Neural correlates of eating behaviour in obesity and after obesity surgery

Thesis submitted for the degree of the Doctor of Philosophy

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To Dad, Mom

Balsam, Nourah

Mazen, Lateen, and Maha

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ABSTRACT

Background: Obesity is a serious, worldwide health concern. The urgent need to find an effective, safe and long-term treatment for this multifaceted chronic disease, requires a full and comprehensive understanding of its pathology. Indeed, eating behaviour is essential in understanding obesity development and consequently, is a key in optimising treatment. Functional imaging resonance imaging has been recently utilized to understand the neural correlates of eating behaviour in obesity, specifically the reward system within the brain.

Objectives: This thesis aimed to investigate the neural correlates of eating behaviour by examining the effect of: (i) obesity surgery, and (ii) body mass index (BMI), (iii) insulin resistance on food cue reactivity and other eating behaviour measures.

Methods: Neural correlates of eating behaviour were examined by performing: (i) a comprehensive systemic review of functional magnetic resonance imaging (fMRI) studies after Roux-en Y gastric bypass (RYGB), vertical sleeve gastrectomy (VSG) and adjusted gastric band (AGB) surgeries; (ii) secondary analysis of three datasets to examine BMI and insulin resistance value as markers of food cue reactivity in three cohorts predominately consisting of patients with obesity.

Results: (i) After obesity surgery, specifically RYGB surgery, high-energy food cue reactivity sometimes decreased or else did not change in striatal, limbic and insula, regions implicated in reward processing. Little evidence is available from VSG and AGB surgeries suggesting changes in food cue reactivity in brain regions involved in reward processing, but a potential effect of VSG surgery on food cue reactivity in the dorsolateral prefrontal cortex. Some consistent evidence for potential role for satiety gut hormones glucagon-like-peptide 1 (GLP-1) and peptide tyrosine tyrosine (PYY) in reduced food cue reactivity after RYGB surgery.

(ii) Contrary to expectations no difference between groups in food cue reactivity to high-energy food pictures in all cohorts. In participants with severe obesity compared to participant with non-severe obesity, *lower* food cue reactivity to low-energy food pictures in one cohort.

(iii) In participants with higher insulin resistance compared to participant with lower insulin resistance, *higher* food cue reactivity to high-energy vs. low-energy food pictures in one cohort; however, findings were not reproducible in other two cohorts. No effect of higher insulin resistance on other eating behaviour measures.

Conclusion: In fMRI studies after obesity surgery, large methodological variation across studies, often with small numbers, with variable results of changes in food cue reactivity after obesity surgery, limits conclusions. Obesity surgeries, specifically RYGB and VSG, alter food cue reactivity in regions involved in reward processing and cognitive control

Heterogeneity in participants across cohorts limited findings replicability; however, findings suggest BMI as a potential marker for altered brain responses in regions implicated in reward processing in obesity. Altered food cue reactivity in obesity is not consistently seen as heightened reactivity for high energy food, it might be manifested as lower reactivity to low energy food. Limited evidence for insulin resistance as a marker for food cue reactivity and other eating behaviour measures in obesity.

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Declaration of originality

The majority of the work described in this thesis was undertaken by the author except for data collection in Chapter 4 and Chapter 5. Analyzed data in Chapter 4 and Chapter 5 were collected by Dr Tony Goldstone and members of his research teams in PsychoNeuroEndocrinology Research Group, Division of Psychiatry and Computational, Cognitive and Clinical Neuroimaging Group, Department of Brain Sciences, Imperial College London, and Metabolic and Molecular Imaging Group, MRC Clinical Sciences Centre.

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Abbreviations

ant	anterior
AgRP	agouti-related protein
aROI	anatomical region of interest
ARC	arcuate nucleus
ACC	anterior cingulate cortex
BMI	body mass index
BAS	Behavioural Activation Scale
BDI-II	Beck Depression Inventory II
BED	Binge Eating Disorder
BIS	Behavioural Inhibition Scale
BOLD	blood oxygen level dependent
CCK	cholycystokinin
CHO	carbohydrate
conc	concentration
corr	correlation
DEBQ	Dutch Eating Behaviour Questionnaire
ED	energy density
EI	Eating Inventory
FDR	false discovery rate
FEAT	fMRI Expert Analysis Tool
fROI	functional region of interest
FSL	FMRIB Software Library: www.fmrib.ox.ac.uk/fsl
FWE	family wise error
fMRI	functional magnetic resonance imgaing
GLP-1	glucagon like peptide 1
HE	high energy
HF	high fat
HS	high sugar
HOMA-IR	homeostasis model of assessment - insulin resistance

IFG	Inferior frontal gyrus
inf	inferior
lat	lateral
LCD	low-calorie diet
LE	low-energy density
LF	low fat
LS	low sugar
med	medial
MTPRT	macronutrient and taste preference ranking task
NAcc	nucleus accumbens
NF	non-food
NS	non-significant
NT	no treatment
NTS	nucleus of the tractus solitarius
NW	normal weight (lean)
o	no change or no
OB	obesity
occ	occipital
OAGB	one-anastomosis gastric bypass
OFC	orbitofrontal cortex
OXM	oxyntomodulin
PET	Positron Emission Tomography
PFC	prefrontal cortex
POMC	proopiomelano- cortin
PYY	peptide YY
RYGB	Roux-Y gastric bypass
SG	sleeve gastrectomy
sv	savoury
SVC	small volume correction
sw	sweet
TFEQ	Three Factor Eating Questionnaire

VTA	ventral tegmental area
WL	Weight loss

Chapter 1 Introduction

1.0 Eating behaviour

Eating behaviour encompasses all human behaviour when it comes to interaction with food. The key components of eating behaviour include hunger, satiation and food preferences, and it is determined in response to numerous internal and external signals in the brain. Hunger and satiation are crucial in understanding eating behaviour, where hunger indicates meal initiation, and satiation refers to the termination of the meal. On the eating episode spectrum, hunger is the first signal to start a meal. During the consumption of that meal, it subsides and satiation increases, signalling the meal's termination. A physiological state that follows each eating episode is termed satiety. It represents the degree of "fullness" between meals in contrast to satiation, which is applied only during a meal.

This introduction will help understand the internal factors that play a crucial role in determining eating behaviour affected by physiological signals, social influences, and psychological traits. These signals are homeostatic and hedonic, peripheral signals and signalling reward systems that interplay to produce specific eating behaviours.

1.1 homeostatic and hedonic food intake control

The framework of homeostatic and hedonic networks controlling food intake is essential in understanding eating behaviour. These networks are not functionally distinct but rather interact continuously. Food deprivation is translated by lower energy and less fat stores; the homeostatic network receives information from the peripheral key messengers (insulin and leptin) to activate hypothalamic orexigenic neurons resulting in increased motivation to eat. Whilst it is not the same for hedonic network, where reward-based regulation is derived by external cues such as smell, picture, and taste of food, along with social and emotional factors (2)

The homeostatic network enables the body to maintain energy, adiposity balance and prevent disruption below a certain setpoint. Gut-derived signals originating from nutrients in the gut and fat stores act directly and indirectly upon a group of cells (nuclei) in the brainstem and hypothalamus. The arcuate nucleus (ARC) is a key hypothalamus region that communicates with other hypothalamic regions. The ARC contains two groups of neurons

with opposite functions involved in feeding control: orexigenic neurons expressing agouti-related proteins (AgRP) that act to motivate increased food intake, and anorexigenic neurons expressing proopiomelanocortin (POMC) that decrease food intake. The ARC receives information directly through the blood-brain barrier from periphery nutrient-sensing or indirectly through peripheral hormonal signals (leptin, insulin, and gut). Finally, peripheral signals from the gastrointestinal tract are also transmitted through the vagal nerve to the nucleus of the tractus solitarius (NTS) in the brain stem and are further integrated to control feeding (3)

The hedonic network refers to the reward-based drive to eat. It includes brain regions that respond to the energy content of food and its hedonic properties such as taste, smell, texture, and psychological and social cues. It incorporates the brain limbic and cortical areas comprising the amygdala, insula, orbitofrontal cortex (OFC). This network relies on dopaminergic neurons released from the ventral tegmental and projected limbic areas (specifically nucleus accumbens) and the prefrontal cortex. Neuron projections and communication between structures within mesocorticolimbic regions perform reward-related functions, including reward evaluation, memory formation, decision making, and motivation. These regions do not function in isolation but also communicate with other regions to control food intake and eating behaviour. Over-stimulation of the hedonic network can lead to the overriding of the homeostatic network, resulting in overeating even in the absence of hunger or high palatable food (4)

1.2 Reward-based eating behaviour

Reward-based eating behaviour is best described by the extent of how rewarding the expectation of a specific food cue is perceived to be. For example, high palatable foods hold high appealing properties such as the smell of cake baking, sweet candy taste, and a cheeseburger picture. These properties motivate individuals to seek and initiate an eating episode. The brain reward structures respond to these high palatable food properties by stimulating neural activity and releasing specific neurotransmitters such as dopamine from the ventral tegmental area (VTA) onto the nucleus accumbens and other reward structures (5). Dopamine is one of the key neurotransmitters in the reward pathway, and it is released

in response to the pleasure associated with food consumption, food memory and anticipation (6).

Food reward can be further broken down into appetitive and consummatory domains. The appetitive reward value of food refers to the extent to which an individual is willing to work to obtain a specific reward (e.g. how much effort will I make for a piece of candy?). While the consummatory reward value refers to the extent of satisfaction elicited when a specific food is consumed (e.g. how much do I like this candy?)(7, 8). Understanding the mechanism underlying these domains is crucial to explain eating behaviour, especially in obesity and weight management. The following is a brief description of the highlighted regions in the brain that have been implicated in reward and cognitive processing and chosen as functional regions of interest.

Reward valuation structures in the brain

Orbitofrontal cortex OFC is an essential part of the brain's reward and cognitive circuitry, located in the frontal lobe. It acts as an integration hub that receives olfactory, gustatory, somatosensory and visual inputs. Then it encodes reward value and signals information to the prefrontal cortex (PFC), which decides on the appropriate action in response to the rewarding stimulus. The integration of these inputs leads to goal-directed behaviour, reward evaluation, and finally, decision making (9). The orbitofrontal cortex communicates with other regions involved in homeostatic and non-homeostatic control of food intake, including the hypothalamus, amygdala, insula, hippocampus, and striatum (10, 11)(Elliott, Agnew, and Deakin 2010).

Amygdala is located in the temporal lobe of the brain and is considered part of the limbic system. It is a binding site for memory formation and emotion processing, which influences behaviour by associating a specific stimulus (i.e. food) to its reward value (12). The amygdala also responds to negative (i.e. anxiety and fear) and positive emotions (reward) and hence, plays a role in adaptive, goal-directed behaviour and aversive learning (12, 13). Projections from the amygdala connect with cortical regions, including the striatum (NAcc), hippocampus, and the OFC, to mediate behaviour subsequently (14). A meta-analysis that included 16 studies reported altered amygdala activity in patients with obesity compared to normal-

weight controls, where an increased BOLD signal to food was seen (15). In an fMRI study, in response to HE/LE foods, the BOLD signal was lower in participants post-RYGB surgery compared to post-LAGB surgery (16) suggesting a lower reward value of food after surgery; hence better weight loss outcome.

The insula is the primary taste cortex, where taste memory is integrated. It is involved in recognition, and memory for taste and conditions taste aversions. It also plays a role in emotional perception and the interpretation of internal and external cues to elicit a behavioural response (17). In healthy volunteers, the increased BOLD signal in insula correlated with food cravings when asked to imagine the sensory characteristics of their favourite food (18). Whereas a higher BOLD signal in the insula in response to a HE food picture in women with obesity compared to women with normal weight may suggest a role of the dysfunctional reward system (19). Moreover, the decrease in BOLD signal to chocolate vs. tasteless tastent in the insula at 1-month post-RYGB surgery, may suggest a reduced preference for high sugar food shortly after surgery (20)

The dorsal striatum consists of the caudate and putamen, and, together with the ventral striatum, they form an integral part of the subcortical basal ganglia. The dorsal striatum receives dopaminergic inputs from substantia nigra and other areas, including the orbitofrontal cortex, somatosensory and motor regions, and plays an important role in decision-making and impulse control (21, 22). The caudate reinforces reward-directed behaviours and learning through working memory to associate a specific action with the expected reward value with goal-directed actions for the future. Whereas, the putamen is thought to be associated with the formation of habitual actions regardless of outcomes (23, 24). A decrease in the BOLD signal was seen in response to HE food picture in putamen (25) and caudate (20) after one month of RYGB surgery. However, an increase in BOLD signal in response to HE vs LE food picture in putamen positively correlated with higher BMI score following a low-calorie diet for one month in a predictive study (26).

