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Obesity surgery and neural correlates of human eating behaviour: A systematic review of functional MRI studies

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ABSTRACT

Changes in eating behaviour including reductions in appetite and food intake, and healthier food cue reactivity, reward, hedonics and potentially also preference, contribute to weight loss and its health benefits after obesity surgery. Functional magnetic resonance imaging (fMRI) has been increasingly used to interrogate the neural correlates of eating behaviour in obesity, including brain reward-cognitive systems, changes after obesity surgery, and links with alterations in the gut-hormone-brain axis. Neural responses to food cues can be measured by changes in blood oxygen level dependent (BOLD) signal in brain regions involved in reward processing, including caudate, putamen, nucleus accumbens, insula, amygdala, orbitofrontal cortex, and top-down inhibitory control, including dorsolateral prefrontal cortex (dlPFC). This systematic review aimed to examine: (i) results of human fMRI studies involving obesity surgery, (ii) important methodological differences in study design across studies, and (iii) correlations and associations of fMRI findings with clinical outcomes, other eating behaviour measures and mechanistic measures.

Of 741 articles identified, 23 were eligible for inclusion: 16 (69.6%) longitudinal, two (8.7%) predictive, and five (21.7%) cross-sectional studies. Seventeen studies (77.3%) included patients having Roux-en-Y gastric bypass (RYGB) surgery, six (26.1%) vertical sleeve gastrectomy (VSG), and five (21.7%) laparoscopic adjustable

Abbreviations: **ant**, anterior; **aROI**, anatomical region of interest; **BA**, Brodmann area; **BAS**, Behavioural Activation Scale; **BDI-II**, Beck Depression Inventory II; **BED**, binge eating disorder; **BIS**, Behavioural Inhibition Scale; **CBT**, cognitive behavioural therapy; **CHO**, carbohydrate; **conc**, concentration; **CONN**, CONN toolbox; **CSF**, cerebrospinal fluid; **DEBQ**, Dutch Eating Behaviour Questionnaire; **DPARSFA**, Data Processing Assistant for Resting-State fMRI Advanced; **DTI**, diffusion tensor imaging; **eCBs**, endocannabinoids; **ED**, energy density; **EDEQ**, Eating Disorder Examination Questionnaire; **EI**, Eating Inventory; **EWL**, excess weight loss; **Ex9-39**, Exendin(9–39); **fALFF**, fractional amplitude of low-frequency fluctuation; **FC**, functional connectivity; **FDR**, false discovery rate; **FEAT**, fMRI Expert Analysis Tool; **fMRI**, functional magnetic resonance imaging; **FPG**, fasting plasma glucose; **fROI**, functional region of interest; **FSL**, FMRIB Software Library; **FWE**, family wise error; **GLP-1**, glucagon-like-peptide-1; **GLP-1R**, GLP-1 receptor; **GM**, grey matter; **HAMA**, Hamilton Anxiety Rating Scale; **HAMD**, Hamilton Depression Rating Scale; **HE**, high-energy density; **HF**, high fat; **HP**, highly palatable; **HPC**, hippocampus; **HS**, high sugar; **IAPS**, International Affective Picture System; **inf**, inferior; **kcal**, kilocalorie; **LAGB**, laparoscopic adjustable gastric banding; **lat**, lateral; **LCD**, low-calorie diet; **LE**, low-energy density; **LF**, low fat; **LFPQ**, Leeds food Preference Questionnaire; **LS**, low sugar; **med**, medial; **mo**, months; **MTPRT**, macronutrient and taste preference ranking task; **n/a**, not applicable; **NF**, non-food; **NO**, non-obese; **NS**, non-significant; **NT**, no treatment; **NW**, normal weight; **o**, no, no change or no difference; **OB**, obesity; **occ**, occipital; **OW**, overweight; **PFS**, Power of Food Scale; **post**, posterior; **PPI**, psychological-physiological interaction; **PYY**, peptide tyrosine tyrosine; **ROI**, region of interest; **rol**, ctivec; **RSFC**, resting state functional connectivity; **RSN**, resting state network; **RYGB**, Roux-en-Y gastric bypass; **RYGB-LS**, RYGB least successful <50% EWL; **RYGB-MS**, RYGB most successful >50% EWL; **sep**, separate; **sig**, significant; **sim**, simulation; **SPM**, Statistical Parametric Mapping; **sup**, superior; **SVC**, small volume correction; **TCA**, temporal clustering analysis; **temp**, temporal; **TFEQ**, Three Factor Eating Questionnaire; **VLCD**, very low-calorie diet; **vox**, voxel; **VSG**, vertical sleeve gastrectomy; **WL**, weight loss; **WM**, white matter; **YFAS**, Yale Food Addiction Scale.

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gastric banding (LAGB). The majority of studies (86.0%) were identified as having a very low risk of bias, though only six (27.3%) were controlled interventional studies, with none including randomisation to surgical and control interventions. The remaining studies (14.0%) had a low risk of bias driven by their control groups not having an active treatment.

After RYGB surgery, food cue reactivity often decreased or was unchanged in brain reward systems, and there were inconsistent findings as to whether reductions in food cue reactivity was greater for high-energy than low-energy foods. There was minimal evidence from studies of VSG and LAGB surgeries for changes in food cue reactivity in brain reward systems, though effects of VSG surgery on food cue reactivity in the dlPFC were more consistently found. There was consistent evidence for post-operative increases in satiety gut hormones glucagon-like-peptide 1 (GLP-1) and peptide YY (PYY) mediating reduced food cue reactivity after RYGB surgery, including two interventional studies. Methodological heterogeneity across studies, including nutritional state, nature of food cues, post-operative timing, lack of control groups for order effects and weight loss or dietary/psychological advice, and often small sample sizes, limited the conclusions that could be drawn, especially for correlational analyses with clinical outcomes, other eating behaviour measures and potential mediators.

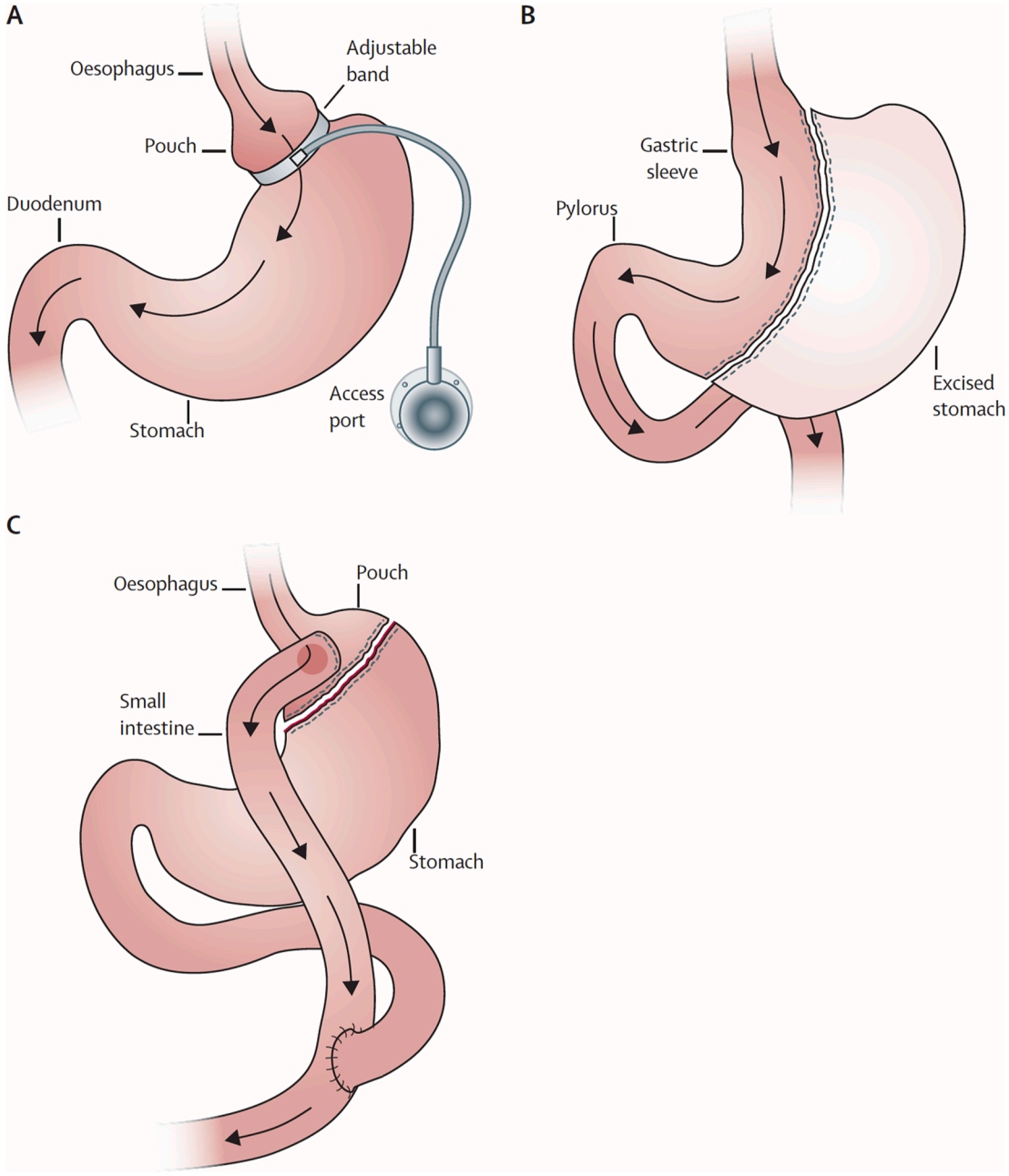

Fig. 1. Gastrointestinal anatomy after different surgical and endoscopic procedures for obesity. (A) Laparoscopic adjustable gastric banding (LAGB), (B) vertical sleeve gastrectomy (VSG), and (C) Roux-en-Y gastric bypass (RYGB) surgical procedures. Arrows indicated passage of ingested nutrients. Taken from (Madsbad et al., 2014) with permission.

This systematic review provides a detailed data resource for those performing or analysing fMRI studies of obesity surgery and makes suggestions to help improve reporting and design of such studies, as well as future directions.

1. Introduction

Surgical approaches for treatment of obesity provide the best long-term treatment, achieving 20–40 % sustained weight loss, with significant improvements in metabolic profile (Sjostrom et al., 2012; Schauer et al., 2014; Adams et al., 2018). Surgical treatments offer a considerable safety profile and minimal surgical complications. Laparoscopic Roux-en-Y gastric bypass (RYGB) and vertical sleeve gastrectomy (VSG) are the most performed procedures with comparable initial weight loss, though there may be some differences in long-term risk of weight regain in some studies (Shoar & Saber, 2017) (Fig. 1). Laparoscopic adjustable gastric banding (LAGB) is used less often in recent years (Rogers et al., 2017).

The mechanisms underlying weight loss after obesity surgery remain under investigation and vary by surgery type through differing post-surgery changes in gut anatomy (Fig. 1) and hormonal alterations after surgery, including satiety hormones glucagon-like peptide-1 (GLP-1) and peptide YY (PYY), and orexigenic acyl ghrelin. Changes in eating behaviour after obesity surgery include decreases in hunger, increases in satiation and satiety, as well as decreases in food hedonics, reward and motivation, changes in food taste and preference, and potentially food aversion or avoidance due to post-ingestive adverse symptoms (Miras & le Roux, 2013; Madsbad et al., 2014; Behary & Miras, 2015; Makaronidis & Batterham, 2016; Akalestou et al., 2022; Al-Alsheikh et al., 2022).

Furthermore, there is heterogeneity in both the initial weight loss responses to bariatric surgery and risk of long-term weight regain. This may be contributed to by: (i) demographic factors including age, ethnicity, sex and obesity severity at baseline, (ii) presence of genetic variants especially in leptin-melanocortin pathway (Campos et al., 2022), (iii) pre-surgical presence of co-morbid disordered eating or other psychopathology, such as binge eating disorder, emotional eating, 'food addiction', impulsivity, (iv) persistence/improvement of disordered eating after surgery, which may in turn also depend on the presence and nature of psychological support before and around surgery, (v) the type of surgery, and (vi) development of surgical complications (Ivezaj et al., 2017; Athanasiadis et al., 2021; Kops et al., 2021; Cohen & Petry, 2023; Park, 2023).

Functional magnetic resonance imaging (fMRI) can be used to investigate brain reward-cognitive-emotional systems, and especially whether obesity surgery can alter the neural response to food cues. Findings from fMRI studies after obesity surgery have often revealed changes in blood oxygen level dependent (BOLD) signal to food cues (pictures or taste) in brain regions that are involved in reward, motivation and emotional processing, including caudate, putamen, nucleus accumbens (NAcc), insula, amygdala, orbitofrontal cortex (OFC), and depending on the exact cognitive task involved in the fMRI paradigms, also brain regions involved in top-down inhibitory control, risk taking, decision making and memory, including dorsolateral prefrontal cortex (dlPFC), inferior frontal gyrus (IFG), and hippocampus (Tonelli et al., 2013; Pursey et al., 2014; Makaronidis & Batterham, 2018; Hankir et al., 2020). Unfortunately, assessments of responses in hypothalamic-brainstem-midbrain appetitive and mesolimbic dopaminergic pathways using fMRI can be problematic due to the small sizes of the nuclei within these regions, difficulties with image registration, and artefacts from cardiac and respiratory cycles. These neuroimaging methodological difficulties and perseveration of the limited choice of regions of interest between studies can lead to some biases in the results obtained.

The reactivity in reward and inhibitory control systems in response to food picture stimuli and anticipatory or actual consummatory food taste is also influenced by the interplay between psychological and hormonal/metabolic factors (Carnell et al., 2012; Burger & Berner, 2014; Neseliler et al., 2017; Zanchi et al., 2017; Schulz et al., 2023). This highlights the importance of correlating fMRI findings with other eating behavioural or hormonal measures to make more meaningful conclusions as to the relationships between functional neuroimaging findings and underlying mechanisms behind post-surgical weight loss. For example, the exaggerated secretion of post-prandial satiety gut hormones GLP-1 and PYY after RYGB surgery might mediate decreases in food hedonic responses, and a shift in food preferences away from high-energy dense foods (Batterham et al., 2007; de Silva et al., 2011; Scholtz et al., 2014; van Bloemendaal et al., 2014; Goldstone et al., 2016; Ten Kulve et al., 2017).

We have recently published a systematic review of effects of bariatric surgery on brain neurotransmitter systems, metabolism and regional cerebral blood flow using positron emission tomography (PET) and single positron emission computed tomography (SPECT) (Al-Alsheikh et al., 2023). PET/SPECT molecular neuroimaging techniques using pharmacological or physiological compounds labelled with radioisotopes have the advantage of quantitatively measuring specific molecular systems including neuroreceptor subtypes (including dopamine, noradrenaline, serotonin and opioids), availability of some neurotransmitter transporters, and metabolism through brain glucose and fatty acid uptake, and regional cerebral blood flow which reflects local neuronal activity (Al-Alsheikh et al., 2023). However, PET/SPECT neuroimaging has reduced temporal and spatial sensitivity compared to measurement of BOLD signal using fMRI. As a result, while PET/SPECT can look at slow changes in glucose uptake or regional blood flow, for example after ingestion of a meal or glucose, PET/SPECT cannot assess rapid changes in neuronal activity in response to food stimuli such as pictures or taste, or other cognitive tasks, unlike fMRI.

There have only been a few previous systematic and narrative reviews of human fMRI studies after obesity surgery, mainly after RYGB and LAGB surgeries (Tonelli et al., 2013; Pursey et al., 2014; Makaronidis & Batterham, 2018; Hankir et al., 2020). However, these reviews did not: (i) report sufficient detail of study design, methodology and analysis to discuss potential reasons for heterogeneity in study findings, (ii) discuss potential confounds that may influence the interpretation of results; (iii) systematically compare differences between obesity surgeries, nor (iv) link fMRI findings with clinical outcomes, other changes in eating behaviour, or potential mechanisms related to the anatomical-physiological gut manipulations arising from obesity surgery.

This current systematic review has therefore sought to interrogate the literature of fMRI studies involving obesity surgery in more detail to fill these gaps in knowledge, provide a detailed data resource for those performing or analysing fMRI studies of obesity surgery, and makes suggestions to help improve reporting and design of such studies, as well as future directions.

2. Methods

2.1. Objectives

This systematic review aimed to assess studies examining the research questions: how does the neural response to food stimuli in humans with obesity change after obesity surgery or predict clinical and eating behaviour outcomes? The primary aim was to review collated results from individual fMRI studies in the literature reporting responses to food stimuli (picture/word cue reactivity, taste or odour) in cross-sectional and longitudinal studies of obesity surgery to examine changes after surgery. Secondary aims were to review: (i) how

heterogeneity in study methodology, design, protocol, and fMRI paradigms and analysis might explain differences between studies; (ii) differences between results particularly in terms of nutritional state and type of obesity surgery; (iii) associations of fMRI findings at baseline or their changes with clinical outcomes, such as weight loss and improvements in glycaemic control; (iv) associations of fMRI findings with other measures of eating behaviour, such as appetite ratings, food liking and wanting, and eating behaviour questionnaires; (v) associations of fMRI findings with potential hormonal mediators, such as appetitive gut hormones PYY, GLP-1 and ghrelin, and results from studies with experimental manipulations investigating their role, such as administration of satiety gut hormone antagonists or suppressants; (vi) inclusion in publications of results of confounding factors that that may affect interpretation of fMRI findings e.g. changes in mood, nausea, order effects, inclusion of control groups, where available.

