emission tomography to compare postprandial brain responses in normal-weight, obese and post-RYGB subjects. Mechanisms for the development food avoidance and reduced appetite after RYGB are proposed, involving altered postprandial gut peptide responses and altered neural activity in brain regions regulating energy balance, inhibitory control and hedonic response.

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Using Magel2 knockout mice as an animal model of Prader-Willi syndrome, this study demonstrates that SG is effective in treating Prader-Willi syndrome, with comparable results to wild-type mice for weight-loss and reduced fat intake.

FIGURES & TABLES

Figure 1: Schematic diagram illustrating recent findings in gut-brain signalling pathways proposed to mediate eating behaviour changes after bariatric surgery

Table 1: Recent findings in gut-brain signalling in the control of eating behaviour

Table 2: Summary of findings from recent neuroimaging studies

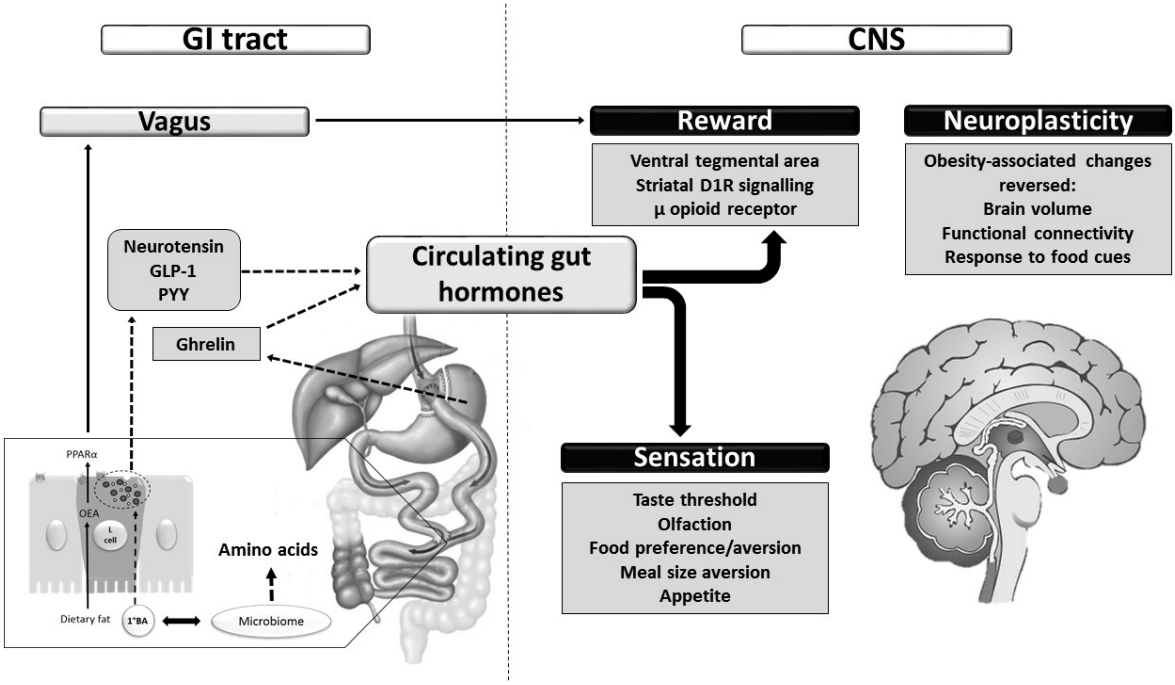

Figure 1: Schematic diagram illustrating recent findings in gut-brain signalling pathways proposed to mediate eating behaviour changes after bariatric surgery.