Nucleus accumbens (Nacc) along with the olfactory tubercle, forms the ventral striatum and extends dorsolaterally into the putamen and dorsomedially into the caudate (27). The NAcc receives dopaminergic projections from the ventral tegmental area (VTA)(28), and it is

implicated in feeding behaviour, reward sensitivity, motivation, and learning (29-32). In fMRI studies, BOLD signal to HE food pictures in NAcc decreased in a month post-RYGB surgery (33). However, an increase in the the BOLD signal was observed after six months of a dietary intervention (34).

The above regions are commonly predefined in fMRI studies as regions of interest based on a well-established body of research associating the activation in these regions with reward-based behaviours. The direction of change in BOLD signal in these regions is important as it shows the effect on feeding behaviour and the alterations in activation.

Inhibitory control structures

The prefrontal cortex PFC is one of the largest cortices in the brain where higher cognitive and executive functions occur. It is involved in reward processing, expectancy and anticipation of reward, and it can be divided into different functional regions, including orbitofrontal cortex (OFC) and dorsolateral PFC (dlPFC). The dorsolateral prefrontal cortex dlPFC has been studied within the context of top-down inhibitory action and decision making, specifically to restrain from an immediate reward in response to its potential negative long term effect (35, 36). In fMRI studies, the BOLD signal to food either increases in dlPFC after weight loss, indicating a better cognitive control (37, 38), or decreases indicating a lower need in response to food(33). Interpretation of fMRI findings, in general, should be done with caution since a specific behaviour can not be directly associated with the activation in the BOLD signal.

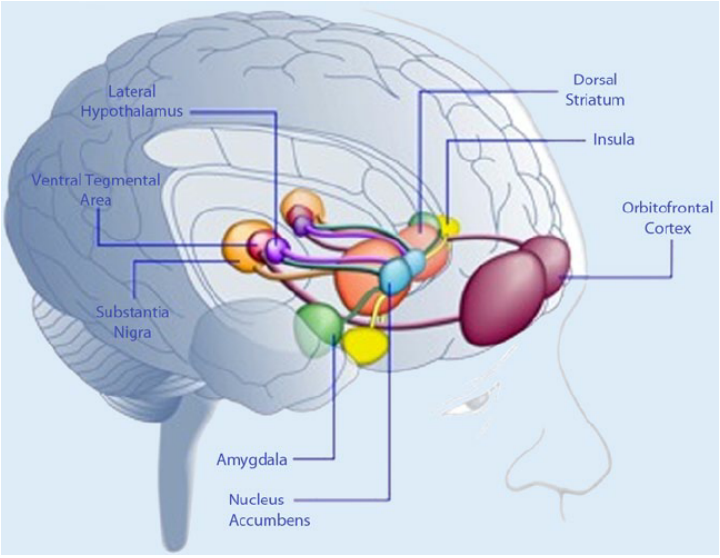

Figure 1.1 Brain regions implicated in food reward processing
The ventral tegmental area projects dopaminergic inputs to the nucleus accumbens and dorsal striatum, mediating the incentive properties of food and regulating motivation. Whilst the OFC and amygdala encode inputs relating to food salience and reward, the insula process information related to the hedonic value of food. Figure taken from (1)

1.3 Peripheral signals

The interaction of sensory inputs in the gut and adipose tissue and hormonal secretion determines eating behaviour. This interaction results in signals sent to the brain to be further encoded and translated into a specific behaviour.

Sensory inputs include taste, odour, the texture of food, which help determine food choices. Taste perception is controlled by central pathways in the brain, including the nucleus of the solitary tract NTS in the brainstem, somatosensory cortex, and frontal lobe (39). Furthermore, taste perception can be divided into three domains: sensory, reward, and physiological domain. The sensory domain usually refers to a specific taste detection, recognition, and intensity threshold measure; for example, 'Is this soup creamy? If yes, how creamy is it?' The physiological domain refers to post-ingestive refluxes, i.e. digestion, absorption, and salivation. Finally, the reward domain is divided into appetitive (liking) and consummatory (wanting) domains. The appetitive domain is described by the extent of effort an individual is willing to make to get a specific food; i.e. How much effort am I willing to put into getting a piece of chocolate cake?. The consummatory domain is described by the actual consumption of a specific food.

Hormonal signals include hormones secreted from the stomach and intestine (GLP-1 and ghrelin), pancreas (insulin), and adipose tissues (leptin). These hormones, once released, are attached directly to specific receptors in the brain via the blood-brain barrier and indirectly via vagal afferent nerve signalling, forming a gut-brain axes communication. These hormones have an orexigenic or anorexigenic effect on feeding.

Ghrelin is a gut-derived peptide identified as the hunger hormone that stimulates food intake. It is released in high concentrations in response to fasting and negative energy balance (diet-induced weight loss)(40, 41). Higher food intake is associated with higher ghrelin concentrations in individuals with obesity and normal weight (41). Ghrelin's role is not limited to the homeostatic network (increased hunger) but extends to the non-homeostatic network by affecting the reward pathway (42). In an interventional study carried out by Malik (2008), acute ghrelin infusion increased BOLD signal to food pictures in the amygdala, OFC, insula, and striatum in participants with normal weight, demonstrating its effect on hedonic

responses favoring food consumption (43). After vertical sleeve gastrectomy VSG surgery, ghrelin levels decreased (44-46); however, association with food cue reactivity and food intake were variable across studies **(Findings from fMRI review chapter 2.0)**

Glucagon-like-peptide-1 (GLP-1) is a neuropeptide hormone released postprandially from L-cells in the gastrointestinal tract. It is released in higher concentration after a meal, signalling satiety and meal termination (47). GLP-1 receptors have been identified in the hypothalamus, indicating its role in appetite control (48, 49). Furthermore, GLP-1 acts on reward-processing brain regions to modulate food intake and enhance weight loss (50, 51). In an fMRI study, the acute administration of GLP-1 and PYY in participants with normal weight lead to reductions in BOLD signal in response to food pictures in average fROIs (amygdala, insula, caudate, NAcc, putamen, OFC), and consequently a reduction in energy intake, demonstrating a crucial role of these satiety peptides in appetite control (52). After RYGB surgery, the increase in GLP-1 was not consistently associated with the decrease in BOLD signal in the brain regions involved in reward processing **(Findings from fMRI review chapter 2.0).** In dietary and lifestyle intervention studies, GLP-1 levels either decreased (53) or increased (54) or did not change (55).

Peptide tyrosine-tyrosine (PYY) is another satiety peptide released from the gastrointestinal tract with a similar effect on appetite and food intake as GLP-1. Intravenous PYY infusion has been found to decrease energy intake and reduce hunger in healthy individuals (56) and those with obesity (57). In interventional studies, PYY is usually co-administered with GLP-1 showing a cumulative effect on food cue reactivity, appetite, and food intake (52, 58). After obesity surgery, PYY levels are increased; however, direct associations with food cue reactivity or food intake are variable **(Findings from fMRI review chapter 2.0)**

Leptin is an adipose-derived hormone that is released into the bloodstream. It crosses the blood-brain barrier and binds to hypothalamus leptin receptors conveying information about body energy stores status. In the ARC of the hypothalamus, leptin mediates satiety by activating POMC neurons and inhibiting NPY/AgRP neurons leading to reduced food intake (59, 60). Leptin levels are proportionate to whole-body adipose tissue mass, which means increased body fat results in increased leptin and ultimately stimulates reduced food intake

(61, 62). However, it has been suggested that the progression of obesity is not a result of leptin deficiency but leptin resistance (60).

Insulin is a pancreatic hormone produced by the β cells in response to meal ingestion. It is known for its role in maintaining glucose homeostasis and controlling food intake through its receptors in several brain regions, which are commonly implicated in the reward system, including the hippocampus, ventral tegmental area (VTA), amygdala and striatum (63, 64). The endogenous insulin release after a meal reduces the BOLD signal to food cues, inhibiting food intake. Conversely, studies in the literature have also shown an enhanced BOLD signal during fasting, when plasma insulin levels are typically decreased (65).

Several interventional studies investigated the effect of insulin administration on food cue reactivity in individuals with normal weight. These studies reported a decrease in BOLD signal in response to food picture was seen in the hippocampus and middle frontal cortex compared to placebo administration after intranasal insulin administration in individuals with normal weight (66). In another study, resting-state activity in the hypothalamus and OFC was reduced after intranasal insulin administration in women with normal weight (67). The intranasal insulin administration allowed examining the central effect of insulin on food cue reactivity and minimised peripheral effects.

Few studies have examined the effect of intranasal insulin on food cue reactivity in patients with obesity. Findings suggest an impaired brain insulin action in obesity whereby brain areas that mediate insulin effects on food intake are resistant to the effect of insulin (68, 69). For example, in one study, intranasal insulin reduced cerebral blood flow in the prefrontal cortex in normal-weight participants, but not in overweight or obese participants. Furthermore, higher BOLD signals to food cues were observed in the VTA and NAcc during intranasal insulin administration in participants with overweight compared to participants with normal weight (70).

In participants with insulin resistance, fMRI studies demonstrated an altered food cue reactivity in individuals with higher Homeostasis Model of Assessment - Insulin Resistance HOMA-IR. For example, a higher BOLD signal to favorite food cue was seen in the amygdala,

insula, putamen and PHG of participants with insulin resistance compared to lean participants (71). Furthermore, another fMRI study investigated functional connectivity in participants with obesity and T2DM compared to participants with normal weight. A positive correlation in functional connectivity between amygdala and insula in participants with obesity and T2DM was seen (72). The latter study suggests a stronger link between brain areas involved in reward and motivation in obesity.

1.2 Functional magnetic resonance imaging fMRI

Neuroimaging is a major area of interest within the field of eating behaviour. More recently, attention has focused on utilising functional magnetic resonance imaging (fMRI) to help understand eating behaviours traits. Functional magnetic resonance imaging principles are similar to those of magnetic resonance imaging, where they both utilise the physical characteristics of the hydrogen nucleus to detect a signal. The advantage of fMRI is that it detects changes in blood flow in metabolically active regions. For example, in response to an external stimulus (food picture), increased demand for oxygenated haemoglobin to an activated region is seen. Oxyhaemoglobin is diamagnetic and has magnetic properties similar to surrounding tissue. Whereas deoxyhaemoglobin is paramagnetic; hence, when a region of the brain is activated, it becomes metabolically active and consumes comparatively more oxygen. As a result, the oxygenated/deoxygenated haemoglobin ratio increases, and this region's blood oxygen level-dependent (BOLD) signal increases. fMRI paradigm aims to detect relative changes in the BOLD signal, from the "resting" baseline to the "activation" signal generated from an external stimulus. Since the "resting" activation is inherently unstable within and between subjects, a difference in the activation elicited in response to a stimulus and the activation elicited in response to a control stimulus is assessed. The haemodynamic response function implies an intrinsic delay before regional vasodilation occurs and flow increases in response to a stimulus. In general, the increase in BOLD signal during fMRI task is presumed to be an increased functionality of the brain region through this neurovascular coupling **Figure 1.2**.