2.2. Literature search

PubMed (Medline) database was searched for studies using a list of keywords (see Supplementary Methods Section 2.3). Relevant manuscript reference lists were also checked for any relevant studies. Only manuscripts written in English and published between January 1990 and July 2021 were included. Studies were included that reported the change/difference in BOLD signal in response to food stimuli (e.g. food picture, taste or odour, Go-NoGo or other cognitive task to food cues), and/or direction or magnitude of functional connectivity during a food-related task, as the main summary measure(s) after RYGB, VSG, LAGB or other obesity surgeries were included. Studies that measured food cue reactivity only after lifestyle modification, pharmacological or psychological interventions were excluded. Non-food related fMRI studies or studies only examining resting state functional connectivity were excluded. Covidence literature screening tool (https://www.covidence.org) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used for this review.

2.3. Data extraction and synthesis

In the description of food stimuli contrasts the following abbreviations are used throughout: (i) high-energy or low-energy density food (i.e. any food) vs. non-food contrast: HE/LE > NF; (ii) high-energy density food vs. non-food contrast: HE > NF; (iii) high-energy vs. low-energy density food contrast: HE > LE; (iv) low-energy density food vs. non-food contrast: LE > NF.

For region of interest (ROI) analyses where BOLD signal is averaged over a number of voxels, the term anatomical ROI (aROI) is used when the brain region is defined solely from an anatomical area e.g. using a structural atlas, while the term functional ROI (fROI) refers to regions determined from a task contrast in fMRI analysis either in the same or other dataset (though this may be further refined by masking with an anatomical atlas and/or using brain spatial coordinates).

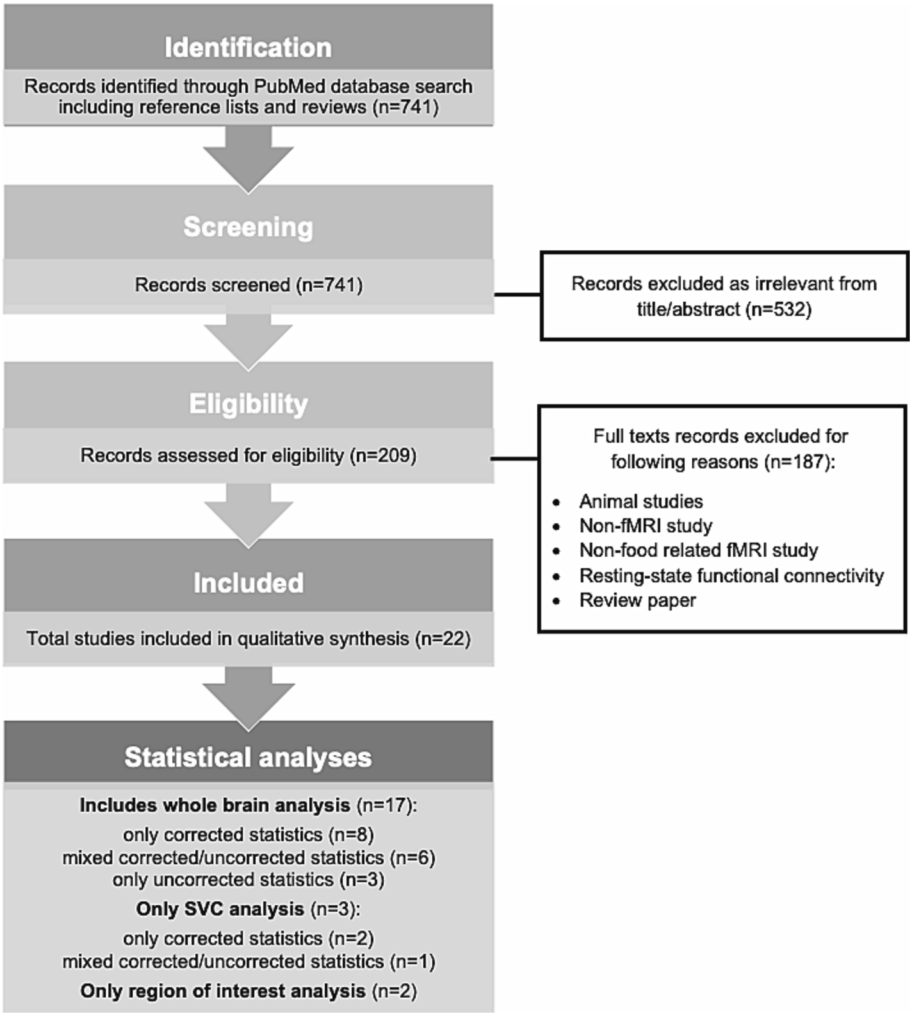

Fig. 2. Flow chart of included and excluded publications in systematic review. Abbreviations: fMRI: functional magnetic resonance imaging; SVC: small volume correction.

2.4. Standardisation of FMRI anatomical reporting

This additional section are included in Supplementary Methods.

2.5. Methodological quality assessment

This additional section are included in Supplementary Methods.

3. Results

3.1. Eligible studies

The literature search resulted in 741 articles that were identified and screened for inclusion (Fig. 2). Twenty-two studies were eligible for inclusion (Ochner et al., 2011; Bruce et al., 2012; Ochner et al., 2012a; Ochner et al., 2012b; Goldman et al., 2013; Bruce et al., 2014; Frank et al., 2014; Ness et al., 2014; Scholtz et al., 2014; Faulconbridge et al., 2016; Frank et al., 2016; Goldstone et al., 2016; Wang et al., 2016; Ten Kulve et al., 2017; Holsen et al., 2018; Zoon et al., 2018a; Zoon et al., 2018b; Baboumian et al., 2019; Li et al., 2019a; Hu et al., 2020; Smith et al., 2020; Salem et al., 2021).

Ten studies appeared to contain overlapping datasets from five cohorts (Ochner et al., 2011; Bruce et al., 2012; Ochner et al., 2012b; Bruce et al., 2014; Ness et al., 2014; Scholtz et al., 2014; Goldstone et al., 2016; Zoon et al., 2018a; Zoon et al., 2018b; Li et al., 2019a; Hu et al., 2020), leaving 17 completely independent datasets.

Study design summary, participants characteristics, and study protocols from individual studies are summarised in Table 1, Table 2 and Table 3 (also downloadable in Excel format in Supplementary Tables document). Text and tables relating to additional results sections are included in Supplementary Results and Supplementary Tables S1-9.

Two of the included 22 studies (9.1 %) included examination of *task-related* functional connectivity in addition to task-related magnitude of changes in BOLD signal before and after VSG in overlapping datasets (Li et al., 2019a; Hu et al., 2020). Ten other studies that only examined *resting state* functional connectivity were excluded from this systematic review, including six studies of RYGB (Sande-Lee et al., 2011; Frank et al., 2014; Olivo et al., 2017; Wiemerslage et al., 2017; Baboumian et al., 2019), four studies of VSG (Li et al., 2018; Cerit et al., 2019; Li et al., 2019b; Zhang et al., 2019), and one study of LAGB (Lepping et al., 2015) surgery. Review of changes in *resting state* functional connectivity were not included in this systematic review.

3.2. Study design by obesity surgery type

3.2.1. RYGB surgery

Sixteen studies (72.7 %) included patients having RYGB surgery: 10 longitudinal (Ochner et al., 2011; Ochner et al., 2012a; Ochner et al., 2012b; Faulconbridge et al., 2016; Wang et al., 2016; Ten Kulve et al., 2017; Zoon et al., 2018a; Zoon et al., 2018b; Baboumian et al., 2019; Salem et al., 2021), one predictive study (Smith et al., 2020), and five cross-sectional (Goldman et al., 2013; Frank et al., 2014; Scholtz et al., 2014; Frank et al., 2016; Goldstone et al., 2016) in design.

Two of these 16 RYGB studies (12.5 %) reported changes in food cue reactivity in both the *fasted and fed nutritional states*, at 1 month after surgery compared to before surgery (Ochner et al., 2012a; Ten Kulve et al., 2017), and one of these also examined the effects on taste responses and administration of the GLP-1 receptor antagonist, Exendin (9–39) (Ten Kulve et al., 2017). Four (23.5 %) longitudinal studies reported changes in food cue reactivity in just the *fasted state* at 4 weeks (Salem et al., 2021), 6 months (Faulconbridge et al., 2016), or taste responses at 12 months (Wang et al., 2016), compared to before surgery. Five (29.4 %) longitudinal studies reported changes in food cue reactivity (Ochner et al., 2011; Ochner et al., 2012b; Zoon et al., 2018a; Baboumian et al., 2019), or odour responses (Zoon et al., 2018b), in just the *fed state*, at 1 month (Ochner et al., 2011; Ochner et al., 2012b), 2 months (Zoon et al., 2018a; Zoon et al., 2018b), or 4 months (Baboumian et al., 2019) compared to before surgery. One predictive study reported correlations of individual differences in baseline pre-operative and post-operative changes at 2 weeks in taste responses in the *pre-meal state* (Smith et al., 2020).

The five cross-sectional RYGB studies compared food cue reactivity in the: (i) *fasted state* at average 8 months (range 3–26) after RYGB surgery against an unoperated group with obesity and post-LAGB surgery (Scholtz et al., 2014), (ii) *pre-meal state* at average 18 months after surgery against an unoperated group with obesity (Frank et al., 2016), (iii) *pre-meal state* at average 33–51 months after surgery between successful and non-successful weight loss maintainers (Goldman et al., 2013), (iv) *fed state* at average 14 months (range 5–24) after surgery with post-LAGB surgery group, and examined acute effects of administration of the somatostatin analogue, Octreotide, to suppress satiety gut hormones PYY and GLP-1 (Goldstone et al., 2016), and (v) *fed state* at average 41 months (range 13–104) after surgery with unoperated obesity and normal weight groups (Frank et al., 2014).

3.2.2. VSG surgery

Six studies (27.3 %) included patients having VSG surgery: all of longitudinal design. Three studies (50.0 %) reported changes in food cue reactivity in the *fasted state,* at 1 month (Li et al., 2019a; Hu et al., 2020), or 6 months (Faulconbridge et al., 2016) after surgery, and all of them included a control group with obesity. Two studies (33.3 %) reported changes in food cue reactivity in the *fed state*, at 4 months (Baboumian et al., 2019) or 12 months (Holsen et al., 2018) compared to before surgery. One predictive study reported correlations of individual differences in baseline pre-operative and 2 weeks post-operative changes in taste responses in the *pre-meal state* (Smith et al., 2020). Two studies examined functional connectivity during a food-related fMRI task at 1 month compared to before surgery (Li et al., 2019a; Hu et al., 2020).

3.2.3. LAGB surgery

Five of the 22 studies (22.7 %) included patients having LAGB surgery: two longitudinal (Bruce et al., 2012; Bruce et al., 2014), one predictive (Ness et al., 2014), and two cross-sectional (Scholtz et al., 2014; Goldstone et al., 2016) in design. Three studies (60.0 %) reported changes in food cue reactivity in both the *pre-meal and fed nutritional state,* at 3 months (Bruce et al., 2012; Bruce et al., 2014) or 6 months (Ness et al., 2014) compared to before surgery. The two cross-sectional studies (40.0 %) compared food cue reactivity in the *fasted state* at average 8 months (range 3–26) months after LAGB with an unoperated group with obesity and post-RYGB surgery groups (Scholtz et al., 2014), and in the *fed state* at average 14 months (range 5–24) after LAGB with a post-RYGB surgery group, and also examined effects of acute Octreotide administration (Goldstone et al., 2016).

3.2.4. Comparative obesity surgery studies

Five (22.7 %) studies directly compared the effect of different surgeries on food cue reactivity: three longitudinal studies compared RYGB with VSG at 2 weeks (Smith et al., 2020), 4 months (Baboumian et al., 2019) or 6 months (Faulconbridge et al., 2016) after surgery; while two cross-sectional studies compared RYGB with LAGB at an average 8 months (Scholtz et al., 2014), or 14 months (Goldstone et al., 2016) after surgery, with the latter also examining the effects of acute Octreotide administration.

3.2.5. Other surgeries

No publications were found that included patients after one-anastomosis gastric bypass (OAGB), also known as “mini-bypass’, or biliary-pancreatic diversion (BPD), a procedure that achieves its effects primarily through malabsorption.

Table 1
Summary of included studies.

Author	Year	Journal	PubMedID	Country	Design	Group(s)	Controlgroup	fMRIParadigm	Activetask	Functionalconnectivity	Nutritionalstateinteraction	AssociationfMRIwithclinicaloutcomes	Appetiteratings	Othereatingbehaviourmeasures	AssociationfMRIvs.appetite/behaviour	Assesmentnauseaordumpingsymptoms	Mechanisticbloodmeasures	AssociationfMRIvs.mechanisticmeasures
RYGB																		
Ochner [a]	2011	Ann Surg	21169809	USA	Longitudinal	RYGB	o	Food cue reactivity	o	o	o	o	o	Yes	o	o	o	o
Ochner [a]	2012b	Neuroscience	22406414	USA	Longitudinal	RYGB	o	Food cue reactivity	o	o	o	o	o	Yes	Yes	o	o	o
Ochner	2012a	Neurosci Res	22921709	USA	Longitudinal	RYGB	o	Food cue reactivity	o	o	o	o	Yes	o	o	o	o	o
Ten Kulve	2017	Diabetes Care	29025878	Netherlands	Longitudinal ± interventional	RYGB	o	Food cue reactivity	o	o	o	o	Yes	o	o	Yes	Yes	Yes
Zoon [b]	2018b	Behav Brain Res	30041007	Netherlands	Longitudinal	RYGB	o	Food cue reactivity	o	o	o	Yes	Yes	Yes	Yes	o	Yes	Yes
							o	Taste	o	o	o	o	o	o	o	Yes	Yes	Yes
							o	Odour	o	o	o	Yes	o	Yes	Yes	o	Yes	Yes
Frank	2016	Diabetes Care	27293200	Germany	Cross-sectional	RYGB, OB	Yes	Food cue reactivity	Yes	o	o	Yes	Yes	Yes	o	o	o	o
Frank	2014	Int J Obesity	23711773	Germany	Cross-sectional	RYGB, OB, NW	Yes	Food memory	Yes	o	o	o	Yes	Yes	o	o	o	o
Goldman	2013	Obesity	24136926	USA	Cross-sectional	RYGB	Yes	Food cue reactivity	Yes	o	o	Yes	o	o	o	o	o	o
Zoon [b]	2018a	Biol Psychol	29944963	Netherlands	Longitudinal	RYGB	o	Food go/nogo	Yes	o	o	Yes	Yes	o	Yes	o	o	o
Wang	2016	Surg Endosc	26099619	USA	Longitudinal	RYGB, NO-NT	Yes	Taste	Yes	o	o	o	o	Yes	o	o	o	o
Salem	2021	Diabetes Care	34158363	UK	Longitudinal	RYGB, VLCD	Yes	Food cue reactivity	o	Yes (rest)	o	Yes	Yes	o	Yes	Yes	Yes	Yes
VSG																		
Li [c]	2019	Psychoneuroendocrinol	30388597	China	Longitudinal	VSG, OB-NT	Yes	Food cue reactivity	o	Yes (task)	o	Yes	Yes	Yes	Yes	o	Yes	Yes
Hu [c]	2020	J Neurology	32170447	China	Longitudinal	VSG, OB-NT	Yes	Food cue reactivity	o	Yes (task)	o	Yes	o	Yes	o	o	o	o
Holsen	2018	Int J Obesity	28894291	USA	Longitudinal	VSG	o	Food cue reactivity	Yes	o	o	Yes	o	Yes	o	o	Yes	o
LAGB																		
Bruce [d]	2012	Surg Obes Relat Dis	21996599	USA	Longitudinal	LAGB	o	Food cue reactivity	o	o	Yes	Yes	o	Yes	Yes	o	o	o
Ness [d]	2014	Surg Obes Relat Dis	25443066	USA	Predictive	LAGB	o	Food cue reactivity	o	o	Yes	Yes	o	o	o	o	o	o
Bruce [d]	2014	Obesity	24115765	USA	Longitudinal	LAGB, LCD	Yes	Food cue reactivity	o	o	Yes	o	Yes	o	o	o	o	o
MULTIPLE																		
Scholtz [e]	2013	Gut	23964100	UK	Cross-sectional	RYGB, LAGB, OB	Yes	Food cue reactivity	Yes	o	o	o	Yes	Yes	Yes	Yes	Yes	Yes
Goldstone [e]	2015	JCEM	26580235	UK	Cross-sectional ± interventional	RYGB, LAGB	No	Food cue reactivity	Yes	o	o	o	Yes	Yes	o	Yes	Yes	Yes
Faulconbridge	2016	Obesity	27112067	USA	Longitudinal	RYGB, VSG, OB-NT	Yes	Food cue reactivity	o	o	o	o	o	Yes	Yes	o	Yes	Yes
Baboumian	2019	Neuroscience	30769095	USA	Longitudinal	RYGB, VSG, OB-LCD/CBT, OB-NT	Yes	Food cue reactivity	o	Yes (task)	o	o	o	o	o	o	Yes	Yes
Smith	2020	JCI	32427584	USA	Predictive	RYGB, VSG	No	Taste	o	No	No	Yes	Yes	Yes	o	o	o	o

Footnotes: [a-d]: probable overlapping datasets, [e] overlapping participants.
Abbreviations: CBT: cognitive behavioural therapy, LAGB: laparoscopic adjustable gastric banding, LCD: low-calorie diet, NO: non-obese, NT: no treatment, NW: normal weight, o: no, OB: obese, OW: overweight, RYGB: Roux-en-Y gastric bypass, UK: United Kingdom, USA: United States of America, VLCD: very low-calorie diet; VSG: vertical sleeve gastrectomy.