Anatomical rearrangement of the gastrointestinal tract leads to reduced circulating levels of ghrelin and increased levels of anorectic gut hormones. Oral intake of the primary bile acid, chenodeoxycholic acid, enhances L-cell release of NT, GLP-1 and PYY even in the absence of luminal nutrients. GLP-1 and PYY act in concert to inhibit energy intake. NT acts synergistically

with GLP-1 and PYY to reduce energy intake and delay gastric emptying. Cross-talk between gut microbiota and bile-acids, in addition to new links between microbiota and circulating metabolites involved in energy homeostasis, may play a role. Pathways involving key brain reward centres are proposed to mediate reduced fat preference and intake post-surgery; ghrelin modulates dopaminergic neuron activity in the VTA, OEA acts via vagal afferents to reduce striatal D1R signalling, and reduced MOR signalling in the striatum and prefrontal cortex have been found. Neuroimaging studies suggest that neuroplastic structural recovery, restoration of functional connectivity and normalisation of brain responses to food cues also occur. These gut-brain signalling pathways manifest in increased taste and olfactory sensitivity, meal-size aversions and reduced hunger. Whether weight loss *per se* leads to changed eating behaviour or whether the pathways described occur directly due to surgical intervention, remains unclear.

BA, bile acid; CNS, central nervous system; D1R, dopamine 1 receptor; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; MOR, μ opioid receptor; NT, neurotensin; OEA, oleoylethanolamide, PPARα, peroxisome proliferator-activated receptor alpha; PYY, peptide YY3-36; VTA, ventral tegmental area.

Study	Mediator	Target site	Findings	Interpretation
Sirohi et al. 2017 (25)*	Ghrelin	GHSR receptor in VTA of midbrain	Alcohol further suppresses acyl-ghrelin level after RYGB. Alcohol dependent behaviours in RYGB rats appear independently to post-surgery decrease in ghrelin and GHSR activity. Blocking GHSR does not decrease VTA dopaminergic neuron activity.	Changes in GHSR activity caused by RYGB may be responsible for increased alcohol intake and dependency behaviours.
Hankir et al. 2017 (33)*	OEA	Brain Dopamine receptor D1R	RYGB reduces OEA production. Vagal-driven increase in striatal dopamine release. RYGB upregulates striatal D1R expression, specifically under high-fat diet conditions.	Dopamine signalling through D1R contributes to effect of RYGB on fat intake and preference.
Hankir et al. 2017 (34)*	Endogenous opioids	Brain μ-opioid receptor MOR	RYGB rats had suppressed high-fat diet intake and preference, reduced MOR availability and downregulation of striatal and prefrontal MOR mRNA level.	Reduced MOR signalling contributes to suppressed fat appetite after RYGB.

Table 1: Recent findings in gut-brain signalling in the control of eating behaviour

D1R, dopamine 1 receptor; GHSR, growth hormone secretagogue receptor; MOR, μ-opioid receptor; OEA, oleoylethanolamide; VTA, ventral tegmental area.

Table 2: Summary of findings from recent neuroimaging studies

RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy; fMRI, function magnetic resonance imaging; PET, positron emission tomography; m, month; w, week; T2DM, type 2 diabetes mellitus; BOLD, blood oxygen level dependent; HCF, high-calorie food; LCF, low-calorie food; VTA, ventral tegmental area; OFC, orbitofrontal cortex.