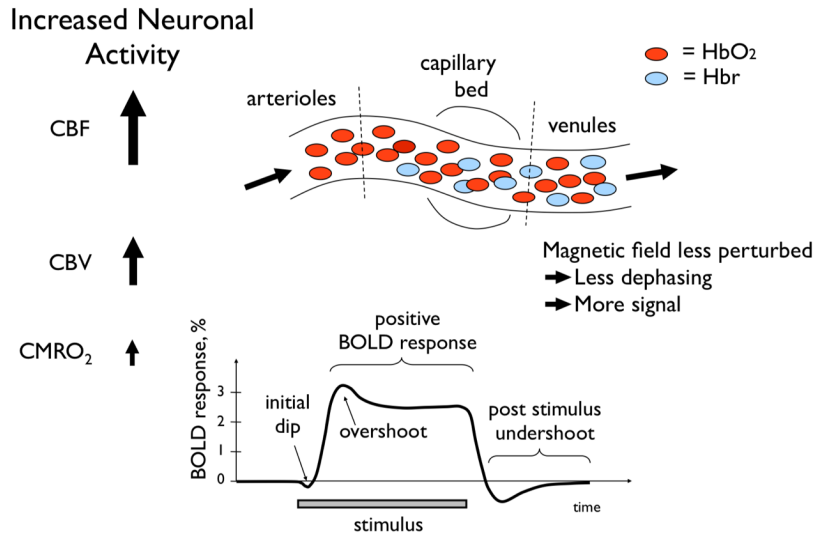

Figure 1.2 fMRI BOLD signal response

Increased neural activity leads to increases in regional cerebral blood flow and decreases to the deoxy-haemoglobin (paramagnetic) to oxy-haemoglobin (diamagnetic) ratio. This results in less perturbance to magnetic field and higher BOLD signal. Abbreviations: BOLD: blood oxygen level dependent; CBF: cerebral blood flow; CBV: cerebral blood volume; $CMRO_2$: cerebral metabolic rate of oxygen; HBO_2: oxy-haemoglobin; Hbr: deoxy-haemoglobin. Figure taken from fMRI of the Brain (FMRIB) Software Library (FSL) *(73)*

1.2.1 fMRI processing and statistical analysis

General linear model: The processing from individual data and up to group comparisons uses a specific format in FSL. The raw activation of a specific voxel in the brain in response to a specific stimulus is averaged across a single scanning session for each subject. Then, each subject's activation is passed on to the group level to allow comparisons between groups. For robust comparisons, the analysis for each group should be "mixed-effects". Meaning, the mean activation incorporates the mean activation of each subject, and the variance incorporates variance across all subjects of the group and not within each subject of the group (fixed effects).

Before analysis, a general linear model is set up in FSL to describe what the BOLD signal in response to the stimuli of the experiment should look like based on our hypothesis; for example, the BOLD signal takes place when a food image is shown compared to when it is not shown (**Figure 1.2**). The analysis software then assesses how well the observed BOLD signal "fits" to the model and provides a measure of goodness of fit (parameter estimate or β; if β is not zero, then this suggests that the stimulus activates the voxel).

The absolute magnitude of the BOLD signal in response to a stimulus is of limited interpretative value as the baseline (i.e. the signal when the stimulus is "off") fluctuates. Therefore, meaningful comparisons can only be made from the *difference* in BOLD activation, or contrast, between 2 different stimuli (e.g. the difference in BOLD signal in response to food vs object pictures). We, therefore, make inferences only from the voxels that best fit our model. The software examines each voxel separately, tries to find which voxels fit the direction of the contrast best, and assigns each voxel with a t-statistic, a measure of "fit". The t-statistic is then converted to a Z statistic. By thresholding the experiment with a specific Z-statistic cut-off, we provide some statistical meaning to the data. For example, if we use a $Z>1.7$ cut-offs with a P-value <0.05, we can be sure that the voxels that are coloured on our screen are statistically significantly activated (as they "survived" the thresholding), whilst accepting that <5% will be falsely positive.

fMRI studies in eating behaviour

For studies on eating behaviour, fMRI paradigms are generally based on task-based subtraction analysis. In other words, inside the scanner, the participant views pictures of high-energy (HE), low-energy (LE), and objects. The BOLD signal when viewing HE food pictures contrasts against the BOLD signal when viewing LE food pictures. The differences in BOLD signal across participants within a group form the group brain activation pattern, indicating that the salience and preferences for HE foods depend on the activation in brain regions involved in the particular task. For instance, when viewing images of HE foods, the BOLD signal in reward- and emotion-processing brain regions such as the amygdala, caudate, insula, the nucleus accumbens (NAcc), and orbitofrontal cortex is increased (1). Disruptions in the reward processing of food cues in these brain regions may contribute to dysregulated food intake and predisposition to obesity. Another advantage of utilising fMRI is combining quantitative BOLD signal changes with other measures, such as hormonal mediators to draw links between the gut-brain axis or behavioural measures such as food intake to examine whether an association exists between the two measures.

1.3 Obesity

Obesity is increasingly recognised as a serious worldwide health concern. The urgent need to find effective and long-term treatment for this multifaceted chronic disease requires a comprehensive understanding of its pathology. It appears to result from several factors such as genetic, environmental, social, psychological, and physiological factors. These factors expand the heterogeneity of obesity and make it more challenging to study. Eating behaviour, for one, plays a vital role in its development and is a crucial target for treating obesity

1.3.1 Potential Causes of obesity

Genetic and environmental factors

Evidence from the literature suggests that body weight is genetically determined by 40-70% (74)and "thinness" is similarly a heritable trait (75). In addition, the mutation in genes involved in the homeostatic and hedonic control of food intake have been identified, such as the genes that encode leptin and leptin receptors. An example of genetic obesity is the Prader-Willi syndrome, where the mutation in the small nucleolar ribonucleic acid clusters (SNORD116) results in increased hunger and hyperphagic obesity phenotype (76).

In the current obesogenic environment in industrialised countries, processed food is more palatable and energy dense. It overrides the satiety mechanism leading to overeating during a meal and contemplating between meals even when not hungry (77, 78). Food advertisements also include appetising pictures and slogans that increase the salience and promote low cost and high calorie processed food compared to healthier food choices. With a fast and busy lifestyle, quick consumption of large portions of food may result in lower production of satiety gut hormones and overall overconsumption during a meal (79). Taken all together, an increase in energy intake in the last 25 years is estimated to be 200-250 kcal/person/day (80). On the other side of the energy balance equation, there is a substantial decrease in energy expenditure due to decreased physical activity and a sedentary lifestyle. Nowadays, individuals spend more time at the office with little physical activity, and with more recent technological advances, more work is done from home.

Eating behaviours and personality-traits

Eating behaviours and personality traits are important contributors to pathological overeating and have been widely studied in obesity research. Overeating may be seen as a coping mechanism for psychological problems, contributing to weight gain as metabolic and psychological comorbidities impose anxiety and mental disorders (81). Dietary restraint refers to the conscious restriction of food intake to inhibit weight gain. It is associated with a high risk of overeating and weight regain after weight loss (82, 83).

Emotional eating is a coping mechanism to negative emotions such as stress and anxiety and leads to overconsumption of energy-dense food in response (82). Fatty foods that are also high in sugar have been shown to increase the release of "happiness" neurotransmitters (i.e. opioid and serotonin) in the brain and therefore enhance mood (84). Previous studies suggest a positive correlation between emotional eating and BMI (85), and a higher BOLD signal to HE food picture in the insula in participants with obesity (86). The insula is a key region in the reward-processing network, and alteration in insula activity is suggested to be associated with emotional dysregulation.

Disinhibited eating refers to overeating in response to an external or internal stimulus, consequently leading to weight gain (82). It can also be associated with impulsivity, where an impulsive action occurs without thinking about long-term consequences. Delay discount tasks assess whether an individual chooses an immediate small reward instead of a bigger reward in the future. Higher impulsivity and delay discounting are associated with overeating and weight gain (87, 88). In addition, external eating that refers to eating in response to an external stimulus is also associated with higher body weight (82)

Eating behaviour questionnaires are extensively used in the context of obesity to assess unhealthy behaviours. Some commonly used questionnaires include the Dutch Eating Behaviour Questionnaire (DEBQ), Three-Factor Eating Behaviour Questionnaire (TFEQ), and Eating Disorder Examination Questionnaire (EDEQ). These questionnaires are known to be more reliable across subjects with varying weights compared to other questionnaires (89).

Obesity adds to the mental burden on patients, linked to higher depression and impulsivity prevalence (90, 91). In order to assess depression and mood, Negative Affect and Positive Affect Schedule and Beck Depression Inventory are used to identify symptoms of depression (92-94).

1.3.2 Physiological factors

Hunger and satiation

The feelings of hunger and satiety are highly subjective, and thus, there is no direct accurate measure. In eating behaviour studies, self-reported appetite ratings are frequently used to measure hunger and satiety in addition to surrogate markers like gut hormones (GLP-1, PYY, and ghrelin). For example, in participants with obesity, ghrelin levels are lower compared to participants with normal weight after a meal and negatively correlates with BMI (95-97). Whilst, GLP-1 and PYY levels are sometimes either lower during fasting or blunted after a meal in obesity (98, 99). These findings suggest an impaired satiety control in obesity.

Another way to assess hunger and fullness is the assessment of actual food intake. While food diaries are usually biased to underreporting in patients with obesity, direct meal laboratory tests show higher consumption (absolute or corrected with energy expenditure) of food in patients with obesity compared to normal weight (100, 101).

Food reward

The hedonic properties of food can promote eating even when energy requirements are met. In the current obesogenic environment, the abundance of high palatable foods has influenced reward signals that can override homeostatic signals leading to overeating and weight gain (102). The available literature in this matter is variable as to whether the consumption of high fat and high sweet food (as these food are perceived more rewarding) is higher in patients with obesity compared to individuals with normal weight (103). Foods high in fat and sugar are innately liked due to their orosensory properties and rewarding post-ingestive effects and have been proven to be particularly palatable (104, 105). Few studies reported no difference between patients with obesity and with normal weight in liking of high fat and sweet foods (106, 107). The inconsistency in the literature can be attributed to methodological heterogeneity across studies, including direct and indirect eating behaviour measures.

There are some consistencies in the literature suggesting a higher reward of high palatable food in obese patients (108). More robust evidence can be provided by incorporating food intake with other behavioural tasks such as progressive ratio tasks, explicit liking and implicit wanting tasks. Progressive ratio tasks can be performed using computer software in which participants are asked to work to obtain an appetising food.

1.3.3 Treatments

Several medical approaches are now available to treat obesity, including lifestyle interventions (i.e. dietary restrictions and increased physical activity), pharmacotherapy, and surgical procedures.

1.3.3.1 Dietary interventions

Lifestyle modification can have positive effects on weight loss. The mean percent weight loss after lifestyle modification usually ranges between 5-15%, and a higher percent is achievable following a very-low calories diet VLCD <800 kcal per day (109). Other metabolic benefits include improved glycemic control and reduced blood pressure. Weight maintenance after dietary interventions usually requires an intensive regimen, including increased physical activity and reduced energy intake. Following an intensive lifestyle intervention in the LOOK-AHEAD study, 50% of participants were able to maintain >5% of weight loss at eight years (110). Furthermore, combined behavioural weight management programs, including restricted diet and increased physical activity, implicated better weight loss outcomes at 12-18 months (111). Findings from DIRECT study showed that only 24% of the participants achieved >15 kg weight loss and 86% of them achieved diabetes remission at 12 months(112).

However, weight loss maintenance remains a challenge for patients with obesity. In particular, dieting that involves caloric restriction results in a compensatory secretion of ghrelin, a finding consistent in eating behaviour studies (55, 95). The effects of energy-restricted induced weight loss on GLP-1 and PYY are inconclusive since some studies reported a decrease in GLP-1 and PYY (53), others an increase (54) and some with no change (55). Nevertheless, Hunger and desire to eat ratings measured using visual analogue scales are significantly higher after energy-restricted weight loss compared to baseline (53, 55). These

physiological responses make adherence to caloric restriction and weight loss challenging and unfortunately lead to weight regain in most people.

1.3.3.2 Pharmacotherapy

Pharmacotherapy for obesity is the adjunct treatment of obesity and lifestyle intervention. It is offered to patients with a BMI > 27 kg/m2 with at least one comorbidity, for example, type 2 diabetes and hypertension, or patients with BMI >30 kg/m^2 with no comorbidities. Anti-obesity medications have been developed with a wide range of mechanisms of action resulting in 5-7% mean percent weight loss. The limited percent weight loss, physiological and psychological side effects, and consequent weight regain in the long-term limit pharmacotherapy's efficacy.