Table 2
Participant demographics in individual studies.

Author	Year	N	Group	Female	Age (y)	T2DM	Caucasian	Control intervention	Time scan pre-intervention (months)	Time between scans (months)	Time scan post-intervention (months)	Baseline BMI	Current/ Post-BMI	Weight loss	Change in glycaemia
				n (%)	mean ± SD or median [IQR] (range)	n (%)	n (%)				mean ± SD or median [IQR] (range)	mean ± SD or median [IQR] (range) kg/m^2		mean ± SD (range) % or kg	change in FPG, fasting insulin, HbA1c
RYGB															
Ochner [f]	2011	10	RYGB	10 (100 %)	35 ± 9 (20–47)	0 (0 %)	2 (20.0 %)	n/a	1 mo	2 mo	1 mo	45.1 ± 5.3 (40–54)	39.8 ± 4.2	11.8 ± 3.1 %	n/a
Ochner [f]	2012b	14	RYGB	14 (100 %)	36 ± 10 (20–54)	0 (0 %)	2 (14.3 %)	n/a	1 mo	2 mo	1 mo	45.5 ± 4.4 *	39.8 ± 3.7 *	9.9 ± 2.9 % *	n/a
Ochner	2012a	5	RYGB	5 (100 %)	36 ± 13 (21–54)	0 (0 %)	0 (0 %)	n/a	1 mo	2 mo	1 mo	45.5 ± 4.4 *	39.8 ± 3.7 *	9.9 ± 2.9 % *	n/a
Ten Kulve	2017	10	RYGB	10 (100 %)	46.5 [40.0, 50.0]	0 (0 %)	n/a	n/a	n/a	1.4–2.8 mo	0.9 mo	39.9 [37.8, 42.5]	36.8 [34.6, 39.1]	~8.2 % [a] (8.8 ± 1.7 kg)	FPG, HbA1c: NS
Zoon [g]	2018b	19	RYGB	15 (78.9 %)	41 ± 10	n/a	n/a	n/a	0.8 ± 0.4 no	mean 2.9 mo	2.1 ± 0.3 mo	41 ± 3	36 ± 4	~13.3 % [a]	n/a
Frank	2016	12	RYGB	10 (83.3 %)	50.0 ± 9.2	12 (100 %)	n/a	n/a	n/a	n/a	17.7 ± 9.3 mo	n/a	35.7 ± 2.9	~31.6 % [b] (ΔBMI −16.5 ± 5.3 kg/m^2)	HbA1c: Δ 1.4 ± 1.7 % sig. vs. control
		12	OB	6 (50.0 %)	50.7 ± 11.4	12 (100 %)		n/a	n/a	n/a		n/a	37.8 ± 4.8	n/a	n/a
Frank	2014	9	RYGB	9 (100 %)	42.0 ± 8.4	n/a	n/a	n/a	n/a	n/a	40.8 ± 28.8 mo (13.2–104.4)	n/a	27.1 ± 2.7	n/a	n/a
		11	OB	11 (100 %)	42.6 ± 13.3	n/a	n/a	n/a	n/a	n/a	n/a	n/a	40.2 ± 2.7	n/a	n/a
		11	NW	11 (100 %)	36.6 ± 12.6	n/a	n/a	n/a	n/a	n/a	n/a	n/a	21.4 ± 1.7	n/a	n/a
Goldman	2013	24	RYGB-MS	19 (79.2 %)	46.6 ± 11.4	n/a	20 (83.3 %)	n/a	n/a	n/a	32.8 ± 21.6 mo	51.6 ± 11.2	30.4 ± 7.2	40.8 ± 8.2 %	n/a
		7	RYGB-LS	7 (100 %)	43.4 ± 10.5	n/a	7 (100 %)				50.6 ± 28.4 mo	50.2 ± 5.4	38.2 ± 3.7	23.6 ± 6.5 %	n/a
Zoon [g]	2018a	18	RYGB	15 (83.3 %)	41 ± 11	n/a	n/a	n/a	0.8 ± 0.4 mo	mean 2.9 mo	2.1 ± 0.3 mo	42 ± 4	36 ± 4	17 ± 3 kg	n/a
Wang	2016	6	RYGB-1mo	3 (50.0 %)	47.0 ± 7.2 (37–56)	0 (0 %) on T2DM meds	n/a	n/a	0.3 ± 0.4 (0–1.0) mo	1.9 ± 1.0 (1.0–3.4) mo	1.6 ± 0.6 (1.0–2.4) mo	43.2 ± 3.6 (38.5–49.1)	39.4 ± 4.6 (35.3–47.9)	9.1 ± 4.1 % (2.4–14.3) [b]	n/a
		6	RYGB-12mo	2 (33.3 %)	48.5 ± 8.9 (37–60)	1 (0 %) on T2DM meds	n/a	n/a	0.4 ± 0.2 (0–1.0) mo	13.3 ± 3.8 (10.0–20.4) mo	12.9 ± 3.4 (9.9–19.4) mo	42.1 ± 4.9 (35.1–49.1)	28.6 ± 3.7 (24.3–34.8)	31.2 ± 12.2 % (9.6–47.0) [b]	n/a

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Table 2 (*continued*)

Author	Year	N	Group	Female	Age (y)	T2DM	Caucasian	Control intervention	Time scan pre-intervention (months)	Time between scans (months)	Time scan post-intervention (months)	Baseline BMI	Current/ Post-BMI	Weight loss	Change in glycaemia
		7	NO-NT	2 (28.5 %)	51.7 ± 7.8	0 (0 %)	n/a	None	n/a	1.2 ± 0.3 mo	n/a	27.0 ± 2.2	n/a	n/a	n/a
Salem	2021	16	RYGB	13 (81.25)	48.6 ± 14.4	16 (100 %)	n/a	n/a	?	?	0.92 mo	wt: 119.9 ± 6.1 kg	wt: 107.7 ± 6.0 kg	wt: −12.3 ± 0.9 (-10.4 ± 0.9 %)	HbA1c: NS FPG: Δ −2.5 ± 0.4 mmol/L NS fasting insulin: Δ −7.1 ± 1.8 mIU/L NS
		19	VLCD	11 (57.89 %)	46.2 ± 10.8	19 (1005)	n/a	VLCD	0.23 mo	1.15 mo	0.92 mo	wt: 109.2 ± 5.0 kg	wt: 100.8 ± 4.5 kg	wt: −8.42 ± 0.7 (-7.7 ± 0.4 %)	HbA1c: NS FPG: Δ −1.8 ± 0.5 mmol/L NS fasting insulin: Δ −6.8 ± 1.2 mIU/L NS
VSG															
Li [h]	2019	22	VSG	13 (59.1 %)	26.6 ± 8.6	n/a	n/a	n/a	n/a	n/a	1 mo	38.1 ± 6.2	34.0 ± 6.1	~10.5 % [a]	n/a
		19	OB-NT	12 (63.2 %)	28.6 ± 9.0	n/a	n/a	None	n/a	1 mo	n/a	35.3 ± 4.4	35.1 ± 4.5	~1.0 % [a]	n/a
Hu [h]	2020	28	VSG	15 (53.5 %)	27.9 ± 7.9	n/a	n/a	n/a	n/a	n/a	1 mo	39.3 ± 4.8	34.7 ± 4.8	~11.2 % [a]	n/a
		22	OB-NT	9 (40.9 %)	28.4 ± 8.4	n/a	n/a	None	n/a	1 mo	n/a	36.9 ± 4.7	36.6 ± 4.7	~0.7 % [a]	n/a
Holsen	2018	18	VSG	16 (88.9 %)	38.4 ± 10.1	0 (0 %)	15 (83.3 %)	n/a	1 mo	13 mo	12 mo	41.8 ± 4.5	29.6 ± 4.0	29.0 ± 7.7 %	FPG: 96.9 ± 18.8 to 80.1 ± 5.5 mg/dL sig.
LAGB															
Bruce [i]	2012	10	LAGB	9 (90.0 %)	40.1 ± 10.3 (21–54)	n/a	n/a	n/a	0.3 ± 0.2 mo	mean 3.8	3.5 ± 0.8 mo	40.6 ± 2.0	36.1 ± 2.3	~11.0 % [b] (Δ −13.4 ± 5.4 kg)	n/a
Ness [i]	2014	19	LAGB	16 (84.2 %)	38.4 ± 11.2	n/a	n/a	n/a	0.3 ± 0.2 mo	3.0 ± 0.4 mo [c]	mean 2.7 mo [c]	42.0 ± 3.1	37.9 ± 3.0[c]	~9.8 % [b c] (%EWL 25.0 ± 11.4 %)	n/a
										5.9 ± 0.8 mo [c]	mean 5.6 mo [c]		35.9 ± 3.5[c]	~14.4 % [b c] (%EWL 36.5 ± 13.4 %)	n/a
Bruce [i]	2014	15	LAGB	12 (80.0 %)	41.4 ± 9.8 (21–56)	n/a	n/a	n/a	n/a	n/a	3.7 mo	n/a	?	9.30 %	n/a

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Table 2 (*continued*)

Author	Year	N	Group	Female	Age (y)	T2DM	Caucasian	Control intervention	Time scan pre-intervention (months)	Time between scans (months)	Time scan post-intervention (months)	Baseline BMI	Current/ Post-BMI	Weight loss	Change in glycaemia
		16	LCD	11 (68.7 %)	40.6 ± 7.1 (23–52)	n/a	n/a	LCD/ behaviour	n/a	n/a	3.7 mo			10.80 %	n/a
MULTIPLE															
Scholtz [j]	2013	21	RYGB	19 (90.5 %)	43.5 ± 9.2 (23.0–59.0)	3 (14.3 %)	16 (76.2 %)	n/a	n/a	n/a	8.1 [5.9, 11.5] mo (2.6–26.2)	48.4 (34.7–74.6)	35.3 ± 1.7 (22.6–52.4)	29.9 % (16.3–40.4)	T2DM prevalence: 48 to 14 % NS
		20	LAGB	19 (95.0 %)	40.9 ± 11.2 (22.0–59.0)	0 (0 %)	15 (75.0 %)	n/a	n/a	n/a	9.1 [5.2, 19.2] mo (3.6–64.6)	44.8 (36.5–57.0)	35.1 ± 1.4 (25.3–49.2)	23.1 % (9.7–52.4)	T2DM prevalence: 10 to 0 %
		20	OW	17 (85.0 %)	39.1 ± 10.3 (20.0–55.0)	2 (10.0 %)	10 (50.0 %)	n/a	n/a	n/a	n/a	n/a	35.4 ± 1.9 (24.7–55.6)	n/a	n/a
Goldstone [j]	2015	7 [e]	RYGB	5 (71.4 %)	46.0 ± 2.6 (42–50)	1 (14.3 %)	7 (100 %)	n/a	n/a	0.5 [0.2, 0.7]	14.2 ± 7.9 mo (5.2–23.9)	55.2 ± 14.0 (38.3–74.6)	38.6 ± 8.2 (29.4–48.8)	29.1 ± 6.3 % (21.1–38.3)	T2DM prevalence: 57 to 14 %
		9	LAGB	8 (88.9 %)	41.8 ± 11.4 (26–59)	0 (0 %)	6 (66.7 %)	n/a	n/a		15.3 ± 10.8 mo (4.0–36.0)	51.7 ± 14.4 (36.5–86.2)	33.2 ± 18.9 (25.2–43.8)	27.4 ± 12.0 % (10.0–52.0)	T2DM prevalence: 0 to 0 %
Faulconbridge	2016	22	RYGB	22 (100 %)	37.2 ± 9.3	0 (0 %)	14 (63.6 %)	n/a	<0.9 mo	~7 mo	6 ± 0.5 mo	44.6 ± 4.3	n/a	23.6 ± 1.4 %	n/a
		18	VSG	18 (100 %)	40.3 ± 8.9	0 (0 %)	4 (22.2 %)	n/a	<0.9 mo	~7 mo		43.9 ± 4.1	n/a	21.3 ± 1.0 %	n/a
		21	OB-NT	21 (100 %)	36.4 ± 8.2	0 (0 %)	3 (15.8 %)	None	n/a	6 ± 0.5 mo	n/a	43.3 ± 4.4	n/a	gain 1.0 ± 0.6 %	n/a
Baboumian	2019	16	RYGB	15 (93.8 %)	38 ± 10	0 (0 %)	6 (10.9 %)	n/a	~1 mo	4.3 ± 1.0 mo	~3.3 mo	44.2 ± 4	35.1 ± 4	~20.6 % [b]	n/a
		9	VSG	9 (100 %)	29 ± 6	0 (0 %)		n/a	~1 mo		~3.3 mo	41.0 ± 3	32.1 ± 4	~21.7 % [b]	n/a
		14	LCD-CBT	10 (71.4 %)	39 ± 10	0 (0 %)		LCD/ behaviour	~1 mo		~3.3 mo	42.7 ± 4	37.5 ± 4	~12.2 % [b]	n/a
		16	OB-NT	14 (87.5 %)	35 ± 12	0 (0 %)		None	n/a		n/a	41.2 ± 3	40.4 ± 3	~1.9 % [b]	n/a
Smith	2020	23 (15–19 fMRI) [d]	RYGB	23 (100 %)	40.0 ± 1.9	5 (21.7 %)	16 (69.6 %)	n/a	0.9–1.8 mo	1.8–3.6 mo	0.9–1.8 mo	44.6 ± 1.1	41.4 ± 1.0	7.1 ± 0.4 %	n/a
		25 (17–20 fMRI) [d]	VSG	25 (100 %)	38.9 ± 1.5	5 (20.0 %)	9 (36.0 %)	n/a	0.9–1.8 mo	1.8–3.6 mo	0.9–1.8 mo	43.4 ± 0.1	40.6 ± 1.0	6.5 ± 0.4 %	n/a

Footnotes: [a] calculated from Δ average weight, [b] calculated from change in average BMI, [c] no scan just time point for weight loss, [d] 1st n Pre- and Post-intervention, 2nd n Pre-intervention only, [e] n = 9 total for RYGB (as n = 2 performed task outside scanner), [f-i] probable overlapping datasets, [j] overlapping participants, * appears to be duplicated data in error.

Abbreviations: Δ: change, BMI: body mass index, CBT: cognitive behavioural therapy, EWL: excess weight loss, FPG: fasting plasma glucose, HbA1c: glycosylated haemoglobin, IQR: interquartile range, LAGB: laparoscopic adjustable gastric banding, LCD: low-calorie diet, meds: medications, mmol/L: millimoles per litre, mo: months, n/a: not applicable, NO: non-obese, NS: not significant, NT: no treatment, NW: normal weight, OB: obesity, OB-NT: obesity no treatment, OW: overweight, RYGB: Roux-en-Y gastric bypass, RYGB-LS: RYGB least successful < 50 % EWL, RYGB-MS: RYGB most successful > 50 % EWL, SD: standard deviation, T2DM: type 2 diabetes mellitus, VLCD: very low-calorie diet, VSG: vertical sleeve gastrectomy, wt: weight, y: years.

3.3. Control groups

Ten out of the 20 non-predictive studies (57.1 %) had a control non-surgical group (Bruce et al., 2014; Frank et al., 2014; Scholtz et al., 2014; Faulconbridge et al., 2016; Frank et al., 2016; Wang et al., 2016; Baboumian et al., 2019; Li et al., 2019a; Hu et al., 2020; Salem et al., 2021). In the 15 longitudinal studies, only seven studies (46.7 %) had a control group(s) to control for order effects, dietary/psychological advice given alongside surgery, and/or reduced energy intake and weight loss itself. Of these, only three studies (20.0 %) included an active intervention: two studies with a group with obesity receiving very low calorie diet (VLCD) for comparison with RYGB (Salem et al., 2021) or LAGB (Bruce et al., 2014), and in one study a group with obesity received an LCD with cognitive behavioural therapy (CBT) for comparison with RYGB/VSG groups (Baboumian et al., 2019). In addition, four studies (26.7 %) included a group with overweight/obesity who received no intervention for longitudinal comparison with RYGB (Faulconbridge et al., 2016; Baboumian et al., 2019; Li et al., 2019a) or VSG (Faulconbridge et al., 2016; Baboumian et al., 2019; Hu et al., 2020) groups, none of whom had any marked weight loss.