Study	Subjects (n)	Surgery	Imaging modality	Intervention	Timing	Outcome variables	Main Results	Interpretation
Goldstone et al. 2016 (23)**	11 RYGB (7 completed) 9 Band 10 Non-obese weight-stable control	RYGB Band	fMRI	Octreotide given. Progressive Ratio Task. Visual Analogue Scale	>5m post-RYGB	- Gut hormone levels - Food appeal and reward rating to visual stimuli - Hunger/satiety score - BOLD activation of brain reward centres	Octreotide suppresses GLP-1, PYY, insulin and FGF19 rise after RYGB, less so after Band. Octreotide associated with lower appeal of palatable food. Octreotide reduced BOLD signal in reward centres upon visual cues of palatable food.	Brain-hedonic responses after RYGB may be directly mediated by the elevation in anorectic gut hormone levels after surgery.
Faulconbridge et al. 2016 (24)*	22 RYGB 18 SG 19 Weight-stable control	RYGB SG	fMRI	Response to images of high-calorie vs. low-calorie foods	<4w Pre-surgery, 6m post-surgery	- Likert scale (11-point) rating of palatability of visual stimulus. - BOLD activation in brain reward regions. - Fasting ghrelin level.	Baseline liking of HCF higher than LCF in all 3 groups. At 6m, RYGB and SG lower liking score of HCF. Reduced liking of HCF relative to LCF: more after RYGB than SG. Post-RYGB, increased BOLD response to LCF and reduced response to HCF in VTA. No change in SG or controls.	VTA is a critical site for modulating post-surgical change in liking of highly palatable food.
Wang et al. 2016 (38)	13 RYGB (6 completed) 7 Non-obese non-surgical control	RYGB	fMRI	Sweet and salt taste testing	Pre-surgery, 1m and 12m post-surgery. Control: 2 scans 1m apart	- Subjective reports of taste preference. - Sensory and reward brain area activation.	In response to sweet taste, significant decrease in brain reward centre activation in both RYGB and control groups. In response salty taste, RYGB increased activation in primary gustatory cortex and reward centres.	fMRI-detected brain activation changes to palatable tastes do not always correlate with subjective reports. Salt taste rather than sweet may be more pivotal post- RYGB.
Frank et al. 2016 (39)	12 RYGB 12 control Both groups with obesity and T2DM	RYGB	fMRI	Food reward task – response to images of high and low calorie foods. Behavioural surveys	>6m post-RYGB	- Likert scale (5-point) for wanting and liking of visual stimulus - BOLD activation of brain regions. - Hunger rating - Three Factor Eating Questionnaire - Power of Food Scale - Beck Depression Inventory	RYGB: Lower liking and wanting ratings; equivalent mood and hunger scores; lower scores in eating behaviour-related traits. RYGB: higher activation in visual, frontal control, somatosensory, motor, memory-related and gustatory regions. Lower activation in inhibition and reward regions and precuneus. Greater HbA1c reduction sig. associated with higher OFC activity for food reward.	Differences in food reward-associated brain functions may be based on substantial weight loss and improved glycaemic control.
Hunt et al. 2016 (40)*	9 RYGB 12 Non-obese control 21 Obese control	RYGB	PET	Mixed meal test and fasting. Somatostatin given	18 months post-RYGB	- Fullness, food-induced sickness rating - *Ad libitum* food consumption - FDG uptake in brain regions	Somatostatin after RYGB gave higher overall fullness and food-induced sickness, lower ad-libitum consumption. Increased activation hypothalamus, pituitary, left medial orbital cortex. Decreased activation right dorsolateral frontal cortex.	Gut peptide alterations after RYGB may mediate the changes in brain responses that influence eating behaviour.
Olivo et al. 2017 (41)**	16 RYGB 12 Non-obese control	RYGB	fMRI	Resting-state fMRI after overnight fast and 260kCal load. Visual Analogue Scale	1m pre-surgery, 1m and 12m post-surgery	- Subjective appetite ratings - Brain region activation and connectivity	Stronger connectivity between regions for reward-driven behaviour and food saliency pre-surgery vs. controls, but weakens over time post-surgery. At 12m, changes in cognitive control over eating. Early reduced connectivity between emotional control and social cognition regions post-surgery, but increases by 12m. Pre-surgery findings predict weight loss.	RYGB may reshape brain functional connectivity. Changes in cognitive control of eating could play major role in success of surgery. May use brain responsivity to predict weight loss response post-surgery.
Zhang et al 2016 (42)**	15 SG 18 Non-obese control	SG	MRI	Overnight fast and 200ml milk meal 30 minutes prior to MRI scan	Pre-surgery and 1m post-surgery	- Fractional anisotropy, mean diffusivity, grey and white matter densities	Decreased FA, GM/WM density and increased MD in brain regions for food intake (caudate, orbitofrontal cortex, body and genu of corpus callosum) and cognitive-emotion regulation (inferior frontal gyrus, hippocampus, insula, external capsule) after SG	Acute neuroplastic structural recovery attributable to SG which may mediate the behavioural effects of SG.