Malabsorption is one of the mechanisms of action to induce weight loss by inhibiting fat absorption. A drug, Orlistat, works by inhibiting fat absorption by the intestine, and it is the only available medication for obesity in the UK National Health Service. A meta-analysis has shown that it causes modest weight loss of -2.12 kg (113).

Another potential mechanism of action of obesity pharmacotherapy is increasing satiety. Glucagon-like peptide-1 (GLP-1) analogues like Liraglutide mimic the effects of the native hormone to increases satiety and reduce food intake. A recent meta-analysis examined 25 trials to determine whether GLP-1 receptor agonists result in weight loss in overweight or obese patients with or without diabetes. Patients treated with GLP-1R agonists achieved a more significant weight loss of -2.9 kg than control groups(114).

1.3.3.3 Obesity surgery

The surgical approach for obesity treatment offers long term weight loss with a significant improvement in metabolic profile. Recent developments in obesity surgeries have heightened the need for more innovative surgical procedures that are less invasive and with fewer complications. Roux-en-Y gastric bypass (RYGB) is considered the gold standard for obesity surgery procedures. Other surgical procedures include the vertical sleeve gastrectomy (VSG), adjustable gastric band (LAGB), and one-anastomosis gastric bypass (OAGB). Weight loss achieved after obesity surgery ranges between 20-40% (115). Some studies reported that

OAGB has a more positive effect on weight loss compared to RYGB and VSG (116, 117). Whilst other studies showed similar weight loss outcomes among RYGB and OAGB (118, 119). RYGB and VSG procedures have comparable weight loss effects(120)

Roux-en Y gastric bypass (RYGB)

RYGB has been the most frequently performed obesity procedure since it was developed. It is a laparoscopic procedure in which a small pouch of the stomach (30 ml) is fashioned and then anastomosed to the proximal jejunum, bypassing the stomach and duodenum (121).

Vertical sleeve gastrectomy (VSG)

VSG is one of the most popular procedures due to its simplicity, and it offers a comparable weight loss effect to RYGB surgery {English, 2020 #21795}{Dang, 2019 #21796}. This surgery involves the dissection of 70% of the stomach, including the fundus and body. This allows rapid nutrients to pass to the duodenum.

An adjustable gastric band (AGB)

It involves inserting an adjustable silicone ring around the proximal aspect of the stomach, immediately below the gastro-esophageal junction creating a small proximal pouch.

Mechanisms of weight loss after obesity surgeries

Reduced hunger and increased satiety

Patients have reported a reduction in hunger and an increase in satiety after RYGB surgery. After RYGB, approximately 50-80% fewer calories were consumed by patients compared to pre-surgery (122). This decrease in calories was demonstrated at 1, 5, and 8-year follow up post-RYGB surgery (123-125). A decrease in portion size 6-weeks post-surgery, and an increase at 1- and 2-years after surgery (126), lower than pre-operative stage has been recorded. Reduction in food intake and hunger was also reported after VSG surgery (127)

Enhanced reward-based eating behaviour

A change in the macronutrients intake has also been reported after RYGB, with patients consuming a lower percentage of fat and low-glycaemic index foods and a higher percentage of protein in the proportion of their total daily calorie intake (16, 124). Despite initial enthusiasm that food preference changes occur in all patients, recent studies have demonstrated that they occur only in a subgroup of patients. These patients lose more weight compared to those in whom food choices have not changed, thus raising the possibility that the shift in food preferences may be an additional weight loss mechanism after RYGB foods (128). Some of the discrepancies on change, magnitude and durability of changes in food preferences could be due to the indirect, self-reported, verbal measurements, allowing for over or under-reporting of the actual intake (129). More robust results can be obtained by directly measuring eating behaviour. Changes in macronutrients intake were also observed after VSG surgery (130-132) and no difference was seen between RYGB and VSG surgeries when comparing the change in food preferences (133).

More recently, attention has shifted to using functional magnetic resonance imaging (fMRI) to help understand the brain reward responses to food that could underlie actual eating behaviours. Weight loss after obesity surgeries can also be due to the changes in the perception of the reward value of food after surgery. Initially, RYGB patients experience reduced brain activity in regions believed to be associated with food reward (16). For example, a cross-sectional study reported lower BOLD signal to HE food picture in the orbitofrontal cortex (OFC), amygdala, caudate nucleus, and hippocampus in response to high-energy food pictures stimuli after RYGB surgery (16). Moreover, a reduction in BOLD signal to HE food picture in the ventral tegmental area (VTA) was also reported 6-months after RYGB and VSG surgeries (46). A recent longitudinal study by Baboumian et al., 2019 aimed to determine the effect of RYGB and VSG surgeries on food cue reactivity using whole-brain analysis (38). This study included four groups: RYGB, VSG, non-surgical weight loss group, and no-treatment group. Four months after surgery, a greater BOLD signal to HE food picture in the dorsal lateral prefrontal cortex (dlPFC) was seen in both surgical groups (38), indicating that these patients exert more cognitive restraint to food cravings (38, 134).

Alterations in hormonal mediators

The anatomical manipulation of the gut during obesity surgeries causes alterations in orexigenic and anorexigenic hormones. For example, in RYGB surgery, fast delivery of nutrients to the distal small intestine results in an increased concentration of plasma satiety hormones like GLP-1 and PYY. The inflated release of these hormones in response to a meal have an appetite-suppressing effect that consequently contributes to the reduction of energy intake and depresses the brain response to food, thus changing food preference (135, 136). After VSG surgery, hunger hormone ghrelin levels are decreased, contributing to changes in food preferences and intake (137). However, after RYGB surgery, some studies have shown that ghrelin levels are either increased, decreased, or remain unchanged compared to pre-surgery(138). Moreover, it is also unclear whether these alterations in hormonal mediators are short-term or whether the surgery has a long-term effect on these hormones.

1.4 Rational for work

Eating behaviour in the disease of obesity is investigated in behavioural and neuroimaging studies in the literature. This is crucial to help understand mechanisms underlying eating behaviour and food choices, then to further advance treatment options and medical innovations. While accumulating evidence demonstrates that obesity surgery is among the most effective and durable treatment for obesity, it is still not clear why patients respond differently to the same surgery. One of the potential mechanisms for weight loss after surgery is the change in food preferences, thus the study of eating behaviour of patients after obesity surgery and their neural correlates is warranted to identify potential predictors of surgery outcomes and mediators of successful weight loss. Studies investigating food cue reactivity after obesity surgery have not been systematically reviewed and analyzed to evaluate the evidence of food cue reactivity alteration after surgery, and the usefulness of fMRI in eating behaviour studies. Hence, I sought to systematically review the available literature on food cue reactivity alteration after obesity surgery.

BMI and insulin resistance are readily available measures in obesity and may fit as markers for food cue reactivity. To examine the value of these markers, I aimed to examine the effect of BMI and insulin resistance on food cue reactivity and other eating behaviour measures in three different cohorts.

Chapter 2 fMRI studies after obesity surgery: A systematic review

2.1 Introduction

Laparoscopic surgical approaches for obesity treatment provide up to 40% sustained weight loss, with a significant improvement in the metabolic profile (139-141). 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 weight loss effect {English, 2020 #21795}{Dang, 2019 #21796}. Other surgical procedures include laparoscopic adjustable gastric banding (AGB), and one-anastomosis gastric bypass (OAGB) are less performed compared to RYGB and VSG (142). There are two potential mechanisms that are suggested to explain sustained weight loss after obesity surgery: (i) reduced hunger and increased satiation; and (ii) shift in food preferences.

Up to now, mechanisms underlying weight loss after obesity surgeries are still under investigation as well as the factors that might affect them, such as surgery type. However, functional magnetic resonance imaging can be utilized to investigate the reward-cognitive system in the brain, and whether obesity surgery can alter the neural response to food cues. Findings from fMRI studies after obesity surgery suggested a decrease in BOLD signal to food cues in some of the areas that are associated associated with reward processing (i.e. OFC, caudate, putamen, NAcc) and food salience (i.e. fusiform gyrus). In addition to enhanced cognitive restraint through increased BOLD signal in inhibitory regions (i.e dlPFC and IFG) in the brain (143).

The activity in reward and inhibitory control systems in response to anticipatory or actual consummatory food stimuli is also influenced by the interplay between psychological and metabolic factors. This highlights the importance of correlating fMRI findings with other behavioural or hormonal measures in order to have more meaningful conclusions as to underlying mechanisms. For example: the exaggerated secretion of post-prandial satiety gut hormones might mediate reductions in food hedonic responses, and shift in food preferences away from energy dense foods.

There have been two previous systematic reviews of fMRI studies of obesity surgery. The first, included obesity surgery as one of the weight loss interventions discussed, and their effect on neural activity and included few studies at the time it was published that examined selective

brain areas activation in response to food stimulus (143). In the latter systematic review, authors included only 3 studies for ALA meta-analysis, this was due to variability of methodology. The second, included only seven fMRI studies, six of them investigated RYGB and one of them AGB(144). Other narrative reviews only included fMIR studies of food cue reactivity (145, 146), and mostly focused on RYGB surgery. Furthermore, they did not report in sufficient detail of study design, methodology and analysis to discuss potential reasons for heterogeneity in study findings, nor discussion of potential confounds that may influence the interpretation of results (143, 145). They also did not systematically review differences between different obesity surgeries, nor link fMRI findings with clinical outcomes, other changes in eating behaviour, nor potential mechanisms related to the anatomical-physiological gut manipulations arising from obesity surgery. Hence, this review sought to more systematically examine the literature of fMRI studies of obesity surgery in more detail.

2.2 Objectives

This systematic review aimed to assess studies examining the research question: how does obesity surgery alter the neural response to food stimuli in humans with obesity?

The primary aim was to review:

(i) collated results from individual studies in the literature reporting changes in responses to food stimuli (picture/word cue reactivity, taste or odour) using fMRI in cross-sectional and longitudinal studies of obesity surgery.

Secondary aims were to review:

(ii) quality of studies and their reporting using published criteria for nutrition-related fMRI studies;

(iii) how heterogeniety in study methodolodogy, design, protocol, and fMRI paradigms and analysis might explain differences between studies;

(iv) differences between results particularly in terms of nutritional state and type of obesity surgery;

(v) associations of fMRI findings at baseline or their changes with clinical outcomes such as weight loss and improvements in glycaemic control;

(vi) associations of fMRI findings with other measures of eating behaviour, such as appetite ratings, food liking and wanting, and eating behaviour questionnaires;

(vii) associations of fMRI findings with potential hormonal mediators, such as appetitive gut hormones, and results from studies with experimental manipulations investigating their role, such as administration of satiety gut hormone antagonists or suppressants;

(viii) 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.

2.4 Methods

Literature search and data extraction

The literature search strategy was based on the PICOS question framework. PubMed and Ovid (Medline) databases were searched for studies using a list of keywords both individually and in combination (MeSH terms) **Appendix 1**

Relevant manuscript reference list were also checked for any relevant studies. Only manuscripts written in English and published between January 1990 and July 2021. 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 cue), and/or direction or magnitude of functional connectivity during a food-related task, as the main summary measure(s) after RYGB, VSG, AGB or OAGB 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 (www.covidence.org) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used for this review.

All included studies were reviewed and screened, then data were extracted from original text and on-line supplementary documents

The following information was extracted from each study:

(i) publication information: author, journal, year of publication, country;

(ii) study summary: study design, sample size, type of surgery, study groups, fMRI paradigm, active task, functional connectivity, association fMRI with clinical/behavioural/mechanistic outcomes, appetite and eating behaviour measures, mechanistic blood measures;

(iii) study demographics: age, sex, ethnicity, control group intervention, time between scans, time scan post-intervention, baseline and post-surgery BMI and weight loss (if not reported, % weight loss was calculated from the change in average of the reported weight or BMI), T2DM status and change in glycaemia;

(iv) fMRI protocol: fMRI paradigm, experiment design, image acquisition parametrs, stimulus, food and non-food categories;

(v) study protocols: state intervention, nutritional state; if fed (after consumption of standardized drink/meal), or fasted (after 12 hour night fast), or pre-meal (when last meal is consumed 4 hours before scanning session); meal information, menstural cycle control, mood assessment;

(vi) fMRI analysis: software, analysis methodology, statistical test and threshold, multiple comparison correction, covariates, motion confound parameter in general linear model (GLM), motion parameter results;

(vii) fMRI results for food stimuli: group effect, task/food contrast, seed for functional connectivity (FC), direction of change/difference in BOLD signal in selective brain regions;

(viii) behavioural measures: appetite, food wanting/liking, food preference, fMRI task specific, food intake, eating behaviour measuements (e.g. appetite visual analogue scale (VAS) ratings, questionnaires), mood, other psychological traits;

(ix) mechanistic measures: e.g. nausea and dumping syndrome, plasma GLP-1, PYY, leptin, ghrelin, serum insulin, insulin resistance, endocannabinoids etc.