In the five cross-sectional studies, the comparison group for the RYGB group was normal weight in one study (Frank et al., 2014), and/or unoperated groups with overweight/obesity in three studies (Frank et al., 2014; Scholtz et al., 2014; Frank et al., 2016), of which only two studies had a control group with similar average BMI to the post-surgical group (Scholtz et al., 2014; Frank et al., 2016). Another study compared successful with unsuccessful weight loss after RYGB surgery (Goldman et al., 2013), and the other just compared RYGB with LAGB groups, together with the effects of acute Octreotide administration (Goldstone et al., 2016). Two of the 21 non-predictive studies (9.5 %) had more than one control group, one longitudinal (Baboumian et al., 2019), and one cross-sectional (Frank et al., 2014).

When comparing the magnitude of weight loss between surgical and controls groups in the same study, percentage weight loss was more pronounced in surgery groups (RYGB/VSG) compared to LCD-CBT intervention (20.6–21.7 % vs 12.2 %) (Baboumian et al., 2019), and RYGB compared to VLCD (10.4 % vs 7.7 %) (Salem et al., 2021), although the latter study also performed sub-group fMRI analyses matching for weight loss, while percentage weight loss was similar after LAGB surgery compared to LCD (10.8 % vs 9.3 %) (Bruce et al., 2014). This is important since food cue reactivity maybe altered by dietary-induced weight loss itself.

3.4. Nutritional status

Study protocols of the individual studies are summarised in Table 3, including nutritional status.

In nine studies (45.5 %), participants were scanned only after an overnight fast (Scholtz et al., 2014; Faulconbridge et al., 2016; Wang et al., 2016; Holsen et al., 2018; Li et al., 2019a; Hu et al., 2020; Salem et al., 2021), or after not eating for four hours (pre-meal) (Frank et al., 2016; Smith et al., 2020); and in six studies (26.1 %), participants were just scanned when fed, shortly (0.25–1.5 h) after a standardised fixed liquid (Ochner et al., 2011; Ochner et al., 2012b; Frank et al., 2014; Baboumian et al., 2019) or solid (Zoon et al., 2018a; Zoon et al., 2018b) meal.

In five studies (22.7 %) participants were scanned in two nutritional states: fasted and fed (0.5–0.75 h after meal) states (Ochner et al., 2012a; Ten Kulve et al., 2017) or pre-meal (>4 h from last meal) and fed (immediately after consuming a 500 kcal meal) states (Bruce et al., 2012; Bruce et al., 2014; Ness et al., 2014). In only one of these five studies, were the fasted and fed visits done on different days and randomised to control for order effects (Ochner et al., 2012a), while in three studies both pre-meal and fed states were examined on the same day but the order of nutritional state sessions were randomized between participants (Bruce et al., 2012; Bruce et al., 2014; Ness et al., 2014), while in the fifth study the fed session was always after the fasted session (Ten Kulve et al., 2017).

3.5. Other study variables

Other similarities and differences between studies, including study design, participant characteristics, time since surgery, magnitude of weight loss after surgery, fMRI paradigms, food stimulus type, confounding factors, and fMRI analysis, are summarised in Table 2, Table 3, Supplementary Table S2 and Supplementary Table S3, and described in Supplementary Results sections 3.1-3.8.

A summary of the number of studies by type of surgery, nutritional state and food picture contrast in fMRI paradigm is given in Fig. 3.

3.6. Quality assessment

Methodological quality assessment is summarised in Supplementary Tables S9 and S10, and described in Supplementary Results Section 3.12.

3.7. Changes in food cue reactivity and taste/smell responses

Unless stated otherwise, to save space the results reported in this systematic review are for passively viewing food pictures and are significant when correcting for multiple comparisons from whole brain or small volume correction (SVC) analyses.

For space reasons, in this section, only fMRI findings in cortical and subcortical areas known to be particularly relevant to appetite regulation, reward processing, emotional responses and inhibitory control are highlighted in description of the results, including ventral (nucleus accumbens) and dorsal (caudate, putamen, pallidum) striatum, amygdala, hippocampus, parahippocampal gyrus, insula, operculum, anterior cingulate cortex (ACC), paracingulate gyrus, OFC and dlPFC ('highlighted regions') as shown in Fig. 4, though results from all brain regions are included in Supplementary Table S3.

Furthermore, the text describing the results only includes results from whole brain and SVC analyses that used appropriate corrections for multiple comparison, though uncorrected statistics are also included in Supplementary Table S3 (where they are placed in square brackets).

Unfortunately, when looking at the summary of findings of individual studies when restricting inclusion to particular food stimuli contrasts e.g. HE food > LE food (Supplementary Table 3a), HE food (Supplementary Table 3b), LE food (Supplementary Table 3c), HE or LE food (Supplementary Table 3d), or taste–smell paradigms (Supplementary Table 3e), there are no completely consistent findings for any brain region from whole brain, SVC and/or ROI analyses.

3.7.1. RYGB surgery

High-energy or low-energy food vs. *non-food contrast:* In one longitudinal study in the *fasted state*, BOLD signal to HE/LE food pictures significantly decreased in caudate and rolandic operculum (but not putamen, amygdala, anterior and posterior insula, and OFC) at 1 month after RYGB surgery (n = 10, using SVC analysis) (Ten Kulve et al., 2017). However, these effects were not seen in the *fed state* (Ten Kulve et al., 2017).

In one longitudinal studies in the *fasted state*: BOLD signal to HE/LE food pictures decreased at 4 weeks after RYGB surgery compared to after a 4 week VLCD in cingulate cortex, vmPFC and OFC in a weight loss matched analysis (n = 7 per group with fixed effects analysis), while in ROI analysis, BOLD signal to HE/LE pictures decreased after RYGB surgery compared to after VLCD in the hypothalamus alone, when averaged across a reward network (NAcc, caudate, putamen, OFC, amygdala, and insula) and executive control network (hippocampus, vmPFC, paracingulate gyrus, MFG, parietal lobule) (n = 16–19), and in both NAcc and putamen alone in a weight loss matched sub-group analysis (n = 7 per group) (Salem et al., 2021). In a cross-sectional

Table 3
Study protocols for individual studies.

Author	Year	State Intervention	Nutritional state	Control feeding / intervention order effects	Meal	Macronutrients (% total kcal)	Time since last meal (h) mean ± SD (range)	Menstrual cycle controlled	Mood assessment
RYGB									
Ochner [a]	2011	n/a	Fed	n/a	250 kcal 250 ml liquid	fat 42.8 %, CHO 40.0 %, protein 18.1 %	1	o	o
Ochner [a]	2012b	n/a	Fed	n/a	250 kcal 250 ml liquid	fat 42.8 %, CHO 40.0 %, protein 18.1 %	1	Yes (matched)	o
Ochner	2012a	n/a	Fasted	Yes	250 ml water	n/a	12	o	o
			Fed		250 kcal 250 ml liquid	fat 42.8 %, CHO 40.0 %, protein 18.1 %	0.75		
Ten Kulve	2017	Placebo vs. GLP-1R antagonist Ex9-39	Fasted	Fasted/Fed: o	n/a	n/a	?	o	o
		Placebo vs. GLP-1R antagonist Ex9-39	Fed	Placebo/Ex9-39: Yes	300 kcal, 200 ml liquid	fat 34.8 %, CHO 50.0 %, protein 16.0 %	0.5		
Zoon [b]	2018b	n/a	Fed	n/a	Pre: 570 kcal male, 421 kcal female Post: 174 kcal male, 107 kcal female mixed	bread roll, margarine, cheese, ham, orange juice	0.25	o	o
Frank	2016	n/a	Pre-meal	n/a	n/a	n/a	≥ 3	o	Yes
Frank	2014	n/a	Fed	n/a	246 kcal, 300 ml liquid	fat 10.2 %, CHO 64.2 %, protein 25.6 %	0.5	o	o
Goldman	2013	n/a	Pre-meal	n/a	n/a	n/a	5.5 ± 5.2	Yes (luteal phase)	Yes
Zoon [b]	2018a	n/a	Fed	n/a	Pre: 570 kcal male, 421 kcal female Post: 174 kcal male, 107 kcal female mixed	bread roll, margarine, cheese, ham, orange juice	0.25	o	o
Wang	2016	n/a	Fasted	n/a	n/a	n/a	12	o	o
Salem	2021	n/a	Fasted	n/a	n/a	n/a		o	o
VSG									
Li [c]	2019	n/a	Fasted	n/a	n/a	n/a	12	o	Yes
Hu [c]	2020	n/a	Fasted	n/a	?	n/a	12	n/a	Yes
Holsen	2018	n/a	Pre-meal	n/a	?	n/a	≥ 4	o	Yes
LAGB									
Bruce [d]	2012	n/a	Pre-meal	o	n/a	n/a	≥ 4	o	o
			Fed		500 kcal mixed	lean meat sandwich wrap, carrot, fruit, skimmed milk	0		
Ness [d]	2014	n/a	Pre-meal	o	n/a	n/a	≥ 4	o	o
			Fed		500 kcal mixed	lean meat sandwich wrap, carrot, fruit, skimmed milk	0		
Bruce [d]	2014	n/a	Pre-meal	o	n/a	n/a	≥ 4	o	o
			Fed		500 kcal mixed	lean meat sandwich/ wrap, carrot, fruit, skimmed milk	0		
MULTIPLE									
Scholtz [e]	2013	n/a	Fasted	n/a	n/a	n/a	16.5 (16.0–17.3) 16.1 (15.6–16.7) 16.4 (15.7–17.0)	Yes (1st 14 days)	Yes
Goldstone [e]	2015	Octreotide-insulin vs. placebo	Fed	Yes	385 kcal 200 ml liquid	fat 16.0 %, CHO 45.6 %, protein 38.4 %	1.6	Yes (1st 14 days)	Yes
Faulconbridge	2016	n/a	Fasted	n/a	n/a	n/a	overnight	o	o

(*continued on next page*)

Table 3 (*continued*)

Author	Year	State Intervention	Nutritional state	Control feeding / intervention order effects	Meal	Macronutrients (% total kcal)	Time since last meal (h) mean ± SD (range)	Menstrual cycle controlled	Mood assessment
Baboumian	2019	n/a	Fed	n/a	250 kcal 250 ml liquid	fat 19.0 %, CHO 40.0 %, protein 18.1 %	1.5	o	o
Smith	2020	n/a	Pre-meal	n/a	n/a	n/a	≥ 4	o	o

Footnotes: [a-d]: probable overlapping datasets, [e] overlapping participants.
Abbreviations: CHO: carbohydrate, Ex9-39: Exendin(9–39), GLP-1: glucagon-like peptide-1, GLP-1R: GLP-1 receptor, h: hours, kcal: kilocalorie, mL: millilitres, n/a: not applicable, o: no, SD: standard deviation

study, BOLD signal during evaluation of wanting or liking to HE/LE foods in hippocampus, anterior insula, rolandic operculum and ACC (BA8) was higher, and in pallidum lower, at 18 months after RYGB surgery for HE vs. LE foods compared to unoperated group with obesity *in pre-meal state* (n = 12) (Frank et al., 2016).

High-energy food vs. *non-food contrast:* In one longitudinal study in the *fed state,* BOLD signal to HE food cues (pictures/words) decreased in putamen, cingulate cortex and other frontal regions, at 1 month after RYGB surgery (n = 5) (Ochner et al., 2012b). However, no changes in BOLD signal were reported in any of our highlighted regions in the other two longitudinal studies: (i) by the same group with identical protocol at 1 month after RYGB surgery (n = 10) (Ochner et al., 2011), (ii) in SVC analysis with food pictures at 1 month after RYGB surgery (n = 10) including caudate, putamen, amygdala, insula, operculum and OFC (Ten Kulve et al., 2017).

In two longitudinal studies, in the *fasted state,* BOLD signal to HE food cues (i) decreased in OFC and caudate (but not putamen, rolandic operculum, amygdala, anterior and posterior insula) using SVC analysis at 4 weeks after RYGB surgery (n = 10) (Ten Kulve et al., 2017), (ii) decreased at 6 months after RYGB surgery in VTA but not in NAcc, amygdala, hippocampus, insula, ACC, OFC or hypothalamus using anatomical ROI (aROI) analysis (n = 22) (Faulconbridge et al., 2016).

In a cross-sectional study in *the fasted state,* BOLD signal during evaluation of HE food did not differ on average 8–9 months after RYGB surgery compared to a BMI-matched control group (n = 21–20) in NAcc, caudate, amygdala, OFC, anterior insula (or in average of all regions) in fROI analysis (Scholtz et al., 2014).

High-energy vs. *low-energy food contrast:* In three longitudinal studies in the *fed state*, BOLD signal to: (i) HE vs. LE food cues (pictures/words) decreased in the NAcc, ACC (BA 23/24/32), dlPFC (BA9/8/45) and other frontal regions at 1 month after RYGB surgery (n = 10) (Ochner et al., 2011); but (ii) did not change in a similar but smaller study (n = 5) by the same group again at 1 month after RYGB (Ochner et al., 2012a); but (iii) for HE vs. LE foods decreased in PHG, and increased in the dlPFC in a larger study (n = 19) at ~ 3 months after RYGB surgery (Baboumian et al., 2019). Furthermore, in the latter study changes in control groups were in the opposite direction with BOLD signal increasing in the PHG in control groups with obesity receiving either LCD-CBT or no treatment, and decreasing in dlPFC in group receiving no treatment, suggesting that the changes are related to the surgery, rather than order effects, dietary/psychological intervention, or weight loss, though the weight loss was as expected greater in the surgical group (Baboumian et al., 2019).

Similarly, in two cross-sectional studies, no difference in BOLD signal during evaluation of wanting or liking of HE vs. LE foods was seen between unoperated group with obesity and those 18 months after RYGB surgery *in pre-meal state* (n = 12) (Frank et al., 2016), nor > 1 year after surgery *in fed state* in a food picture memory task (n = 9) (Frank et al., 2014).

However, one longitudinal study comparing *fed and fasted states* did report decreased BOLD signal to HE vs. LE foods in insula and dlPFC (and other frontal and temporal regions) in the *fasted state* at 1 month after RYGB surgery despite the small sample size (n = 5) (Ochner et al.,

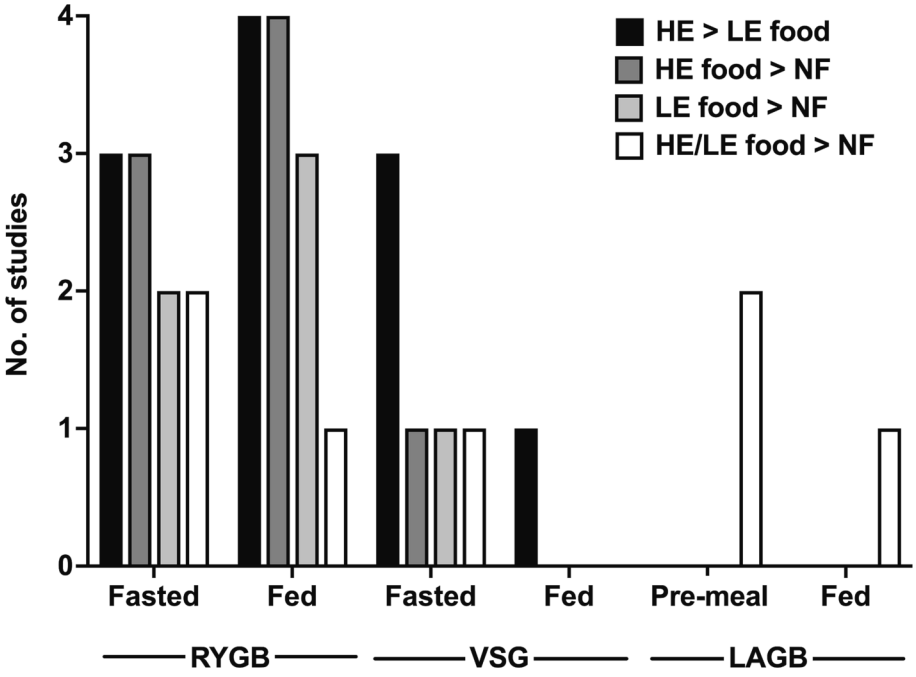
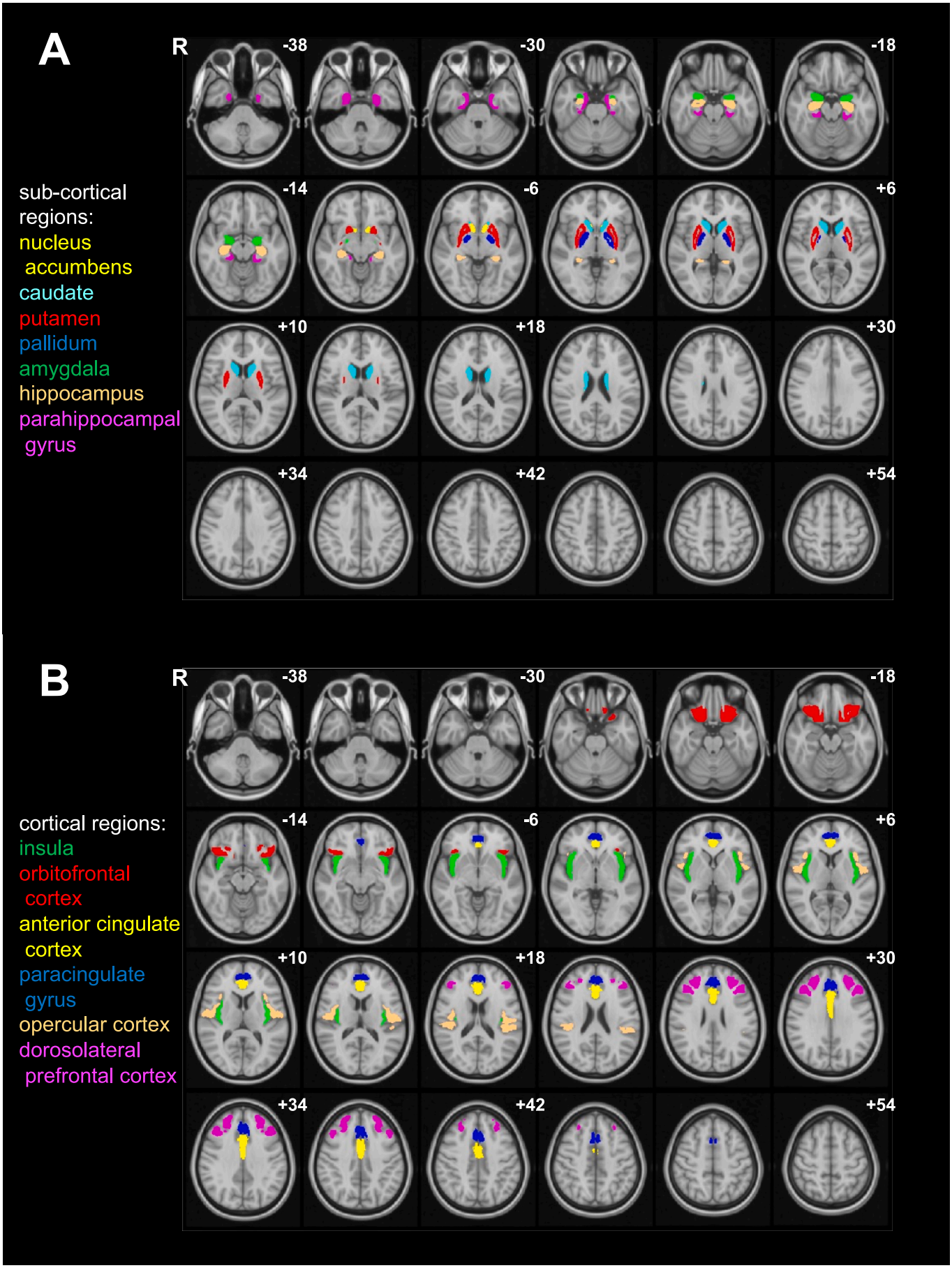