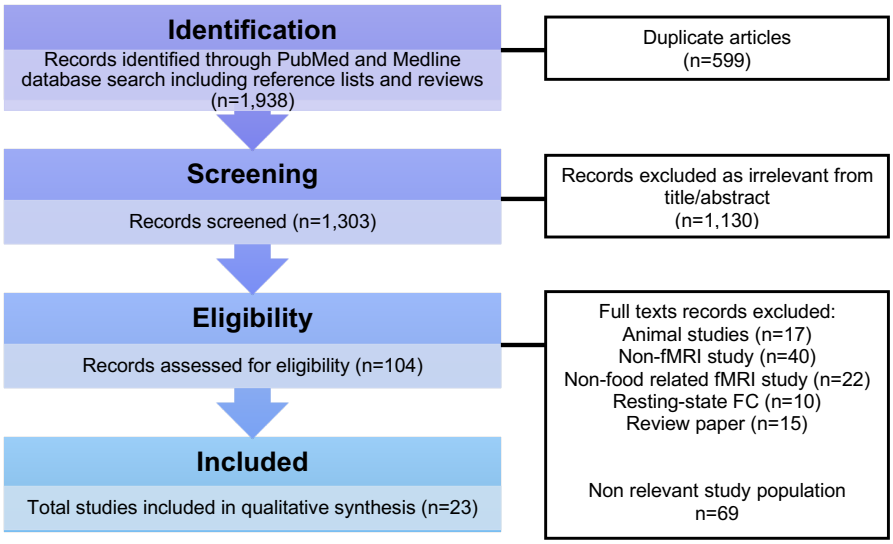

Figure 2.1 ***Flow chart of included and excluded publications in systematic review.***

Quality assessment

Included articles were checked for quality assessment and reviewed using a 6-criterion quality assessment adapted from a recent review of good practices in nutrition-related functional neuroimaging studies (147). These criteria included requirements for reported summary measures, methods, and results in articles original text, including information about the following: participants' description, eating disorder scales, study design/ procedure, fMRI task, fMRI data analysis, and statistical inference/ interpretation. The criteria categorised the requirements into mandatory, highly recommended, and recommended requirements.

Standarisation of fMRI findings

In order to provide consistency in the reported findings, where BOLD signal in cortical and subcortical regions was given using spatial coordinates, these were checked against the Harvard-Oxford cortical and subcortical atlases (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases). In addition, the reported MNI coordiantes for the frontal lobe and cingulate regions were checked against the Sallet Dorsal Frontal connectivity-based parcellation (148).

The following criteria was applied:

(i) if Talariach coordinates were reported in original paper (149-151), they were converted to MNI coordinates using the Yale BioImage Suite Package (http://sprout022.sprout.yale.edu/mni2tal/mni2tal.html);

(ii) if coordinates were reported for the prefrontal cortex (PFC), it was replaced by the relevant region from the Harvard-Oxford Cortical Structural Atlas including frontal pole, paracingulate gyrus, IFG, MFG or SFG, and dlPFC using the Sallet atlas (defined as Brodmann areas 8/9/45/45/46);

(iii) if dmPFC was reported in original paper, it was replaced by a change in SFG;

(iv) Broadman areas were added (if not reported in original article), and if the reported coordinates were outside BA definition, the closest BA was estimated based on reported coordinates and cluster size using the Yale BioImage Suite Package (http://sprout022.sprout.yale.edu/mni2tal/mni2tal.html) (152).

2.5 Results

2.5.1 Eligible studies

The literature search resulted in 1,938 articles that were identified and screened for inclusion **Figure 2.1**. Twenty-three studies were eligible for inclusion (16, 20, 25, 33, 38, 46, 134, 153-160)(44-46, 161)(149-151, 162, 163).

Two of the 23 studies (8.7%) included examination of *task-related functional connectivity* before and after VSG in overlapping datasets (44, 161). Ten other studies that only examined *resting state* functional connectivity were excluded from this systematic review, including six studies of RYGB (38, 158, 163-167), four studies of VSG (168-171), and one study of AGB (172).

Nine studies appeared to contain overlapping datasets from four cohorts:(16, 25, 44, 149-151, 160, 161, 173), leaving 18 completely independent datasets. Twelve of the 23 studies (52.2%) and nine of the 18 datasets (50.0%) were conducted in the USA, with nine studies (39.1%) and eight datsasets (44.4%) in Europe, and two studies (8.7%) and one dataset (5.6%) in China.

2.5.2 Study design

Study design of the individual studies are summarized in **Table 2.1 Figure 2.2**

Of the 23 included studies, 16 (69.6%) were of a longitudinal design, with participants scanned both before and after surgery (20, 25, 38, 44-46, 149, 150, 153-156, 161-163, 173); two (8.7%) were of a predictive design, where only inter-individual differences in baseline (151, 157) or early post-operative changes (157) in food cue or taste reactivity were correlated with post-surgical weight loss; while five studies (21.7%) were cross-sectional in design, in which participants after surgery were compared with control groups of normal weight and/or with overweight/obesity (16, 134, 158-160).

Appetite ratings were examined in 13 studies (56.5%): hunger, fullness, desire/volume to eat, or pleasantness to eat (16, 20, 44, 150, 153, 155-160, 162, 163); food wanting in nine studies (39.1%) (16, 25, 33, 44, 45, 156, 159, 160, 162), food liking in 8 studies (34.8%) (16, 25, 46, 154, 156, 157, 159, 162), food preference in three studies (13.0%) using macronutrient and taste preference ranking task (MTPRT) (156), taste intensity (154), or Leeds Food Preference Questionnaire (LFPQ) (162); food intake in two studies (8.7%) from *ad libitum* test meal (162), or *ad libtum* ice-cream intake and 3-day food diary (16); eating behaviour questionnaires in eight studies (34.8%) including Three Factor Eating Questionnaire (TFEQ) (45, 158, 159, 162), Yale Food Addiction Scale (YFAS) (44, 162), Eating Inventry (EI) (149), Binge Eating Disorder (BED), Eating Disorder Examination Questionnaire (EDEQ) (16, 162), and Dutch Eating Behaviour Questionnaire (DEBQ) (16, 162, 163).

Only five (21.7%) studies reported assessment of nausea and/or dumping syndrome (16, 20, 160, 162, 163). Hormonal mediators were measured in 12 studies (52.2%), including plasma/serum glucagon-like-peptide-1 (GLP-1) (16, 20, 38, 160, 162, 163), peptide tyrosine tyrosine (PYY) (16, 160, 162, 163), GIP (163), and FGF19 (160, 162), bile acids (16), ghrelin (16, 44-46, 156, 163), glucose (16, 20, 45, 158, 160, 162, 163), insulin (16, 44, 45, 160, 162, 163), leptin (45), and enocannabinoid concentrations (156).

Association of fMRI outcomes were examined in 12 studies (52.2%) with clinical outcomes such as weight loss or change in glycaemic control (44, 45, 134, 149-151, 155-157, 159, 161,

163), in nine studies (39.1%) with appetite or eating behavioural measures (16, 25, 44, 46, 149, 155, 156, 162, 163), and in 10 studies (43.5%) with hormones measures (16, 20, 38, 44, 46, 149, 156, 160, 162, 163).

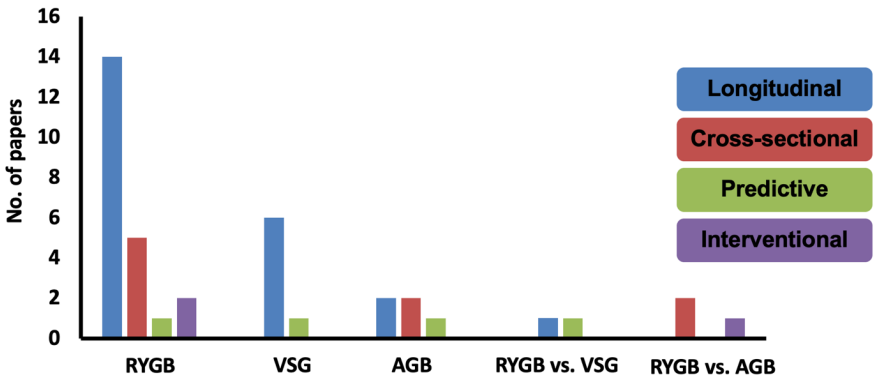

Figure 2.2 Summary of included studies by study design

AGB: Adjusted gastric band, **RYGB**: Roux-Y gastric bypass, **VSG:** vertical sleeve gastrectomy

Table 2.1 Summary of included studies

Author	Year	Journal	Country	Design	Groups	Control group	fMRI Paradigm	Active task	Functional connectivity	Nutritional state interaction	Corr. fMRI with clinical outcomes	Appetite ratings	Other eating behaviour measures	Corr. fMRI vs. appetite/behaviour	Assesment nausea or dumping symptoms	Hormonal blood measures	Corr. fMRI mechanist measure
RYGB																	
Ochner [i]	2011	Ann Surg	USA	Longitudinal	RYGB	o	Food cue reactivity	o	o	o	o	o	Yes	o	o	o	o
Ochner [i]	2012	Neuro-science	USA	Longitudinal	RYGB	o	Food cue reactivity	o	o	o	o	o	Yes	Yes	o	o	o
Ochner	2012	Neuro Res	USA	Longitudinal	RYGB	o	Food cue reactivity	o	o	o	o	Yes	o	o	o	o	o
Ten Kulve	2017	Diabetes Care	Netherlands	Longitudinal ±	RYGB	o	Food cue reactivity	o	o	o	o	Yes	o	o	Yes	Yes	Yes
				Interventional			Taste	o	o	o	o			o	Yes	Yes	Yes
Zoon	2018	Behav Brain Res	Netherlands	Longitudinal	RYGB	o	Food cue reactivity	o	o	o	Yes	Yes	Yes	Yes	o	Yes	Yes
							Odour	o	o	o	Yes			Yes			Yes
Aldubaikhi	2020		UK	Longitudinal	RYGB, OW-LCD, OW-NT	Yes	Food cue reactivity	Yes	o	o	o	Yes	Yes	Yes	Yes	Yes	Yes
Frank	2016	Diabetes Care	Germany	Cross-sectional	RYGB, OB	Yes	Food cue reactivity	Yes	o	o	Yes	Yes	Yes	o	o	o	o
Frank	2014	Int J Obesity	Germany	Cross-sectional	RYGB, OB, NW	Yes	Food memory	Yes	o	o	o	Yes	Yes	o	o	o	o
Goldman	2013	Obesity	USA	Cross-sectional	RYGB	Yes	Food cue reactivity	Yes	o	o	Yes	o	o	o	o	o	o
Zoon	2018	Biol Psychol	Netherlands	Longitudinal	RYGB	o	Food go/nogo	Yes	o	o	Yes	Yes	o	Yes	o	o	o
Wang	2016	Surg Endosc	USA	Longitudinal	RYGB, NO-NT	Yes	Taste	Yes	No	o	o	o	Yes	o	o	o	o
Salem	2021	Diabetes Care	UK	Longitudinal	RYGB, VLCD	Yes	Food cue reactivity	o	Yes (rest)	o	Yes	Yes	o	Yes	Yes	Yes	Yes
VSG																	
Li [m]	2019	Psychoneuro endocrinol	China	Longitudinal	VSG, OB-NT	Yes	Food cue reactivity	o	Yes (task)	o	Yes	Yes	Yes	Yes	o	Yes	Yes
Hu [m]	2020	J Neurology	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	USA	Longitudinal	VSG	o	Food cue reactivity	Yes	o	o	Yes	o	Yes	o	o	Yes	o
AGB																	
Bruce [o]	2012	Surg Obes Relat Dis	USA	Longitudinal	AGB	o	Food cue reactivity	o	o	Yes	Yes	o	Yes	Yes	o	o	o
Ness [o]	2014	Surg Obes Relat Dis	USA	Predictive	AGB	o	Food cue reactivity	o	o	Yes	Yes	0	o	o	o	o	o
Bruce [o]	2014	Obesity	USA	Longitudinal	AGB, LCD	Yes	Food cue reactivity	o	o	Yes	o	Yes	o	o	o	o	o

Table 2.1 Summary of included studies																	
Author	**Year**	**Journal**	**Country**	**Design**	**Groups**	**Control group**	**fMRI Paradigm**	**Active task**	**Functional connectivity**	**Nutritional state interaction**	**Corr. fMRI with clinical outcomes**	**Appetite ratings**	**Other eating behaviour measures**	**Corr. fMRI vs. appetite/behaviour**	**Assesment nausea or dumping symptoms**	**Hormonal blood measures**	**Corr. fMRI vs. mechanistic measures**
MULTIPLE																	
Scholtz [P]	2013	Gut	UK	Cross-sectional	RYGB, AGB, OB	Yes	Food cue reactivity	Yes	o	o	o	Yes	Yes	Yes	Yes	Yes	Yes
Goldstone [P]	2015	JCEM	UK	Interventional	RYGB, AGB	No	Food cue reactivity	Yes	o	o	o	Yes	Yes	o	Yes	Yes	Yes
Faulconbridge	2016	Obesity	USA	Longitudinal	RYGB, VSG, OB-NT	Yes	Food cue reactivity	o	o	o	o	o	Yes	Yes	o	Yes	Yes
Baboumian	2019	Neuro-science	USA	Longitudinal	RYGB, VSG, LCD-CBT, OB-NT	Yes	Food cue reactivity	o	Yes	o	o	o	o	o	o	Yes	Yes
Smith	2020	JCI	USA	Predictive	RYGB, VSG	No	Taste	o	No	No	Yes	Yes	Yes	o	o	o	o

Table 2.1 Summary of included studies

Footnotes: [I-P]: probable overlapping datasets

Abbreviations: **CBT**: cognitive behavioural therapy, **LCD**: low-calorie diet, **NT**: no treatment, **NW**: normal weight (lean), **OB**: obesity, **OW**: overweight, **NO**: Non-obesity, **RYGB**: Roux-Y gastric bypass, **VSG**: Vertical sleeve gastrectomy, **AGB**: Adjusted gastric band

2.5.3 Participant characteristics

Participant characteristics and clinical outcomes of the individual studies are summarized in **Table 2.2 and 2.3**

The total number of participants having obesity surgery across all studies was 446, and the majority were female (n=387, 86.8%), with seven studies including only females (20, 25, 46, 153, 157, 158, 173), while otherwise the prevalence of females in individual studies ranged from 50.0-95.0%. Participant age ranged from 18-66 years, and the average age of obesity surgical group(s) in each study ranged from 26.6 to 50.0 years.

With regards to sample size in the obesity surgery group(s): nine studies included <= 10 participants (20, 33, 38, 134, 149, 153, 154, 158, 160), 14 studies included 11-20 participants (16, 25, 38, 45, 46, 150, 151, 154-157, 159, 162, 163), and six studies included >20 participants (16, 44, 46, 134, 157, 161). Only 7 studies (30.4%) reported any power calculations (20, 25, 45, 153, 160, 163, 173).

Two studies (8.7%) were conducted exclusively on patients with type 2 diabetes mellitus (T2DM) (159, 163), five studies (21.7%) included some participants with T2DM ranging in prevalence from 14.3 to 35.7% (16, 154, 157, 160, 162), while nine studies (40.9%) had no patients with T2DM (20, 25, 38, 45, 46, 153, 173) or only in one surgical group (16, 160). Nine studies (39.1%) did not report the prevalence of T2DM in their cohort (44, 134, 149-151, 155, 156, 158, 161). Post-surgical changes in glycaemia were only reported in 6 studies (26.1%), as a reduction in HbA1c, fasting plasma glucose and/or T2DM prevalence (16, 20, 45, 159, 160, 163).

Eleven studies (47.8%) reported ethnicity in the surgical groups (16, 25, 38, 45, 46, 134, 153, 160, 162, 173), and in these studies only 148 of 446 total participants (33.2%) were of white Caucasian ancestry.

2.5.4 Time since surgery

The time since surgery varied greatly between studies **Table 2.2**. In the 17 longitudinal studies, the average time of follow-up fMRI scanning after surgery was 1-2 months in 10 studies (20, 25, 153-156, 173)(44, 161, 163), 3-6 months in five studies (38, 46, 149, 150, 162), and 12-13 months in 2 studies (45, 154), including one study that scanned participants at both 1 month and 12 months after surgery (154).

In the five cross-sectional studies, the average time of fMRI scanning after surgery ranged from 9 months (16), 15 months (160), 18 months (159), to 2.7-4.2 years (134, 158), and the individual ranges in each study were also broad.

None of the studies reported information about the nature and duration of the post-operative diet, and particularly when participants switched from a liquid to solid diet relative to the time of post-operative scanning, which may influence the findings, especially in those studies with post-operative scanning early in the first 1-3 months after surgery.

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2.5.5 Study design by obesity surgery type

RYGB surgery: Seventeen studies (77.3%) included patients having RYGB surgery: 11 longitudinal (20, 25, 38, 46, 153-156, 162, 163, 173), one predictive study (157), and five cross-sectional in design (16, 134, 158-160).

Two of these 16 RYGB studies (11.8%) reported changes in food cue reactivity in *both the fasted and fed nutritional state*, before and 1 month after surgery (20, 153), with one of these also examined the effects on taste responses and the effects of administration of the GLP-1 receptor antagonist, Exendin(9-39) (20). Four (23.5%) longitudinal studies reported changes in food cue reactivity in just the *fasted state* at 4 weeks (163), 14 weeks (162) or 6 months (46), or taste responses at 12 months (154), after surgery.

Five (29.4%) longitudinal studies reported changes in food cue reactivity (25, 33, 38, 155), or odour responses (156), in the *fed state*, before and 1 month (25, 33), 2 months (155, 156), or 4 months (38), after 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* (157).

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-AGB surgery (16), (ii) *pre-meal state* at average 18 months after surgery against an unoperated group with obesity (159), (iii) *pre-meal state* at average 33-51 months after surgery between successful and non-successful weight loss maintainers (134), (iv) *fed state* at average 14 months (range 5-24) after surgery with post-AGB surgery group, and examined acute effects of administration of the somatostatin analogue, Octreotide, to suppress satiety gut hormones PYY and GLP-1 (160), and (v) *fed state* at average 41 months (range 13-104) after surgery with unoperated obese and normal weight groups (158).

VSG surgery: Six studies (26.1%) included patients having VSG surgery: all of longitudinal design. Three studies (50.0%) reported changes in food cue reactivity in the *fasted state,* before and 1 month (44, 161), or 6 months (46) 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*, before and 4 months (38) or 12 months (45) after 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* (157). Two studies examined functional connectivity during food-related task before and 1 month (44, 161).

AGB surgery: Five of the 23 studies (21.7%) included patients having AGB surgery: two longitudinal (149, 150), one predictive (151), and two cross-sectional (16, 160) in design. Three studies (60.0%) reported changes in food cue reactivity in *both the pre-meal and fed nutritional state,* before and 3 months (149, 150) or 6 months (151) after 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 AGB with an unoperated group with obesity and post-RYGB surgery groups (16), and in the *fed state* at average 14 months (range 5-24) after AGB with a post-RYGB surgery group, and also examined effects of acute Octreotide administration (160).

Comparative obesity surgery studies: Five (21.7%) studies compared the effect of different

surgeries on food cue reactivity:three longitudinal studies compared RYGB with VSG at 2 weeks (157), 4 months (38) or 6 months (46) after surgery; while two cross-sectional studies compared RYGB with AGB at an average 8 months (16), or 14 months (160) after surgery, with the latter also examining the effects of acute Octreotide administration.

Other surgeries: No publications were found that included patients after one-anastamosis gastric bypass (OAGB), also known as "mini-bypass', or biliary-pancreatic diversion, a procedure that achieves its effects primarily through malabsorption.

2.5.6 Magnitude of weight loss after surgery

Weight loss outcomes for the individual studies are summarized in **Table 2.3**. As would be anticipated, the magnitude of weight loss at the time of post-operative scanning was also variable, related to the variable times since surgery and different procedures. The average percentage weight loss ranged in RYGB studies from <10% (20, 25, 153, 157), 10-20% (156, 162, 163, 173), 20-30% (16, 38, 46, 160), 30-40% (154, 159), >40% (134); in VSG studies from <10% (157), 10-20% (44, 161), to 20-30% (38, 45); and in AGB studies <10% (150, 151), 10-20% (149) to 20-30% (16, 160). One study did not report the degree of weight loss (158), and in another study of RYGB surgery, percentage weight loss could not be estimated from the reported absolute weight loss (155).

Control groups

Thirteen out of the 21 non-predictive studies (61.9%) had a control non-surgical group (16, 38, 44, 46, 150, 154, 158, 159, 161-163) (Table 2).

In the 17 RYGB longitudinal studies, only seven studies (41.2%) 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 four studies included an active intervention, three studies with a group with overweight or obesity receiving just a low-calorie diet (LCD) for comparison with RYGB (162) or AGB (150), or very low calorie diet (VLCD) for comparison with RYGB (163), and in one study a group with obesity receiving an LCD with cognitive behavioural therapy (CBT) for comparison with RYGB/VSG groups (38). In addition, three studies included a group with overweight/obesity who received no intervention for

longitudinal comparison with RYGB (38, 46, 162) or VSG (38, 46, 161) groups, and one study included a group with obesity receiving no intervention for longitudinal comparison with RYGB (154), 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 (158), and/or unoperated groups with overweight/obese in three studies (16, 158, 159), of which only two studies had a control group with similar average BMI to the post-surgical group (16, 159). Another study compared successful with unsuccessful weight loss after RYGB surgery (134), and the other just compared RYGB with AGB groups, together with the effects of acute Octreotide administration (160).

Three of the 21 non-predictive studies (14.3%) had more than one control group, two longitudinal (38, 162), and one cross-sectional (158).

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%) (38), and RYGB compared to VLCD (10.4% vs 7.7%) (163), although the latter study also performed sub-group fMRI analyses matching for weight loss, while percentage weight loss was similar after AGB surgery compared to LCD (10.8% vs 9.3%) (150).