Fig. 3. Number of fMRI studies by surgery type, nutritional state and food cue contrast. Abbreviations: HE: high-energy density, LAGB: laparoscopic adjustable gastric banding, LE: low-energy density, NF: non-food, RYGB: Roux-Y gastric bypass, VSG: vertical sleeve gastrectomy.



(caption on next page)

Fig. 4. Anatomical distribution of highlighted brain regions in systematic review. Axial brain slices with (A) subcortical and (B) cortical anatomical regions of interest taken from Harvard subcortical-cortical and Sallet atlases, thresholded at 50 % probability, overlaid on to MNI 152 standard 1 mm structural T1 brain magnetic resonance image. Colour codes: (A) yellow: nucleus accumbens, light blue: caudate, red: putamen, dark blue: pallidum, green: amygdala, beige: hippocampus, magenta: parahippocampal gyrus; (B) green: insula, red: orbitofrontal cortex, yellow: anterior cingulate cortex, dark blue: paracingulate gyrus, beige: opercular cortex (frontal, central, parietal), magenta: dorosolateral prefrontal cortex (Sallet atlas clusters 5 and 6, Brodmann areas 9/46 V and 9/46D). R indicates right, z coordinates given in Montreal Neurological Institute (MNI) space with slice separation 4 mm. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2012a). This suggests that the effects of RYGB surgery on HE food cue reactivity may be greater in the fasted than fed state. However, another larger longitudinal study in the *fasted state*, found only a decrease in BOLD signal to HE vs. LE foods in the VTA (but not NAcc, thalamus, amygdala, hippocampus, hypothalamus, insula, ACC, OFC, prefrontal cortex) at a later point ~ 6 months after RYGB surgery (n = 22), that was not seen in a control group with obesity not receiving treatment (n = 21–22), this study used anatomical as opposed to fROIs (Faulconbridge et al., 2016).

Low-energy food vs. *non-food contrast:* In three longitudinal studies in the *fed state*, BOLD signal to LE food cues did not change at 1 month after RYGB surgery (n = 10–14) (Ochner et al., 2011; Ochner et al., 2012b), nor at later time 3 months after RYGB surgery (n = 19) (Zoon et al., 2018b).

Taste/odour: In three longitudinal studies, no change in BOLD signal was seen for HE food odour 2 months after RYGB surgery in the *fed* state (n = 19) (Zoon et al., 2018b), nor sweet taste 1 month or 12 months after RYGB surgery in the *fasted* state and during intensity and pleasantness evaluation (n = 6) (Wang et al., 2016), but a decrease in BOLD signal for chocolate taste was seen 1 month after RYGB surgery in the *fasted* state in anterior insula (but not caudate, putamen, amygdala, OFC) using SVC analysis (n = 10) (Ten Kulve et al., 2017).

3.7.2. VSG surgery

High-energy or low-energy food vs. *non-food contrast:* No studies of VSG surgery were found with this food stimulus contrast.

High-energy vs. *low-energy food contrast:* In two longitudinal studies with overlapping datasets in the *fasted state*, BOLD signal to HE vs. LE food cues decreased in the dlPFC at 1 month after VSG surgery (n = 22–28), but did not change in the control group with obesity receiving no treatment (n = 19) (Li et al., 2019a; Hu et al., 2020), while BOLD signal to HE vs. LE food pictures did not change at ~ 6 months after VSG surgery in any aROIs (VTA, NAcc, thalamus, amygdala, hippocampus, hypothalamus, insula, ACC, OFC, prefrontal cortex) (n = 22) (Faulconbridge et al., 2016).

One longitudinal study in the *fed state,* BOLD signal to HE vs. LE food cues decreased in PHG, but increased in the dlPFC, at ~ 3 months after VSG surgery (n = 9) (Baboumian et al., 2019). Furthermore, changes in control groups were in the opposite direction with BOLD signal increasing in the PHG in control groups with obesity receiving either LCD-CBT or no treatment, and decreasing in dlPFC in group receiving no treatment, suggesting that the changes are related to the surgery, rather than order effects, dietary/psychological intervention, or weight loss, though the weight loss was as expected greater in the surgical group (Baboumian et al., 2019).

High-energy food vs. *non-food contrast:* In one longitudinal study in the *fasted state*, BOLD signal to HE food decreased in the dlPFC at 1 month after VSG surgery (n = 22), but did not change in the control group with obesity receiving no treatment (n = 19) (Li et al., 2019a). One longitudinal study examining effects of active cognitive restraint to highly palatable HE/LE food pictures in *fasted state,* BOLD signal decreased in NAcc, caudate, pallidum, amygdala (but not hypothalamus, VTA, ant. insula, dmPFC), and increased in dlPFC, for the regulate vs. enhance contrast at 1 year after VSG surgery using SVC analysis (n = 18) (Holsen et al., 2018).

Low-energy food vs. *non-food contrast:* In one longitudinal study in the *fasted state*, BOLD signal to LE food pictures did not change 1 month after VSG surgery nor in group with obesity not receiving treatment (n = 22–19) (Li et al., 2019a).

3.7.3. LAGB surgery

High-energy or low-energy food vs. *non-food contrast:* In one longitudinal study in the *pre-meal state,* BOLD signal to HE or LE food pictures increased in the MFG at 3.5 months after LAGB surgery, but not in the *fed* state (n = 10) (Bruce et al., 2012). Though in this same study using SVC analysis, in the *pre-meal* state, there were trends for increases and decreases in BOLD signal to HE or LE food pictures in frontal regions, and in the *fed* state, trends for decreases in BOLD signal to HE or LE food pictures in PHG, insula and frontal regions at 3.5 months after LAGB surgery (n = 10) (Bruce et al., 2012).

In a cross-sectional study in the *fasted state*, BOLD signal during evaluation of HE or LE food cues did not differ at average 8 months after LAGB surgery compared to unoperated BMI-matched control using fROI analysis (NAcc, caudate, amygdala, OFC, anterior insula) (n = 20–21) (Scholtz et al., 2014).

High-energy food vs. *non-food contrast:* In a cross-sectional study in the *fasted state*, BOLD signal during evaluation of HE food cues did not differ at average 8 months after LAGB surgery compared to unoperated BMI-matched control using fROI analysis (NAcc, caudate, amygdala, OFC, anterior insula, n = 20–21) (Scholtz et al., 2014).

Low-energy food vs. *non-food contrast:* In a cross-sectional study in the *fasted state*, BOLD signal during evaluation of LE food cues did not differ at average 8 months after LAGB surgery compared to unoperated BMI-matched control using fROI analysis (NAcc, caudate, amygdala, OFC, anterior insula, n = 20–21) (Scholtz et al., 2014).

3.7.4. Comparison of RYGB with LAGB surgery

High-energy or low-energy food vs. *non-food contrast:* In a cross-sectional study comparing patients after RYGB and LAGB surgery in the *fasted* state, BOLD signal during evaluation of HE/LE food pictures was lower in the NAcc, caudate, putamen, subcallosal cortex, OFC in patients on average 8–9 months after RYGB than after LAGB surgery (despite groups being of similar BMI) using whole brain analysis (Scholtz et al., 2014). Furthermore, using fROI analysis BOLD signal during evaluation of HE/LE food pictures was lower in average of all reward system fROIs, and in amygdala and OFC individually (but not NAcc, caudate, anterior insula) in patients after RYGB compared to LAGB surgery (n = 20–21) (Scholtz et al., 2014).

High-energy food vs. *non-food contrast:* In this same cross-sectional study, in the *fasted* state, BOLD signal during valuation of HE food pictures was again lower in the NAcc, caudate, putamen, subcallosal cortex, OFC and also hippocampus, brainstem, paracingulate gyrus in patients on average 8–9 months after RYGB than after LAGB surgery, and using fROI analysis in average of all reward system fROIs, and OFC individually (but not NAcc, caudate, amygdala anterior insula) (n = 20–21) (Scholtz et al., 2014).

Low-energy food vs. *non-food contrast:* In this same cross-sectional study, in the *fasted* state, BOLD signal during valuation of LE food pictures was lower in just the subcallosal cortex and OFC in patients on average 8–9 months after RYGB than after LAGB surgery, but not in any regions using fROI analysis (NAcc, caudate, amygdala, OFC, anterior insula, or average of all fROIs) (n = 20–21) (Scholtz et al., 2014).

3.7.5. Comparison of RYGB with VSG surgery

High-energy or low-energy food vs. *non-food contrast:* In a longitudinal study in *the fed* state, the increase in BOLD signal to HE vs. LE food cues in dlPFC at 3 months after RYGB surgery was greater than after VSG surgery (n = 9–15) (Baboumian et al., 2019). Although another

longitudinal study examined BOLD signal to HE vs. LE food pictures in the *fasted* state in two separate groups after RYGB and VSG surgery, no direct statistical comparison was made between the two surgical groups (Faulconbridge et al., 2016).

3.8. Correlations of fMRI findings with clinical outcomes

Findings for correlations of pre-operative and post-operative fMRI measures with clinical outcomes are summarised in Supplementary Table S4 and described in Supplementary Results section 3.10.

3.9. Correlations of post-operative fMRI findings with behavioural measures

Findings for changes in eating behaviour measures, mood and other cognitive or psychological outcomes are summarised in Supplementary Table S5, described in Supplementary Results section 3.11. Their correlations with post-operative fMRI measures are summarised in Supplementary Table S6 and described in Supplementary Results section 3.12.

3.10. Mechanistic Studies, hormonal Mediators, and correlations with fMRI findings

Results of hormonal and metabolic measures from individual studies are summarised in Supplementary Table S7, findings from interventional and correlational analysis examining relationships between potential mechanistic mediators and fMRI findings are summarised in Supplementary Table S8, and results described below.

3.10.1. Interventional studies

Two interventional studies examined the potential role for appetitive gut hormones in changes in food cue reactivity after obesity surgery.

In a longitudinal study of RYGB surgery in *fasted* and *fed* states, acute intravenous infusion of the GLP-1 antagonist, Exendin(9–39), increased BOLD signal to HE/LE food pictures (with a similar trend for HE food alone) in the caudate (but not in putamen, amygdala, insula, operculum, OFC) using SVC analysis at four weeks after RYGB surgery compared to pre-operatively in the *fasted* state (Ten Kulve et al., 2017). However, these findings were not seen in the *fed* state, despite only the fed state being associated with higher plasma GLP-1 concentrations after RYGB surgery compared to pre-operatively (n = 10) (Ten Kulve et al., 2017). Similarly, in this study in the *fasted* state, Exendin(9–39) had a greater effect to increase BOLD signal during taste of chocolate in the posterior insula (but not in caudate, putamen, amygdala, insula, operculum, OFC) using SVC analysis at 4 weeks after RYGB surgery compared to pre-operatively (n = 10) (Ten Kulve et al., 2017). However, acute intravenous infusion of Exendin(9–39), did not change appetite for savoury and sweet foods after RYGB surgery (Ten Kulve et al., 2017).

In a cross-sectional study in the *fed state,* the acute subcutaneous administration of the somatostatin analogue, Octreotide, abolished the higher post-prandial plasma GLP-1 and PYY concentrations after RYGB compared to LAGB surgery, by lowering both plasma concentrations (Goldstone et al., 2016). This was associated with an increase in HE/LE food appeal and increase in BOLD signal during valuation of HE/LE foods averaged across all reward system fROIs and in the NAcc alone (but not the other fROIs caudate, amygdala, anterior insula) in the group at average of 8 months after RYGB but not LAGB surgery (n = 7–9). Furthermore, a greater suppression of plasma PYY and GLP-1 by Octreotide was associated with a greater increase in BOLD signal during valuation of HE/LE foods averaged across all the fROIs in the combined RYGB/LAGB groups (Goldstone et al., 2016). Likewise, in a separate cohort of patients after RYGB surgery, acute Octreotide administration increased motivation to earn sweets using a progressive ratio task (Goldstone et al., 2016), with motivation previously shown to decrease after RYGB surgery (Miras et al., 2012).

3.10.2. Measurements of hormonal and metabolic measures

Results of hormonal and metabolic measures from individual studies are summarised in Supplementary Table S7.

Twelve studies out of 22 (54.5 %) measured hormonal and metabolic mediators, including plasma/serum GLP-1, PYY, FGF-19, ghrelin, glucose, insulin, insulin resistance, leptin and enocannabinoids.

Post-RYGB: In longitudinal studies, no changes were found in *fasting* plasma GLP-1 at 1 months (Ten Kulve et al., 2017), total ghrelin at 3 months (Zoon et al., 2018b), acyl ghrelin at 6 months (Faulconbridge et al., 2016) concentrations. In agreement, from a cross-sectional study at ~ 8 months post-surgery, *fasting* plasma GLP-1 and acyl ghrelin were similar after RYGB surgery and both after LAGB surgery and BMI-matched unoperated controls, while *fasting* PYY was higher after RYGB surgery than after LAGB surgery though not BMI-matched controls (Scholtz et al., 2014).

In the *fed state*, in longitudinal studies post-prandial plasma GLP-1 increased at 1 month (Ten Kulve et al., 2017) after RYGB surgery. In a longitudinal study, there was no difference in fasting insulin or glucose at 4 weeks after RYGB surgery compared to VLCD, but they did not report changes in fasting gut hormones, only reporting correlations with fMRI findings (Salem et al., 2021).

In cross-sectional studies plasma GLP-1, PYY and bile salts, but not FGF-19, were higher at average 8 months after RYGB than LAGB surgery, while fasting insulin was similar between the surgical groups (Scholtz et al., 2014; Goldstone et al., 2016).

Post-VSG: In longitudinal studies, *fasting* total or acyl ghrelin at 1 month (Li et al., 2019a), 6 months (Faulconbridge et al., 2016) and 12 months (Holsen et al., 2018), glucose at 12 months (Holsen et al., 2018), and leptin and insulin at 1 month (Holsen et al., 2018; Li et al., 2019a) decreased after VSG surgery. In the *fed state*, post-prandial plasma GLP-1 increased at 4 months after VSG surgery to a similar degree as after RYGB surgery (Baboumian et al., 2019).

Post-LAGB: Hormonal changes were not assessed in any longitudinal studies after LAGB surgery. In a cross-sectional study, *fasting* PYY, GLP-1, acyl ghrelin, insulin and total bile acids did not differ at average 8 months after LAGB surgery from BMI-matched controls (Scholtz et al., 2014).