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Table 2.2 Participant characteristics and clinical outcomes of the individual studies										
Author	**Year**	**N**	**Group**	**Female** n (%)	**Age (y)** mean ± SD or median [IQR] (range)	**Caucasian** n (%)	**Control intervention**	**Time scan pre-intervention (months)**	**Time between scans (months)**	**Time scan post-intervention (months)** mean ± SD or median [IQR] (range)
RYGB										
Ochner [I]	2011	10	RYGB	10 (100%)	35 ± 9 (20-47)	2 (20.0%)	n/a	1 mo	2 mo	1 mo
Ochner [I]	2012	14	RYGB	14 (100%)	36 ± 10 (20-54)	2 (14.3%)	n/a	1 mo	2 mo	1 mo
Ochner [I]	2012	5	RYGB	5 (100%)	36 ± 13 (21-54)	0 (0%)	n/a	1 mo	2 mo	1 mo
Ten Kulve	2017	10	RYGB	10 (100%)	46.5 [40.0, 50.0]	n/a	n/a	n/a	1.4-2.8 mo	0.9 mo
Zoon	2018	19	RYGB	15 (78.9%)	41 ± 10	n/a	n/a	0.8 ± 0.4	mean 2.9 mo	2.1 ± 0.3 mo
Aldubaikhi	2020	14	RYGB	13 (92.9%)	47.9 ± 10.3	9 (64.3%)	n/a	n/a	n/a	~3.5 mo
		10	OW-LCD	6 (60.0%)	33.4 ± 6.3 (24-41)	6 (60.0%)	500 kcal / day deficit	3.0 ± 0.2 (2.7-3.3)	5.8 ± 0.3 (5.3-6.5)	2.9 ± 0.4 (2.4-3.6) mo
		11	OW-NT	8 (72.7%)	34.3 ± 11.5 (20-54)	4 (36.4%)	None	n/a	9.8 ± 4.2 (5.3-19.6)	n/a
Frank	2016	12	RYGB	10 (83.3%)	50.0 ± 9.2	n/a	n/a	n/a	n/a	17.7 ± 9.3 mo
		12	OB	6 (50.0%)	50.7 ± 11.4		n/a	n/a	n/a	
Frank	2014	9	RYGB	9 (100%)	42.0 ± 8.4	n/a	n/a	n/a	n/a	40.8 ± 28.8 mo (13.2-104.4)
		11	OB	11 (100%)	42.6 ± 13.3	n/a	n/a	n/a	n/a	n/a
		11	NW	11 (100%)	36.6 ± 12.6	n/a	n/a	n/a	n/a	n/a
Goldman	2013	24	RYGB-MS	19 (79.2%)	46.6 ± 11.4	20 (83.3%)	n/a	n/a	n/a	32.8 ± 21.6 mo
		7	RYGB-LS	7 (100%)	43.4 ± 10.5	7 (100%)				50.6 ± 28.4 mo
Zoon	2018	18	RYGB	15 (83.3%)	41 ± 11	n/a	n/a	0.8 ± 0.4	mean 2.9 mo	2.1 ± 0.3 mo
										(1.8-2.8)
Wang	2016	6	RYGB-1mo	3 (50.0%)	47.0 ± 7.2 (37-56)	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
		6	RYGB-12mo	2 (33.3%)	48.5 ± 8.9 (37-60)	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

Table 2.2 Participant characteristics and clinical outcomes of the individual studies										
Author	**Year**	**N**	**Group**	**Female** n (%)	**Age (y)** mean ± SD or median [IQR] (range)	**Caucasian** n (%)	**Control intervention**	**Time scan pre-intervention (months)**	**Time between scans (months)**	**Time scan post-intervention (months)** mean ± SD or median [IQR] (range)
		7	NO-NT	2 (28.5%)	51.7 ± 7.8	n/a	None	n/a	1.2 ± 0.3 mo	n/a
Salem	2021	16	RYGB	13 (81.25)	48.6 ± 14.4	n/a	n/a			
		19	VLCD	11 (57.89%)	46.2 ± 10.8	n/a	VLCD			
VSG										
Li [m]	2019	22	VSG	13 (59.1%)	26.6 ± 8.6	n/a	n/a	n/a	n/a	1 mo
		19	OB-NT	12 (63.2%)	28.6 ± 9.0	n/a	None	n/a	1 mo	n/a
Hu [m]	2020	28	VSG	15 (53.5%)	27.9 ± 7.9	n/a	n/a	n/a	n/a	1 mo
		22	OB-NT	9 (40.9%)	28.4 ± 8.4	n/a	None	n/a	1 mo	n/a
Holsen [n]	2018	18	VSG	16 (88.9%)	38.4 ± 10.1	15 (83.3%)	n/a	1 mo	13 mo	12 mo
AGB										
Bruce [o]	2012	10	AGB	9 (90.0%)	40.1 ± 10.3 (21–54)	n/a	n/a	0.3 ± 0.2 mo	mean 3.8	3.5 ± 0.8 mo
Ness [o]	2014	19	AGB	16 (84.2%)	38.4 ± 11.2	n/a	n/a	0.3 ± 0.2 mo	3.0 ± 0.4 mo [c]	mean 2.7 mo [c]
						n/a			5.9 ± 0.8 mo [c]	mean 5.6 mo [c]
Bruce [o]	2014	15	AGB	12 (80.0%)	41.4 ± 9.8 (21-56)	n/a	n/a	n/a	n/a	3.7 mo
		16	LCD	11 (68.7%)	40.6 ± 7.1 (23-52)	n/a	LCD/behaviour	n/a	n/a	3.7 mo
MULTIPLE										
Scholtz [p]	2013	21	RYGB	19 (90.5%)	43.5 ± 9.2 (23.0-59.0)	16 (76.2%)	n/a	n/a	n/a	8.1 [5.9, 11.5] mo (2.6-26.2)
		20	AGB	19 (95.0%)	40.9 ± 11.2 (22.0-59.0)	15 (75.0%)	n/a	n/a	n/a	9.1 [5.2, 19.2] mo (3.6-64.6)
		20	OW	17 (85.0%)	39.1 ± 10.3 (20.0-55.0)	10 (50.0%)	n/a	n/a	n/a	n/a

Table 2.2 Participant characteristics and clinical outcomes of the individual studies										
Author	**Year**	**N**	**Group**	**Female** n (%)	**Age (y)** mean ± SD or median [IQR] (range)	**Caucasian** n (%)	**Control intervention**	**Time scan pre-intervention (months)**	**Time between scans (months)**	**Time scan post-intervention (months)** mean ± SD or median [IQR] (range)
Goldstone [p]	2015	7 [e]	RYGB	5 (71.4%)	46.0 ± 2.6 (42-50)	7 (100%)	n/a	n/a	0.5 [0.2, 0.7]	14.2 ± 7.9 mo (5.2-23.9)
		9	AGB	8 (88.9%)	41.8 ± 11.4 (26-59)	6 (66.7%)	n/a	n/a		15.3 ± 10.8 mo (4.0-36.0)
Faulconbridge	2016	22	RYGB	22 (100%)	37.2 ± 9.3	14 (63.6%)	n/a	<0.9 mo	~7 mo	6 ± 0.5 mo
		18	VSG	18 (100%)	40.3 ± 8.9	4 (22.2%)	n/a	<0.9 mo	~7 mo	
		21	OB-NT	21 (100%)	36.4 ± 8.2	3 (15.8%)	None	n/a	6 ± 0.5 mo	n/a
Baboumian	2019	16	RYGB	15 (93.8%)	38 ± 10	6 (10.91%)	n/a	~1 mo	4.3 ± 1.0 mo	~3.3 mo
		9	VSG	9 (100%)	29 ± 6		n/a	~1 mo		~3.3 mo
		14	LCD-CBT	10 (71.4%)	39 ± 10		LCD via meal supplements (910 kcal/d 2mo, 1200 kcal/d 1 mo, 1500 kcal/d 1mo) + CBT	~1 mo		~3.3 mo
		16	OB-NT	14 (87.5%)	35 ± 12		None	n/a		n/a
Smith	2020	23 (15-19 fMRI) [d]	RYGB	23 (100%)	40.0 ± 1.9	16 (69.6%)	n/a	0.9-1.8 mo	1.8-3.6 mo	0.9-1.8 mo
		25 (17-20 fMRI) [d]	VSG	25 (100%)	38.9 ± 1.5	9 (36.0%)	n/a	0.9-1.8 mo	1.8-3.6 mo	0.9-1.8 mo

Table 2.2 Demographics of included studies

Footnotes: [a]: calculated from Δ average weight, [b]: calculated from Δ average BMI, [c]: no scan just time point for weight loss, [d]: 1st n Pre & Post, 2nd n Pre only, [e]: n=9 for RYGB (n=2 performed task outside scanner), [j]: n=11 (different participants at 1 month and 1 year), [l-p]: probable overlapping datasets

Abbreviations: **CBT**: cognitive behavioural therapy, **FPG:** fasting plasma glucose**, LCD**: low-calorie diet, **NT**: no treatment, **NW**: normal weight (lean), **OB**: obesity, **OB-NT:** obesity no treatment **, OW**: overweight, **NO**: Non-obesity, **RYGB**: Roux-Y gastric bypass, **VSG**: Vertical sleeve gastrectomy, **AGB**: Adjusted gastric band, **o:** no change, **n/a:** not available, **RYGB-LS:** least successful < 50EWL, **RYGB-MS:** most successful > 50EWL, **mo:** months

Table 2.3 summary of clinical outcomes							
Author	**Year**	**Group**	**T2DM** n (%)	**Baseline BMI** mean ± SD (range)	**Current/Post-BMI** mean ± SD or median [IQR] (range) kg/m²	**Weight loss** mean ± SD (range) % or kg	**Change in glycaemia**
RYGB							
Ochner [l]	2011	RYGB	0 (0%)	45.1 ± 5.3 (40-54)	39.8 ± 4.2	11.8 ± 3.1 %	n/a
Ochner [l]	2012	RYGB	0 (0%)	45.5 ± 4.4 *	39.8 ± 3.7 *	9.9 ± 2.9 % *	n/a
Ochner [l]	2012	RYGB	0 (0%)	45.5 ± 4.4 *	39.8 ± 3.7 *	9.9 ± 2.9 % *	n/a
Ten Kulve	2017	RYGB	0 (0%)	39.9 [37.8, 42.5]	36.8 [34.6, 39.1]	~8.2 % [a] (8.8 ± 1.7 kg)	Fasted glucose: NS
							Pre: 4.8 [4.5, 5.1], Post: 4.7 [4.4, 4.9] mmol/L
							HbA1c: NS
							Pre: 37 [34, 50], Post: 37 [34, 37] mmol/mol
Zoon	2018	RYGB	n/a	41 ± 3	36 ± 4	~13.3 % [a]	n/a
Aldubaikhi	2020	RYGB	5 (35.7%)	44.1 ± 4.1	n/a	n/a	n/a
		OW-LCD	0 (0%)	29.5 ± 2.2 (26.2-33.4)	29.2 ± 2.4 (25.6-33.0)	gain 0.4 ± 2.8 %	n/a
		OW-NT	1 (9.1%)	36.8 ± 6.5 (26.5-46.4)	36.5 ± 6.2 (27-46)	gain 0.3 ± 2.0 %	n/a
Frank	2016	RYGB	12 (100%)	n/a	35.7 ± 2.9	~31.6 % [b] (Δ BMI -16.5 ± 5.3 kg/m²)	HbA1c: 7.1 ± 1.7 to 5.7 ± 0.6% (Δ 1.37 ± 1.7%) Sig. compared to control
		OB	12 (100%)	n/a	37.8 ± 4.8	n/a	n/a
Frank	2014	RYGB	n/a	n/a	27.1 ± 2.7	n/a	n/a
		OB	n/a	n/a	40.2 ± 2.7	n/a	n/a
		NW	n/a	n/a	21.4 ± 1.7	n/a	n/a
Goldman	2013	RYGB-MS	n/a	51.6 ± 11.2	30.4 ± 7.2	40.8 ± 8.2 %	n/a
		RYGB-LS	n/a	50.2 ± 5.4	38.2 ± 3.7	23.6 ± 6.5 %	n/a
Zoon	2018	RYGB	n/a	42 ± 4	36 ± 4	17 ± 3 kg	n/a
Wang	2016	RYGB-1mo	0 (0%) on T2DM meds	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
		RYGB-12mo	1 (0%) on T2DM meds	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
		NO-NT	0 (0%)	27.0 ± 2.2	n/a	n/a	n/a