3.10.3. Correlations of post-operative fMRI findings with hormonal and metabolic measures

Results of correlations of fMRI measures with potential hormonal and metabolic mediators from individual studies are summarised in Supplementary **Table S8** and described below.

RYGB/VSG: In four longitudinal studies of correlation with plasma ghrelin: (i) in the *fed state,* the change in BOLD signal to HE food or HE vs. LE food pictures in the precuneus, and to LE food picture in SFG (region showing uncorrected significant change after surgery) at 2 months after RYGB surgery did not correlate with the change in pre-meal plasma total ghrelin (or endocannabinoids including anandamide or others) after RYGB surgery, though on average ghrelin did not change after surgery (n = 19) (Zoon et al., 2018b); (ii) in the *fasted* state, a greater decrease in BOLD signal to HE vs. LE food in the VTA (the only aROI showing a significant change after RYGB surgery) at 6 months after both RYGB and VSG surgery was associated with a greater decrease in fasted total ghrelin after surgery, although the ghrelin only decreased in the VSG group, and BOLD signal in VTA only decreasing in the RYGB group (Faulconbridge et al., 2016); (iii) in the *fasted* state, a greater decrease in BOLD signal to HE vs. LE food pictures in the dLPFC at 12 month after VSG surgery (only region that significantly changed after surgery) was associated with a greater decrease in fasted total ghrelin after surgery (but there was no correlation with the decrease in fasted serum insulin or leptin) (Li et al., 2019a); (iv) in the *fasted* state, changes in BOLD signal to HE/LE food pictures in any fROI (hippocampus, caudate, insula, amygdala, NAcc) at 4 weeks after RYGB surgery (or VLCD) did not correlate with changes in fasting plasma total ghrelin, though overall changes in ghrelin were not reported (n = 16–19) (Salem et al., 2021).

In two longitudinal studies of correlation with satiety gut hormones: (i) in the *fed* state, a greater increase in BOLD signal to HE vs. LE food cues in the parcingulate gyrus and frontal lobe at 3 months after RYGB surgery (n = 16) (but not VSG surgery, n = 9) tended to be associated with a greater increase in post-prandial plasma total GLP-1 after surgery, despite similar increases in post-prandial GLP-1 after the two surgeries (Baboumian et al., 2019); (ii) in the *fasted* state, changes in BOLD signal to HE/LE food pictures in any fROI (hippocampus, caudate, insula, amygdala, NAcc) at 4 weeks after RYGB surgery (or VLCD) did not correlate with changes in fasting plasma active GLP-1, total PYY or GIP, but post-prandial changes in gut hormones were not reported (n = 16–19) (Salem et al., 2021).

In a cross-sectional study in the *fasted state,* there were no significant correlations between BOLD signal during evaluation of HE/LE, HE or LE foods in OFC or amygdala using fROI analysis and fasted or post-prandial plasma GLP-1, PYY, and bile acids at ~ 8 months after RYGB surgery (n = 21) (Scholtz et al., 2014).

3.10.4. *Correlations of post-operative fMRI findings with aversive measures*

Findings for changes in aversive measures such as nausea and dumping syndrome are given in Supplementary Table S5, and correlations with post-operative fMRI given in Supplementary Table S6 and described below.

In a cross-sectional study in the *fasted* state, no correlations were seen between BOLD signal during valuation of HE foods averaged across all fROIs (NAcc, caudate, amygdala, anterior insula, OFC) or in OFC or amygdala alone at ~ 8 months after RYGB surgery with retrospective dumping syndrome scores in the three months following surgery (n = 21) (Scholtz et al., 2014). There were also no differences in fasting or post-prandial nausea ratings between the RYGB and LAGB surgery despite differences in food cue reactivity and appeal between the groups (Scholtz et al., 2014).

Two longitudinal studies reported either increases (Ten Kulve et al., 2017) or no change (Salem et al., 2021) in nausea ratings after RYGB surgery, but no correlations with fMRI finding were made.

4. Discussion

This systematic review aimed to review the literature for fMRI studies that investigated food cue reactivity, and taste and odour responses, assessed by BOLD signal, in patients with obesity undergoing bariatric surgery, as well as correlations of BOLD signal with clinical, behavioural, or hormonal outcomes after obesity surgery, or cross-sectional comparisons between operated and unoperated patients with obesity. Secondary objectives aimed to review and discuss the heterogeneity in study methodology, and how different clinical, behavioural, and hormonal factors might be associated with the changes/differences in brain responses to food stimuli.

Results from the 22 studies were highly variable with limited evidence for reproducibility, but this heterogeneity in the findings is unsurprising given the great variation seen in the following factors between studies: type of obesity surgery, study design, participant characteristics (e.g. sex, T2DM), sample sizes (often small), fMRI food cue paradigm, nutritional status, statistical analysis (whole brain, SVC, fROI, aROI analyses) and thresholds (and sometimes inclusion of uncorrected results), tools used to assess eating behaviour (appetite ratings, liking/wanting/hedonic ratings, eating behaviour questionnaires, test meals), and limited studies measuring hormonal mediators. Furthermore, confounding factors were infrequently reported that may contribute to variability in results e.g. menstrual cycle (Frank et al., 2010), motion in scanner, mood assessment (Killgore & Yurgelun-Todd, 2006).

Unfortunately, the low number of studies when classifying by study design (longitudinal, cross-sectional), surgery type (RYGB, VSG, LAGB), nutritional state (fasted, fed, pre-meal) and food picture contrast (HE > LE food, HE food > non-food, LE food > non-food, HE/LE food > non-food), did not allow performance of an activation likelihood estimation (ALE) meta-analysis, especially as not all of the studies included whole brain analysis, some had no significant results from whole brain analysis, and some datasets were overlapping Fig. 3. Therefore, drawing conclusions about the effects of obesity surgery on brain responses to food stimuli must rely on cautious comparison of results from a limited number of individual studies in an attempt to find any overlap in results or conclusions.

4.1. *Food cue, taste and odour reactivity using fMRI after obesity surgery*

When looking at effects of RYGB and VSG surgery, research has consistently found decreases in appetite (Miras & le Roux, 2013; Manning et al., 2015), food liking/wanting (Hansen et al., 2016) and food intake (Al-Najim et al., 2018; Janmohammadi et al., 2019), and healthier eating behaviours (Hankir et al., 2020), after surgery that will contribute to the marked weight loss. This will also enable sustained weight loss when compared to dietary interventions (Halliday et al., 2019; Pucci & Batterham, 2019). Consistent with this literature, such changes in eating behaviour were also seen in many studies that also included fMRI with reduced food cue reactivity in brain regions associated with reward processing and evaluation. These reductions implicate reduced post-operative food cue reactivity and reward processing and suggest that this may be preferentially seen for HE compared to LE foods. However, it may be difficult to prove this change in food preference from fMRI studies (i.e reductions in food cue reactivity to HE food vs. non-food but *not* LE food vs. non-food, or reductions for HE vs. LE food), since these contrasts were not consistently tested, and studies are generally under-powered for comparisons between food categories.

However, preferential reductions in liking, wanting, appeal, preference and motivation for HE food (high fat, sweet) than LE food (low fat, savoury) has been seen using other behavioural measures such as rating scales, choice paradigms or progressive ratio task both longitudinally after RYGB surgery and cross-sectionally in those with optimal vs. sub-optimal post-RYGB weight loss or compared to those after gastric banding surgery (Ochner et al., 2011; Miras et al., 2012; Ochner et al., 2012b; Scholtz et al., 2014; Faulconbridge et al., 2016; Zoon et al., 2018b; Nymo et al., 2022).

By contrast, preferential reductions in actual consumption of HE over LE foods in *ad libitum* test meals have not been seen longitudinally after RYGB surgery (different from that expected from self-reports) with more general reductions seen across all food categories, indicating that methodological issues may be important when assessing changes in food preference after obesity surgery (Nielsen et al., 2017; Kapoor et al., 2021; Redpath et al., 2021; Livingstone et al., 2022).

For example, subcortical (caudate, nucleus accumbens, putamen, pallidum), limbic regions (amygdala, hippocampus, PHG), insula (Brodmann area (BA) 13), orbitofrontal cortex (BA11) and anterior cingulate cortex (ACC) [BA24 (dorsal ACC), BA25 (subgenual ACC), BA32 (pregenual ACC), BA33 (rostral ACC)] are brain regions involved in reward processing, including motivation, salience, emotional responses, decision making, and conditioned learning. After RYGB or VSG surgery, it would be expected to see reduced food cue reactivity in these brain regions to HE or HE/LE food pictures. Overall, the fMRI findings after RYGB/VSG surgery agreed with this hypothesis. Food cue reactivity either decreased (Ochner et al., 2011; Ochner et al., 2012a; Ochner et al., 2012b; Faulconbridge et al., 2016; Ten Kulve et al., 2017; Baboumian et al., 2019; Salem et al., 2021), or did not change (Zoon et al., 2018a; Zoon et al., 2018b; Li et al., 2019a; Hu et al., 2020). Even no change in food cue reactivity may be interpreted as a relative decrease, since non-surgical or non-pharmacological dietary and psychological interventions for weight loss might be expected to increase food cue reactivity (Hermann et al., 2019; Neseliler et al., 2019; Simon et al., 2018; McDermott K.D. et al. 2019). Higher BOLD signal in ventral striatum to a food incentive delay task was reported after successful and unsuccessful weight loss at six months after dietary intervention (Simon

et al., 2018). Furthermore, higher BOLD signal in caudate, pallidum and ventral striatum was associated with less weight loss at six months after a one-month dietary intervention (Hermann et al., 2019), indicating a counteracting effect of brain response to food after lifestyle intervention. Indeed, greater post-RYGB and post-VSG decreases in food cue reactivity (brain reward systems, fusiform and parahippocampal gyrus) were seen in overweight/obesity compared to after no intervention or non-surgical/non-pharmacological interventions such as after LCD or VLCD, including when weight loss matched, indicating lack of order effects, or similar effects from weight loss or dietary/psychological changes (Baboumian et al., 2019; Salem et al., 2021).

Only one cross-sectional study demonstrated that those after RYGB surgery had higher HE/LE food cue reactivity in the insula, hippocampus and cingulate cortex compared to a control unoperated group with obesity (Frank et al., 2016). This discrepancy could be explained by the different fMRI paradigm used in this study where participants were asked simultaneously to rate wanting and liking of highly palatable food pictures, compared to passive picture viewing in most studies. However, an active evaluation task did not preclude lower food cue reactivity being seen cross-sectionally after RYGB surgery (Scholtz et al., 2014).

Food preference was further examined by gustatory stimuli in two longitudinal studies. There was a decrease in BOLD signal to chocolate tastant in the insula, the primary gustatory cortex, in one study after RYGB surgery (Ten Kulve et al., 2017). Interestingly, in a longitudinal study with a predictive design, the baseline BOLD signal to high fat and high sugar tastants in VTA (but not insula or rolandic operculum) negatively correlated with percent weight loss at six months after RYGB but not VSG surgery (Smith et al., 2020). While evidence on taste detection thresholds after RYGB surgery is variable, a recent systematic review on taste change after RYGB and VSG surgeries by our group concluded that a short-term increase in sweet taste detection accompanied by a decrease in preference for sweet food might serve as an underlying mechanism for food preference alteration in a sub-group of patients (Al-Alsheikh et al., 2022).

These changes in food cue reactivity after obesity surgery should also be viewed in the context of their abnormalities in obesity itself. There is a large and variable literature as to whether there is enhanced HE food or HE/LE food cue reactivity, or even attenuated LE food cue reactivity, in those with vs. without obesity (Carnell et al., 2012; Ziauddeen et al., 2012; Morys et al., 2020; Yang et al., 2021). This will again depend on differences in samples sizes, study and fMRI design, nature of food cues and nutritional state. However, recent meta-analyses of food cue reactivity found no differences in any food (mixture of HE and LE food stimuli) nor HE food cue reactivity in obesity vs. normal weight, though interpretation of such meta-analyses may be limited by the highly variable nature of fMRI paradigms and statistical analyses used (Morys et al., 2020; Yang et al., 2021). Unfortunately, none of the studies in the current systematic review included comparison of groups with obesity before bariatric surgery with groups without obesity. As a result, it cannot be easily concluded that post-operative changes in food cue reactivity represent a 'normalisation' of alterations in pre-operative HE or HE/LE food cue reactivity in obesity using identical fMRI paradigms.

4.2. Relationship with other eating behaviour measures

Indeed, evidence from fMRI studies that examined associations with appetitive (liking) and consummatory (wanting) measures support the suggested change in food preference after obesity surgery. A decrease in HE food craving and wanting was reported after RYGB (Ochner et al., 2011; Ochner et al., 2012b; Scholtz et al., 2014; Faulconbridge et al., 2016; Frank et al., 2016; Zoon et al., 2018b) and VSG (Faulconbridge et al., 2016; Holsen et al., 2018; Li et al., 2019a) surgeries. However, fMRI correlations were rarely examined between decrease in BOLD signal to HE foods and decreases in food hedonics (Ochner et al., 2012b; Zoon et al., 2018b), but these were in the direction expected, and correlations with appetite ratings were not performed in RYGB/VSG surgery. Only two significant correlations were reported: (i) decrease in BOLD signal in dlPFC to HE food positively correlated with decrease in HE food liking (Li et al., 2019a), (ii) BOLD signal during evaluation of HE foods in average of all fROIs (caudate, NAcc, amygdala, OFC, anterior insula) positively correlated with ice-cream taste pleasantness in a cross-sectional study both after RYGB and LAGB surgery, with both HE food cue reactivity and pleasantness being lower after RYGB than LAGB surgery (Scholtz et al., 2014).

Furthermore, associations with other eating behaviour measures, such as direct food intake was only measured in one cross-sectional study showing that participants after RYGB surgery consumed less percentage of total energy intake from fat compared to those who had LAGB using 3-day food diary (Scholtz et al., 2014). However, the literature on dietary measures, specifically food intake after obesity surgery consistently indicates lower total energy intake, but have not consistently reported differential food preference away from HE towards LE (low fat and low sugar) foods (Mathes & Spector, 2012; Nielsen et al., 2017). While most studies focused on HE food consumption, liking and wanting, little is known about preferentially reduced HE food responses or intake (Ochner et al., 2011). The available evidence indicates that change in food preference might serve as an additional function of RYGB surgery and implicates better weight loss outcomes (Nielsen et al., 2017; Sondergaard Nielsen et al., 2018). Four out of six longitudinal studies after RYGB and VSG surgeries reported a decrease in BOLD signal to HE vs. LE in NAcc, insula, VTA, PHG and frontal pole (dlPFC) (Ochner et al., 2011; Ochner et al., 2012a; Faulconbridge et al., 2016; Baboumian et al., 2019; Li et al., 2019a; Hu et al., 2020), suggesting a selective reduction in food preference to HE food mediated by reduced food cue reactivity in brain regions mostly associated with reward processing.

Reduction in food cue reactivity and actual food intake are also consistent with decreases in hunger and desire to eat, and increases in fullness ratings only after RYGB surgery when measured by VAS (Ochner et al., 2011; Ochner et al., 2012a; Ten Kulve et al., 2017; Zoon et al., 2018a; Smith et al., 2020). Taken together, reduced food intake might be a result of reduced hunger, increased fullness, together with reductions in food cue reactivity, that will reduce motivation towards hedonic reward value of food, especially HE foods.

Psychological traits are important contributors to shaping eating behaviour. The most frequently used eating behaviour questionnaires were TFEQ and DEBQ across studies, to measure dietary restraint (tendency to restrain from food intake to prevent weight gain or lose weight), disinhibition (tendency to eat in response to food cues), hunger (eating in response to subjective feeling of hunger and food cravings), external eating (tendency to eat in response to external food cues), and emotional eating.

Changes or differences in dietary restraint were variable across fMRI studies: restraint was either lower after RYGB surgery than LAGB surgery (Scholtz et al., 2014) or did not differ compared to unoperated controls (Frank et al., 2014; Frank et al., 2016), or longitudinally increased after RYGB (Salem et al., 2021), VSG (Holsen et al., 2018), and LAGB surgeries (Bruce et al., 2012). This may contribute to variability in fMRI findings since dietary restraint may influence food cue reactivity, although the correlational literature is quite variable which may depend on nutritional state, fMRI paradigm, analysis methodology and other patient characteristics. For example: dietary restraint showed either (i) a *positive correlation* with BOLD signal in NAcc (Born et al., 2011), insula (Demos et al., 2011) and dlPFC (Hollmann et al., 2012) in *fasted state*, and in putamen, caudate (Demos et al., 2011), OFC, dlPFC (Demos et al., 2011) in *fed state*; or (ii) a *negative correlation* with BOLD signal in dlPFC (Coletta et al., 2009) NAcc, caudate, putamen in *fasted state* (Demos et al., 2011), and in amygdala in *fed state* (Demos et al., 2011), or no effect with BOLD signal in *fasted state* (Cornier et al., 2010; Burger & Stice, 2011).

Finally, disinhibited eating was lower after RYGB surgery than unoperated controls with obesity (Frank et al., 2016) or did not change after RYGB surgery (Frank et al., 2014). Disinhibited eating also

decreased after LAGB surgery (Bruce et al., 2012). However, correlations of changes in disinhibited eating with changes in food cue reactivity were either not examined (Frank et al., 2014) or not significant (Bruce et al., 2012). Disinhibited eating has been associated with enhanced food cue reactivity (Lee et al., 2013; Aviram-Friedman et al., 2018; Drummen et al., 2019), enhanced insula and NAcc responses to palatable food taste (Kroemer et al., 2016; Nakamura & Koike, 2021), and altered functional connectivity between inhibitory control and reward brain regions (Dietrich et al., 2016; Zhao et al., 2017).

To further examine importance of dietary restraint after obesity surgery, examination of the fMRI findings within the frontal pole may shed some light on changes in cognitive control after surgery, since this involves brain regions involved in top-down inhibitory control. However, changes in BOLD signal to HE food pictures in the frontal lobe defined by BA 6 (supplementary area), 8 (pre-supplementary area), 9 (dlPFC), 10 (frontoparietal cortex), 11 (OFC), 44 (opercular IFG), 45 (IFG), 46 (medial PFC), 47 (vlPFC) were variable and often changed in opposite directions across studies. Food cue reactivity in the frontal pole is often difficult to compare across studies, as this is one of the largest lobes in the brain and there is variation in the definition of different frontal regions, where PFC, dlPFC, MFG and SFG were used interchangeably. The dlPFC is crucial in cognitive control and decision making and top-down inhibitory control (Hare et al., 2009). In addition, the OFC is essential in subjective reward evaluation including food (Small et al., 2007; Goldstone et al., 2009; Rudebeck & Murray, 2014).

This is an example of the overlapping changes in responses between these regions as a result of their functioning in synergy to co-ordinate subjective reward-value, decision making, and finally behavioural approach. Furthermore, a decrease in BOLD signal in the prefrontal cortex might reflect less of a need for cognitive-inhibitory circuit recruitment to food cues as they may hold a lower reward value or salience after surgery, while an increase in BOLD signal in the same region might also indicate better cognitive control in response to food cues. As a result, caution should be practiced when interpreting these responses and allocating specific behaviours to specific brain areas.

The most consistent finding was a decrease in BOLD signal to HE vs. LE food pictures in dlPFC after VSG surgery suggesting an enhanced inhibitory effect (Li et al., 2019a; Hu et al., 2020). BOLD signal in other frontal regions (IFG, MFG, SFG) decreased (Ochner et al., 2011; Ochner et al., 2012a; Ochner et al., 2012b; Frank et al., 2016) or increased (Goldman et al., 2013; Frank et al., 2016; Zoon et al., 2018a) after RYGB surgery. Contradictory comparisons with non-surgical interventions were reported for changes of dlPFC responses to HE vs. LE foods with greater increase after RYGB and VSG surgery than LCD (Baboumian et al., 2019), but a decrease seen after VSG but not LCD in another study, though with no significant difference between the two interventions (Li et al., 2019a).

Favourable weight loss outcomes has also been associated with enhancement of cognitive control in frontal regions in lifestyle and dietary intervention studies. Increased BOLD signal in the dlPFC to HE/LE food cues was associated with better weight loss at 1 and 3 months, and less weight regain at 2 years, after a low-calorie diet intervention (Neseliler et al., 2019). Similarly, in the Look AHEAD study, those participants with overweight/obesity and T2DM receiving intensive lifestyle intervention with greater HE food cue reactivity in MFG, experienced greater weight loss (McDermott K.D. et al. 2019).

Therefore, an important factor that may contribute to the variability in response of food cue reactivity to bariatric surgery is inter-individual differences, not only in the eating behaviours discussed above (external and disinhibited eating, or dietary restraint), but also the overlapping presence or symptoms of 'food addiction', emotional eating and binge eating disorder, which may not only influence clinical outcomes after bariatric surgery (Ivezaj et al., 2017; Athanasiadis et al., 2021; Kops et al., 2021; Cohen & Petry, 2023), but also food cue reactivity and hedonics both at baseline and follow-up (Bohon et al., 2009; Chechlacz et al., 2009; Gearhardt et al., 2011; Finlayson, 2017; Schulte et al., 2019; Constant et al., 2020; Som et al., 2022; Vrieze & Leenaerts, 2023). This will be contributed to by variability in the effects of different surgeries on eating behaviours and the degree/nature of their pre-, peri- and post-operative psychological and dietary management which will vary between centres.

4.3. Comparison of different obesity surgery procedures

Across LAGB studies, food cue reactivity to HE food pictures was only decreased in clusters within the frontal pole BA9/10 in two longitudinal studies (Bruce et al., 2012; Bruce et al., 2014), and in paracingulate gyrus and precuneus in participants after LAGB surgery and LCD group in one study (Bruce et al., 2014). In both these studies, reduction in BOLD signal was more pronounced in the pre-meal state but not fed state (Bruce et al., 2012; Bruce et al., 2014). The comparable effect on food cue reactivity in participants after LAGB surgery and LCD group in the latter study suggests a similar response to this surgery and dietary interventions. Furthermore, when participants after LAGB surgery were compared with BMI-matched participants in a cross-sectional study, there was no difference in food cue reactivity, fullness ratings, HE and LE food wanting, and eating behaviour questionnaires (Scholtz et al., 2014). Evidence from a systematic review of dietary intake after LAGB surgery support these findings (Dodsworth et al., 2011). In a longitudinal study, increased energy intake from high fat and high sugar foods was reported after LAGB surgery compared to RYGB surgery at 1 year (Olbers et al., 2006). Furthermore, this does seem to be different from the fMRI studies of RYGB/VSG since no reductions in food cue reactivity were seen in brain reward processing regions (including striatum, amygdala, OFC) in any longitudinal fMRI studies of LAGB surgery.

Only two studies directly compared food cue reactivity longitudinally in RYGB vs. VSG surgeries (Baboumian et al., 2019) or cross-sectionally after RYGB vs. LAGB surgery (Scholtz et al., 2014). They found enhanced BOLD signal to HE vs. LE food picture in dlPFC after RYGB compared to VSG surgery (Baboumian et al., 2019), and reduced BOLD signal to HE food picture in regions implicated in reward processing regions (NAcc, caudate, putamen) after RYGB compared to LAGB surgery (Scholtz et al., 2014). The available literature mostly investigated RYGB surgery accounting for 73.9 % of included studies compared to 26.1 % and 21.7 % for VSG and LAGB surgeries respectively. Behavioural non-fMRI studies have shown comparable effects of RYGB and VSG surgeries on eating behaviour (specifically food intake and food preference) (Moizé et al., 2013; Janmohammadi et al., 2019), and their superior effect to LAGB surgery in terms of sustained weight loss (Akalestou et al., 2022) and changes in hunger, fullness, and food preferences (Al-Najim et al., 2018). Possibly as a consequence of these differential effects on food cue reactivity and eating behaviour, a systematic review that examined the effect of obesity surgeries (RYGB, VSG and LAGB) on energy intake suggests a reduced energy intake after one year of these surgeries, with a superior effect of RYGB and VSG surgery on weight loss and energy intake (Zarshenas et al., 2020). This leaves a gap in the literature as to whether the change in food preferences and HE vs. LE food cue reactivity is a unique feature of RYGB and possibly VSG but not LAGB surgeries.

No published studies were found examining changes or comparisons in food cue reactivity using fMRI after the other surgical procedures of one-anastomosis/mini gastric bypass surgery (OAGB), which may produce greater malabsorption due to a long biliopancreatic limb, or after the malabsorptive biliopancreatic diversion procedure (Lee et al., 2019).

4.4. Quality of studies

On formal but non-nutritional specific criteria all studies showed a very low risk of bias. However, when looking at best practice in nutritional neuroimaging research (Smeets et al., 2019), the important practices that are likely to aid reproducibility, replication and optimisation of interpretation of fMRI findings were not fulfilled in many of the

studies included: (i) collecting and correlating other behavioural measures to support fMRI findings interpretation (e.g. food ratings, appetite, food intake), (ii) reporting food stimulus details, (iii) standardising nutritional state before scanning (this includes reporting time since last meal if scanning takes place in fasted state, standardising and reporting meal information if takes place in fed state), (iv) lack of control groups for order effects, dietary/psychological interventions and weight loss, (v) statistical issues (lack of power calculation and use of uncorrected statistics), and (vi) assessment of potential confounds (e.g. mood and menstrual cycle).

Only six longitudinal studies of RYGB and VSG surgery included a control group with overweight/obesity, whom either received no treatment to control for order effects (Faulconbridge et al., 2016; Li et al., 2019a; Hu et al., 2020) or dietary/lifestyle intervention and weight loss itself (Bruce et al., 2014; Baboumian et al., 2019; Salem et al., 2021). However, the degree of weight loss was not generally comparable between surgical and non-surgical groups, other than in one study of LAGB (Bruce et al., 2014), and one study comparing RYGB with VLCD which performed a sub-group analysis for matched weight loss (Salem et al., 2021). As a result, this lack of adequate control intervention groups is a major limitation when interpreting most fMRI studies of obesity surgery.

Since females represent most of the study participants, it is crucial to account for phase of menstrual cycle effect at time of scanning, which was only done in a few studies (Ochner et al., 2012b; Goldman et al., 2013; Scholtz et al., 2014; Goldstone et al., 2016). Early and late follicular phase have differential effect on fMRI food cue reactivity in brain regions implicated in salience and reward processing (Dreher et al., 2007; Alonso-Alonso et al., 2011).

4.5. Heterogeneity between studies

Fig. 5 summarises the factors contributing to heterogeneity in results between studies.

4.5.1. Participant characteristics

Within participants characteristics across the 22 studies, female sex would be an important confounding factor that may contribute to variability in food cue reactivity after obesity surgery. Although the majority of studies included higher number of females compared to males, there is no evidence of differences in weight loss after obesity surgery between males and females (Mousapour et al., 2021). In a systematic review of 15 studies that examined the effect of sex on BOLD signal to food pictures, females showed higher BOLD signal to food cues in in striatal, limbic and frontal regions compared to males (Chao et al., 2017).

Ethnicity did vary between studies; there is evidence of ethnic differences in obesity surgery outcomes with less weight loss in those of non-Hispanic white heritage from a recent systematic review (Zhao et al., 2021), but there have not been any studies of influence of ethnicity on food picture cue reactivity, though ethnicity differences (Hispanic and African-Americans) have been in seen in brain responses to sweet taste (Szajer et al., 2017; Gilbert et al., 2018).

T2DM status (and presumably degree of insulin resistance) was also variable across studies and may influence food cue reactivity findings. In participants with obesity and prediabetes compared to participants with obesity and without prediabetes, *lower* BOLD signal to HE food in putamen and insula has been seen, suggesting a potential role for insulin resistance in food cue reactivity (Farr & Mantzoros, 2017). By contrast, in another cross-sectional study, participants with obesity but not normal weight showed positive correlations of insulin resistance with BOLD signal to favorite-food cues in thalamus, insula, putamen and hippocampus (Jastreboff et al., 2013).

4.5.2. Time since surgery

The variation in time since surgery in longitudinal studies might explain some of the variability in food cue reactivity responses. Early fMRI scans at two weeks and one month after surgery, represent a catabolic phase (or negative energy balance) where body weight is rapidly declining, and importantly post-surgery diet restrictions such as a liquid diet are still in place.

Although direct comparison between studies is difficult given the variable designs, changes in food cue reactivity in reward processing regions were especially seen in early timepoint longitudinal studies of RYGB surgery, with decreased BOLD signal to HE food pictures at 1 month in caudate (Ten Kulve et al., 2017), putamen (Ochner et al., 2012b), and at 6 months in VTA (Faulconbridge et al., 2016). This might support the hypothesis that it is only shortly after RYGB surgery that there is a preferential reduction in HE food cue reactivity, that habituates over time. This might be a factor contributing to weight regain after obesity surgery, but this has yet to be investigated using food cue reactivity with fMRI. Although differences in food cue reactivity have been compared between successful vs. unsuccessful weight loss after RYGB surgery, the latter group did not distinguish between weight regain and poor initial weight loss response (Goldman et al., 2013).

These temporal factors might also apply to changes in food cue reactivity in inhibitory control regions that might change over time. For example, an initial early decrease in BOLD signal to HE vs. LE food in the dlPFC was seen at 1 month after RYGB (Ochner et al., 2011; Ochner et al., 2012a) and VSG (Li et al., 2019a; Hu et al., 2020) surgeries, while there is a later increase in BOLD signal to HE vs. LE food in dlPFC at 4 months after RYGB surgery (Baboumian et al., 2019) and 1 year after VSG surgery (Holsen et al., 2018). This might be interpreted as indicating that initially after surgery patients do not need to engage their inhibitory circuits as much as before surgery (due to early reductions in HE food cue reactivity, and/or perhaps also food aversion or post-surgery discomfort), but over time increased engagement of these inhibitory circuits is needed to sustain weight loss.

4.5.3. Nutritional state

Based on previous literature, fed and fasted states differentially modulate appetitive hormones and neural responses to food cues, with suppressed food cue reactivity when fed, including amygdala, OFC, caudate, putamen, NAcc in normal weight and/or obesity (LaBar et al., 2001; Fuhrer et al., 2008; Goldstone et al., 2009; Siep et al., 2009; Goldstone et al., 2014; Legget et al., 2018).

Since post-prandial satiety hormone responses such as PYY and GLP-1 are exaggerated after RYGB surgery, but fasting hormone concentrations may be unchanged or only slightly increased (Scholtz et al., 2014; Yousseif et al., 2014; Zakeri & Batterham, 2018; Akalestou et al., 2022), food cue reactivity changes would be expected to be more marked in the fed than fasted state. However, contrary to this hypothesis, changes in HE vs. LE food, HE food, and HE/LE food cue reactivity were more apparent in the fasted state in longitudinal RYGB surgery studies that examined both fasted and fed nutritional states (Ochner et al., 2012a; Ten Kulve et al., 2017). A similar effect was seen in two fMRI cross-sectional studies by the same group using a similar paradigm where HE/LE food cue reactivity in pre-meal state was higher in pallidum, hippocampus, rolandic operculum, ACC, and lower in pallidum, precuneus, cingulate and other regions in frontal, parietal and occipital lobes after RYGB surgery than unoperated controls with obesity (Frank et al., 2016), whilst no differences in food cue reactivity were seen in the fed state (Frank et al., 2014).

This may be explained by a floor effect, whereby food cue reactivity is already suppressed to some degree in the pre-operative fed state, not only through increases in anorexigenic plasma PYY and GLP-1, but also increases in plasma glucose (Page et al., 2011), insulin (Tiedemann et al., 2017) and decreases in the orexigenic hormone acyl ghrelin (Malik et al., 2008; Goldstone et al., 2014; Schulz et al., 2023), depending on the size and satiating effects of the meal. After RYGB or VSG obesity surgery, food cue reactivity might not be reduced any further when fed, compared to before surgery, even when post-prandial

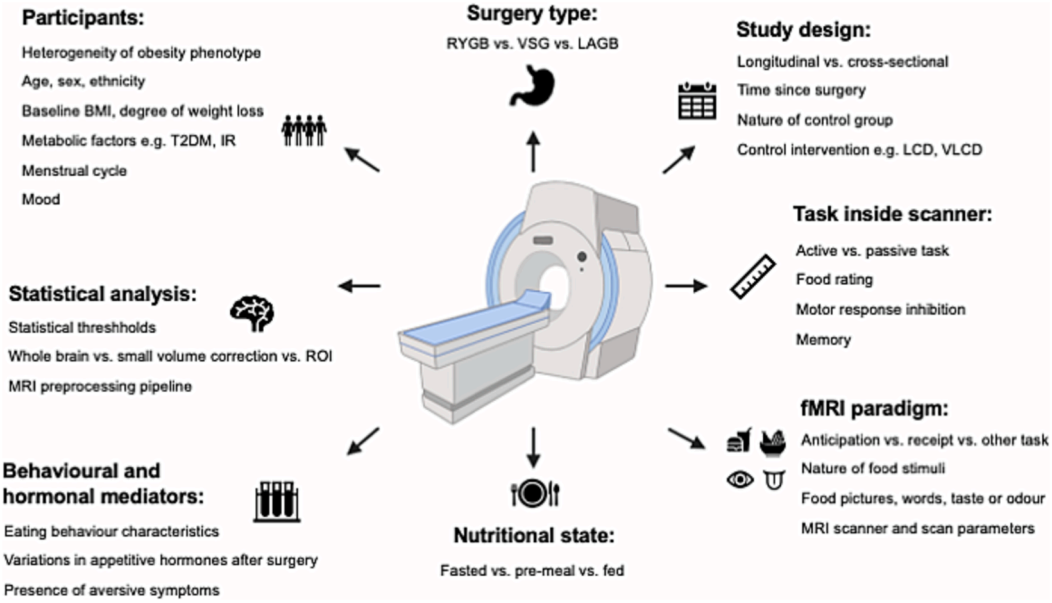


Fig. 5. Schematic representation of factors contributing to variability in fMRI studies of eating behaviour after obesity surgery. Abbreviations: BMI: body mass index, fMRI: functional magnetic resonance imaging, IR: insulin resistance; LAGB: laparoscopic adjustable gastric banding, LCD: low-calorie diet, MRI: magnetic resonance imaging, ROI: region of interest, RYGB: Roux-en-Y gastric bypass, T2DM: type 2 diabetes mellitus, VLCD: very low-calorie diet, VSG: vertical sleeve gastrectomy. Figure images taken from https://biorender.com.

plasma PYY and GLP-1 responses are exaggerated. Furthermore, there may be a long-lasting acting anorexigenic effect of increased post-prandial plasma PYY and GLP-1 concentrations even after levels return to baseline after fasting. Reductions in fasting plasma acyl ghrelin after RYGB surgery could also be important here, though the literature on the effects of RYGB on the ghrelin system are highly variable (Pournaras & le Roux, 2010).

4.5.4. *fMRI protocol*

Only 50 % of the studies reported details of the food stimuli (macronutrient and energy content) and how different food/control picture categories were matched and chosen. This is an important factor in food-related fMRI protocols as subjective evaluation of each picture relies heavily on presentation and is subject to inter-individual food preference variation, though this is likely less of an issue with longitudinal compared to cross-sectional studies. Contrasts that have been included in the fMRI analysis models include HE vs. LE food, HE food vs. non-food, LE food vs. non-food, or HE/LE vs. non-food pictures. An important outstanding question, that seems to depend on the particular outcome measure used, is whether changes in food cue reactivity after obesity surgery are a preferential reduction for HE food or similar across HE and LE food categories, or indeed might even reflect an increase in LE food cue reactivity. Lack of detail of the exact nature of the food stimuli used in the fMRI studies complicates interpretation of these findings.

Furthermore, few longitudinal studies examined cue reactivity changes to LE food, usually finding no changes after RYGB surgery (Ochner et al., 2011; Ochner et al., 2012b; Zoon et al., 2018b) or VSG surgery (Li et al., 2019a).

Most of the fMRI studies used paradigms involving food pictures or occasionally other cues such as spoken or visual food words, and many (40.9 %) involved passive viewing/listening of the food cues. Comparison of these findings with other studies that used active fMRI tasks, including simultaneous evaluation of the food picture appeal (Scholtz et al., 2014; Goldstone et al., 2016), liking/wanting ratings (Frank et al., 2016), craving or resisting of desire for the food (Goldman et al., 2013; Holsen et al., 2018), or performed a 1-back memory task (Frank et al., 2014) will be problematic because of the different cognitive process and regional brain engagement that this will involve.

This is also seen when comparing longitudinal effects of obesity surgery on responses to anticipatory food cues and gustatory fMRI studies (Wang et al., 2016; Ten Kulve et al., 2017). Previous research has suggested that patients with obesity may display opposite differences in brain responses to food anticipation than actual receipt of food. Using a highly palatable chocolate milkshake, heightened responsivity to anticipatory cues of imminent taste delivery were seen in insula and operculum, and reduced responsivity to the actual taste delivery were seen in the caudate in adolescents with higher BMI (Stice et al., 2008).

4.5.5. *fMRI analysis and interpretation*

Most of the studies that performed exploratory analyses of associations of fMRI findings with clinical, hormonal and behavioural outcomes performed numerous correlations without any correction for multiple comparisons (Zoon et al., 2018a; Zoon et al., 2018b).

Different analytical and statistical methods including neuroimaging processing software and pipelines, and choices of whole brain, small volume correction (SVC), functional regional of interest (fROI) and anatomical (aROI) analysis, and sometimes use of uncorrected statistics, will have greatly contributed to inconsistencies in findings between studies in addition to differences in study designs. Neuroimaging analysis holds a wide margin of analytical variability even within the same dataset. A single neuroimaging data set was analysed by 70 independent teams testing the same hypothesis using different processing pipelines showed substantial variability in findings (Botvinik-Nezer et al., 2020).

In five of the included studies in this systematic review, covariates that were included in the fMRI analysis were factors that did or would have been expected to change, as a result of the obesity surgery (Ochner et al., 2011; Ochner et al., 2012a; Ochner et al., 2012b; Holsen et al., 2018; Baboumian et al., 2019). As a result, their inclusion may have attenuated the ability to detect changes in food cue reactivity or taste responses in these studies, since they would not have been orthogonal to the primary fMRI outcome. This includes longitudinal studies which used covariates such as change in BMI (Ochner et al., 2011; Ochner et al., 2012a; Ochner et al., 2012b; Baboumian et al., 2019), desire to eat rating (Holsen et al., 2018), and hunger rating (Baboumian et al., 2019).

Moreover, several fMRI studies limited examination to *a priori* brain regions in their ROI and SVC analyses there can be a repeated self-

selection for particular regions with exclusion of other important areas. Additionally, there was great heterogeneity in the method of determination between studies, for example anatomical versus functional ROIs and use of spheres rather than voxel clusters.

Reverse inference in fMRI interpretation is a serious issue when assigning increased or decreased BOLD signal to a specific behaviour. Since all eating behaviour systems (reward, inhibitory, cognitive) in the brain function act in a synergic and interconnected pattern, a single linear pathway cannot be defined for the processes involved in decision making around food intake. Correlations of regional fMRI outcomes with changes in eating behaviour measures may be helpful in this regard.

4.5.6. Associations of fMRI findings with clinical outcomes

Only a few studies examined correlations between changes in fMRI measures and variability in weight loss. Changes in BOLD signal to food pictures after RYGB did not correlate with weight loss after RYGB (Goldman et al., 2013; Zoon et al., 2018a; Zoon et al., 2018b) nor VSG (Li et al., 2019a), when using corrected statistics.

There was a negative correlation between weight loss at 4 weeks post-RYGB (but not VLCD) and change in BOLD signal to HE/LE food pictures at 4 weeks in a hypothalamic aROI in one study (Salem et al., 2021). In another study using gustatory fMRI, weight loss at 6 months was positively correlated with change in BOLD signal to high fat and high sucrose tastants in the VTA at 2 weeks after RYGB but not LVSG surgery, though the latter did not appear to change on average in either group (Smith et al., 2020). However, the hypothalamus and VTA are difficult areas to assess using standard fMRI parameters because of motion artefacts, partial volume effects from neighbouring cerebrospinal fluid, difficulties in registration and small volumes, and are better assessed using correction for cardiac and respiratory cycles and dedicated small voxel imaging of the region (D'Ardenne et al., 2008).

Although interpretation is difficult because of the small number of such studies, small sample sizes and short durations of follow-up, there is thus minimal evidence available that differential changes in food reward processing or inhibitory control as assessed by fMRI explain variability in weight loss after RYGB or VSG surgeries. Greater weight loss after RYGB surgery has been associated with greater reductions in motivation to receive sweets using a progressive ratio task (Miras et al., 2012).

A few studies looked at correlations of baseline fMRI measures and weight loss. In a predictive gustatory fMRI study, the lower BOLD signal in VTA to high fat, high sweet or preferred tastants pre-operatively, the greater weight loss at 6 months after RYGB but not VSG surgery, suggesting RYGB has more favourable outcomes in patients with high sugar/fat food taste responsivity (Smith et al., 2020). Similarly, lower BOLD signal to HE/LE food pictures in NAcc pre-operatively was associated with more weight loss at 12 months after VSG surgery (Holsen et al., 2018). Pre-operatively, greater BOLD signal in MFG and lower BOLD signal in IFG to HE/LE food pictures was associated with greater weight loss after LAGB surgery (Ness et al., 2014). The VTA and NAcc are known regions implicated in reward processing, whilst MFG and IFG are implicated in inhibitory and cognitive control.

Relationships between fMRI findings and weight loss have also been reported in non-surgical interventions. Lower BOLD signal to HE vs. LE food picture in putamen and pallidum at one month of LCD was associated with more weight loss at 6 months of intervention (Hermann et al., 2019). BOLD signal to HE vs. LE food or HE/LE foods did not change between groups of high and medium protein intake during a two-year weight maintenance study (Drummen et al., 2018). However, the change in BOLD signal to HE vs. LE in insula and ACC after high or medium protein diet intervention was positively correlated with weight loss (Drummen et al., 2018). Finally, in a 12-week psychosocial weight loss program, greater BOLD signal to HE food picture in NAcc, ACC, insula at baseline was associated with less weight loss at the end of intervention (Murdaugh et al., 2012).

Improvements in glycaemic control after RYGB surgery including reductions in HbA1c, fasting glucose or T2DM prevalence were reported in six studies (Scholtz et al., 2014; Frank et al., 2016; Goldstone et al., 2016; Ten Kulve et al., 2017; Holsen et al., 2018; Salem et al., 2021). However, none of these studies correlated changes in food cue reactivity and improvements in glycaemic control. Changes in prevailing glucose may also influence fMRI outcomes given glucose influence on brain food cue reactivity (Page et al., 2011).

4.5.7. Associations of fMRI findings with potential hormonal mediators

Hormonal mediators have been implicated in favourable weight loss after surgery through promoting satiety and decreasing hunger (increased GLP-1 and PYY and decreased ghrelin) and altering food cue reactivity and salience.

A potential role for intestinal satiety hormones GLP-1 and PYY in reduced food cue reactivity after RYGB surgery has been suggested from several hormonal infusion studies, in addition to their known effects to reduce food intake (Verdich et al., 2001; Batterham et al., 2003; Batterham et al., 2007; de Silva et al., 2011). Acute PYY infusion in participants with normal weight decreased BOLD signal at rest in OFC, caudate, and insula (Batterham et al., 2007). Infusion of GLP-1 (and by using a clamp regimen with stabilisation of blood glucose and insulin concentrations) to adults with obesity (with and without T2DM) decreased BOLD signal to HE/LE foods in insula, amygdala, putamen and OFC, that was blocked by co-administration of the GLP-1 receptor antagonist, exendin(9-39) (van Bloemendaal et al., 2014). Co-infusion of PYY_{3-36} and GLP-1 was associated with decreased BOLD signal to HE/LE food pictures in the insula and across brain reward regions (de Silva et al., 2011).

Furthermore, acyl ghrelin is a stomach-derived orexigenic hormone that promotes meal initiation, food intake and hedonics through agonism at the constitutively active growth hormone secretagogue receptor (GHSR) after conversion from the inactive precursor desacyl ghrelin (Druce et al., 2005; Muller et al., 2015; Han et al., 2018; Hagemann et al., 2022). Acyl ghrelin increases food cue reactivity in reward processing regions and HE food appeal, mimicking the effects of endogenous hyperghrelinaemia produced by overnight fasting (Malik et al., 2008; Goldstone et al., 2014). Associations between decreases in plasma total ghrelin (acyl and desacyl) and decreases in BOLD signal to HE food pictures in dlPFC were seen after VSG surgery (Li et al., 2019a), and in VTA after RYGB but not VSG surgery, though this was despite only VSG surgery decreasing plasma total ghrelin (Faulconbridge et al., 2016).

From the current review, there were no associations between plasma GLP-1 (Baboumian et al., 2019) in the *fed state* and BOLD signal to HE vs. LE food at 4 months after RYGB. Similarly, after on average 8–9 months in a cross-sectional study, there were no associations between plasma GLP-1 in the *fasted state* and BOLD signal to HE nor HE/LE food pictures after RYGB surgery (Scholtz et al., 2014).

This causative role for post-RYGB increases in plasma PYY and GLP-1 in changes in food cue reactivity is supported by the findings from two interventional studies modifying their secretion or signalling. BOLD signal to HE/LE food pictures increased in caudate during administration of GLP-1R antagonist Exendin(9–39) after RYGB surgery, though surprisingly this was in fasted, but not fed state (Ten Kulve et al., 2017). Acute suppression of post-prandial plasma PYY and GLP-1 using the somatostatin analogue, Octreotide, reduced HE/LE food appeal and HE/LE food cue reactivity averaged across NAcc, caudate, amygdala and anterior insula (and in NAcc alone) in patients after RYGB but not LAGB surgery (Goldstone et al., 2016). Furthermore, the greater the suppression of post-prandial PYY (with a similar trend for GLP-1) across both surgical groups, the greater the increase in HE/LE food cue reactivity averaged across these brain reward regions (Goldstone et al., 2016). These findings suggest a potential role for increased satiety gut hormones GLP-1 and PYY in reduced food cue reactivity after RYGB surgery.

4.6. Conclusions and future directions

The large methodological variation across studies, often with small numbers, with variable results of changes in food cue reactivity after obesity surgery, limits conclusions. Obesity surgery can affect responses in reward processing regions and restraint and cognitive control regions. Lower food cue reactivity in striatum, limbic and OFC regions was often, but not consistently, seen after RYGB and VSG surgery in longitudinal and cross-sectional studies. However, more variable directions of change in response of dlPFC and regions implicated in restraint and cognitive control were seen. There was some consistent evidence for potential role for satiety gut hormones GLP-1 and PYY in reduced food cue reactivity after RYGB surgery.

There was limited evidence from fMRI results of preferential reduction in HE vs. LE food cue reactivity, despite this often being seen with other non-fMRI measures, though this was not always studied and likely underpowered in fMRI studies. Although uncommonly studied, greater weight loss after RYGB and VSG operations did not correlate with changes in food cue reactivity, though there were suggestions that baseline food cue reactivity may predict weight loss in some circumstances. Additionally, there was large variability in eating behavioural measures studied, which were usually indirect such as with questionnaires. Although they consistently show a shift to healthier eating behaviours after surgery, correlations with fMRI outcomes were uncommonly reported, variable and inconsistent. There was general lack of inclusion of several important neuroimaging analysis and reporting requirements. fMRI studies were generally underpowered by small sample sizes, and power calculations were infrequently included.

Furthermore, it should be emphasised that these fMRI studies are not able to determine the underlying effects of bariatric surgery on brain neurotransmitter systems, such as dopamine, serotonin, noradrenaline, opioid, which requires PET or SPECT neuroimaging, with only a limited number of such studies (Al-Alsheikh et al., 2023).

In the light of findings from this systematic review, the following recommendations are suggested to optimize future fMRI studies of eating behaviour after obesity surgery:

(i) establishment of multi-centre collaborations to allow for greater sample sizes, hence minimizing effects of participant variability and maximizing effect size.
(ii) standardising fMRI paradigms and protocols (including food pictures, nutritional state, time since surgery) as this will allow combination of multiple datasets.
(iii) inclusion of control groups (either different surgery or dietary intervention, especially VLCD to achieve similar weight loss at least over short term) to account for order, parallel dietary/psychological interventions and weight loss effects.
(iv) inclusion of other eating behavioural measures to support and correlate with fMRI findings, including appetite, food hedonics (e.g. liking, wanting and preference), food intake, eating behaviour questionnaires, presence of food addiction and binge eating disorder.
(v) inclusion of measures of addictive behaviours that can contribute to overeating in obesity, including impulsivity, compulsivity, motor response inhibition and negative emotional reactivity / stress sensitivity using questionnaire, computer based or fMRI tasks (Lavagnino et al., 2016; Michaud et al., 2017; Nightingale & Cassin, 2019).
(vi) further evaluation of whether there are differential changes in HE food and LE food cue reactivity, which likely need larger sample sizes.
(vii) more studies are needed to identify baseline and longitudinal changes in brain function that correlate with clinical outcomes, especially weight loss, to identify potential biomarkers of the initial response to surgery with sufficient time post-surgery of at least 6–12 months. This will also be important at longer time periods to identify potential reasons behind weight regain at several years after surgery.
(viii) more direct comparisons of different surgical procedures to identify differential effects on food cue reactivity and eating behaviour, which might aid more personalised selection of surgical interventions based on baseline characteristics. Including newer variations on surgical procedures such as OAGB.
(ix) study of additional procedures to isolate particular mechanisms behind complex surgeries, such as the endoscopically-inserted duodenal jejunal bypass liner (Endobarrier™ device) that excludes ingested nutrients from the lumen of the proximal small bowel mimicking one part of RYGB surgery (Ruban et al., 2020; Ruban et al., 2022).
(x) inclusion of blood hormonal and metabolic measures, as well as other metabonomic and microbiome biomarkers from biofluids such as urine and faeces, as these may reflect or cause changes in dietary exposure and gut microbiome (Garcia-Perez et al., 2017; Gasmi et al., 2023), to correlate with fMRI and behavioural outcomes to help identify potential mediators of the changes in eating behaviour after obesity surgery, which may in turn help the identification and development of non-surgical interventions for obesity treatment.

It is hoped that this systematic review provides a detailed data resource for those performing or analysing fMRI studies of obesity surgery and has enabled helpful suggestions to improve reporting and design of such studies in the future.

CRediT authorship contribution statement

Shahd Alabdulkader: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Writing – original draft, Writing – review & editing, Visualization. **Alhanouf S. Al-Alsheikh:** Validation, Investigation, Writing – review & editing. **Alexander D. Miras:** Writing – review & editing, Supervision. **Anthony P. Goldstone:** Conceptualization, Methodology, Validation, Formal analysis, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

All generated data is already included in supplementary tables

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Institutional Review Board Statement

As a systematic review of previous publications, ethical review and approval were not needed for this study.

Informed Consent Statement

Not applicable as systematic review of previously publications.

Appendix A. Supplementary data

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