Table 2.3 summary of clinical outcomes							
Author	**Year**	**Group**	**T2DM** n (%)	**Baseline BMI** mean ± SD (range)	**Current/Post-BMI** mean ± SD or median [IQR] (range) kg/m^2	**Weight loss** mean ± SD (range) % or kg	**Change in glycaemia**
Salem	2021	RYGB	16 (100%)	weight: 119.9 ± 6.1	weight: 107.7 ± 5.98	weight: -12.3 ± 0.89 (-10.42 ± 0.86%)	HbA1c: 53.9 ± 2.65 to 46.0 ± 1.97) NS
							fasting glucose: 8.37 ± 0.46 to 5.89 ± 0.25 (Δ-2.48 ± 0.44 mmol/L) NS
							fasting insulin: 19.52 ± 1.73 to 12.38 ± 1.40 (Δ -7.13 ± 1.82mIU/L) NS
		VLCD	19 (1005)	weight: 109.2 ± 4.98	weight: 100.8 ± 4.54	weight: -8.42 ± 0.66 (-7.66.42 ± 0.39%)	HbA1c: 53.1 ± 2.52 to 46.6 ± 2.1% NS
							fasting glucose: 7.64 ± 0.60 to 5.83 ± 0.25 (Δ -1.88 ± 0.50 mmol/L) NS
							fasting insulin: 16.23 ± 1.38 to 9.43 ± 0.84 (Δ -6.81 ± 1.15mIU/L) NS
VSG							
Li [m]	2019	VSG	n/a	38.1 ± 6.2	34.0 ± 6.1	~10.5 % [a]	n/a
		OB-NT	n/a	35.3 ± 4.4	35.1 ± 4.5	~1.0 % [a]	n/a
Hu [m]	2020	VSG	n/a	39.3 ± 4.8	34.7 ± 4.8	~11.2 % [a]	n/a
		OB-NT	n/a	36.9 ± 4.7	36.6 ± 4.7	~0.7 % [a]	n/a
Holsen [n]	2018	VSG	0 (0%)	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.
AGB							
Bruce [o]	2012	AGB	n/a	40.6 ± 2.0	36.1 ± 2.3	~11.0 % [b] (Δ -13.4 ± 5.4 kg)	n/a
Ness [o]	2014	AGB	n/a	42.0 ± 3.1	37.9 ± 3.0 [c]	~9.8 % [b c] (%EWL 25.0 ± 11.4 %)	n/a
			n/a		35.9 ± 3.5 [c]	~14.4 % [b c] (%EWL 36.5 ± 13.4 %)	n/a
Bruce [o]	2014	AGB	n/a	n/a	n/a	9.3 %	n/a
		LCD	n/a			10.8 %	n/a
MULTIPLE							
Scholtz [p]	2013	RYGB	3 (14.3%)	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
		AGB	0 (0%)	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%
		OW	2 (10.0%)	n/a	35.4 ± 1.9 (24.7-55.6)	n/a	n/a
Goldstone [p]	2015	RYGB	1 (14.3%)	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%

Table 2.3 summary of clinical outcomes							
Author	**Year**	**Group**	**T2DM** n (%)	**Baseline BMI** mean ± SD (range)	**Current/Post-BMI** mean ± SD or median [IQR] (range) kg/m^2	**Weight loss** mean ± SD (range) % or kg	**Change in glycaemia**
		AGB	0 (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	RYGB	0 (0%)	44.6 ± 4.3	n/a	23.6 ± 1.4 %	n/a
		VSG	0 (0%)	43.9 ± 4.1	n/a	21.3 ± 1.0 %	n/a
		OB-NT	0 (0%)	43.3 ± 4.4	n/a	gain 1.0 ± 0.6 %	n/a
Baboumian	2019	RYGB	0 (0%)	44.2 ± 4	35.1 ± 4	~20.6 % [b]	n/a
		VSG	0 (0%)	41.0 ± 3	32.1 ± 4	~21.7 % [b]	n/a
		LCD-CBT	0 (0%)	42.7 ± 4	37.5 ± 4	~12.2 % [b]	n/a
		OB-NT	0 (0%)	41.2 ± 3	40.4 ± 3	~1.9 % [b]	n/a
Smith	2020	RYGB	5 (21.7%)	44.6 ± 1.1	41.4 ± 1.0	7.1 ± 0.4 %	n/a
		VSG	5 (20.0%)	43.4 ± 0.1	40.6 ± 1.0	6.5 ± 0.4 %	n/a

Table 2.3 Summary of clinical outcomes

Footnotes: [a]: calculated from Δ average weight, [b]: calculated from Δ average BMI, [c]: no scan just time point for weight loss, [l-p]: probable overlapping datasets, [*]: duplicated data in error, **Δ:** change

Abbreviations: **CBT**: cognitive behavioural therapy, **FPG:** fasting plasma glucose**, LCD**: low-calorie diet, **NT**: no treatment, **NW**: normal weight (lean), **OB**: obesity, **OB-NT:** obesity no treatment, **OW**: overweight, **NO**: Non-obesity, **RYGB**: Roux-Y gastric bypass, **VSG**: Vertical sleeve gastrectomy, **AGB**: Adjusted gastric band, **o:** no change, **n/a:** not available, **RYGB-LS:** least successful < 50EWL, **RYGB-MS:** most successful > 50EWL, **mo:** months, **NS:** not significant

2.5.7 fMRI paradigms

Summary of the fMRI scanning protocols including task design for individual studies is given in **Table 2.4**.

For 21 studies assessing food cue reactivity, four studies involved passive viewing of food pictures and words (25, 33, 38, 153), nine studies passive viewing of food pictures only (20, 44, 46, 149-151, 156, 161, 163), four studies involved simultaneous food picture rating for appeal (16, 160, 162) or liking/wanting (159) during the fMRI session, and four studies involved other active tasks with food pictures, in which participants exercised different motivational tasks (e.g. crave or resist, regulate or enhance) (45, 134), inhibited a motor response in a Go-NoGo task (155), or performed a 1-back memory task (158).

In three gustatory fMRI studies, participants passively consumed a liquid tastant (20, 157) or actively rated intensity/pleasantness of tastants (154), while one olfactory study involved passive smelling of food odours (156).

2.5.8 Food stimulus type

Twenty-one studies used food pictures/words as a stimulus, which were generally described as high energy (HE) or low-energy (LE) **Table 2.4**. The majority, 16 (76.2%), of these studies used fMRI tasks that presented both HE and LE food stimuli separately (16, 20, 25, 38, 44, 46, 153, 155, 156, 158-163, 173), while one study included just HE foods (134), and four studies a mixture of HE and LE foods together in meals (158)(45, 46)(149-151). However, only seven of these studies (33.3%) reported the actual energy density of food pictures (16, 25, 33, 38, 153, 160, 162).

In the 21 studies reporting the effects of obesity surgery on food stimuli contrasts, 10 studies (47.6%) reported results for the HE food vs. LE food contrast (33, 38, 44, 46, 153, 156, 158, 159, 161, 162), 11 studies (55.0%) for HE food vs. non-food contrast (16, 20, 25, 33, 44, 46, 134, 155, 156, 158, 162), nine studies (45.0%) for LE food vs. non-food contrast (16, 25, 33, 44, 46, 155, 156, 158, 162), and 11 studies (52.4%) for any food (i.e. HE or LE food) vs. non-

food contrast (16, 20, 45, 149-151, 158-160, 162, 163).

A variety of control stimuli were used for contrasting BOLD responses with food pictures/words including office supplies (25, 38, 153, 173), plants and minerals (20), household or other non-food related objects (16, 134, 158, 160, 162, 163), animals (158)(45, 46)(149-151), rest baseline (44, 46, 155, 161, 163), or unspecified (156, 159).

The three gustatory fMRI studies used chocolate milk, or solutions with different concentrations of sucrose or fat (milk/cream mixtures) as tastants (20, 154, 157), and the olfactory fMRI study used high fat/sweet (chocolate and caramel) or vegetable (tomato and cucumber) odours (156) **Table 2.4**.

Only two studies, cross-sectionally comparing post-operative RYGB and ABG surgical groups, and BMI-matched unoperated controls, included a control non-food related fMRI task to confirm that obesity surgery or acute interventions had no non-specific effects on BOLD signal, for example by changing neurovascular coupling (16, 160).

Table 2.4 Summary of the fMRI scanning protocols including task design for individual studies

Author	Year	fMRI paradigm	fMRI task	Design	Tesla scanner	TR (sec)	Voxel size (mm^3) in-plane x slice thickness	Stimulus	Food categories	Non-food category	Control fMRI task for non-specific effects BOLD signal
RYGB											
Ochner [I]	2011	Pictures / spoken words	Passive	Block	1.5	4.00	1.5 x 1.5 x 4	HE, LE, NF	HE: 571 ± 219 kcal, 430 ± 140 kcal/100g (>350), 44.6 ± 6.8 fat (% kcal) e.g. pepperoni pizza, fudge sundae	Office supplies	o
									LE: 23 ± 11 kcal, 50 ± 10 kcal/100g (<100), 1.1 ±0.2 fat (% kcal) e.g. raw vegetables		
Ochner [I]	2012	Pictures / spoken words	Passive	Block	1.5	4.00	1.5 x 1.5 x 4	HE, LE, NF	HE: 571 ± 219 kcal, 430 ± 140 kcal/100g (>350), 44.6 ± 6.8 fat (% kcal) e.g. pepperoni pizza, fudge sundae	Office supplies	o
									LE: 23 ± 11 kcal, 50 ± 10 kcal/100g (<100), 1.1 ±0.2 fat (% kcal) e.g. raw vegetables		
Ochner [I]	2012	Pictures / spoken words	Passive	Block	1.5	4.00	1.5 x 1.5 x 4	HE, LE, NF	HE: 571 ± 219 kcal, 430 ± 140 kcal/100g (>350), 44.6 ± 6.8 fat (% kcal) e.g. pepperoni pizza, fudge sundae	Office supplies	o
									LE: 23 ± 11 kcal, 50 ± 10 kcal/100g (<100), 1.1 ±0.2 fat (% kcal) e.g. raw vegetables		
Ten Kulve	2017	Pictures	Passive	Block	3.0	2.16	3 x 3 x 3	HE, LE, NF	HE: sweet/savoury e.g. ice cream, chocolate chip cookies	Nature: shrubs, trees, flowers	o
									LE: fruit/vegetables e.g. fruit salad, salad, apples, strawberries		
		Gustatory	Passive	Event	3.0	2.16	3 x 3 x 3	HE, NF	chocolate milk	artificial saliva	
Zoon	2018	Pictures	Passive	Event	3.0	2.24	3 x 3 x 3	HE, LE, NF	HE: HF/HS	Rest	o
									LE: LF/LS		
		Odors	Passive	Event	3.0	2.24	3 x 3 x 3	HE, LE, NF	HE: HF/HS: chocolate caramel	Rest	o
									LE (LF/LS): cucumber, tomato		
Aldubaikhi	2020	Pictures	Appeal rating	Block	3.0	RYGB: 2.25	RYGB: 3 x 3 x 3	HE, LE, NF, blurred	HE: 834 ± 100 kCal, 321 ± 13 kCal/100g, 42 ± 2 % fat, 48 ± 1 % CHO, 10 ± 1 % protein	Objects	o

Table 2.4 Summary of the fMRI scanning protocols including task design for individual studies

Author	Year	fMRI paradigm	fMRI task	Design	Tesla scanner	TR (sec)	Voxel size (mm^3) in-plane x slice thickness	Stimulus	Food categories	Non-food category	Control fMRI task for non-specific effects BOLD signal
									e.g. sweet (cake, biscuits, panckakes etc.), savoury (burgers, pizza etc.) - 1/3 each		
			(5-point Likert scale)			OW-LCD/OW-NT: 3.00	OW-LCD/IW-NT: 2 x 2 x 3.25		LE: 157 ± 18 kCal, 64 ± 5 kCal/100g, 35 ± 3 % fat, 35 ± 3 % CHO, 29 ± 3% protein e.g. vegetables, salad, fish (no fruit)		
Frank	2016	Pictures	Wanting and Liking rating(5-point Likert scale)	n/a	3.0	2.00	3.3 x 3.3 x 3.2	HE, LE	n/a	n/a	o
Frank	2014	Pictures	1-back memory task	Block	1.5	2.00	3 x 3 x 4	HE, LE, NF	HE: sweet/savoury	Objects e.g. chair, umbrella,	o
			Passive button press (control)						LE e.g. salad, fruit, vegetables	toy, money, car, jewelry	
Goldman	2013	Pictures	Crave or Resist	Block	3.0	1.75	3 x 3 x 3	HE, NF	HE: sweet/savoury e.g. ice cream, cheese-burgers, pizza, potato chips	Varied e.g. snowman, pennies, stairs	o
Zoon	2018	Pictures	Go/No-Go task	Block	3.0	2.24	3 x 3 x 3	HE, LE	HE: dessert e.g. ice cream, cake, frozen yogurt,	Rest	o
									LE: vegetables e.g. corn, peas, Brussel sprouts, radishes,		
Wang	2016	Gustatory	Intensity and Pleasantness rating	Event	3.0	2.00	2.9 x 2.9 x 4	0.12mL Sucrose 0.01, 0.75 M	n/a	n/a	o
			(4-point Likert rating)					0.12mL NaCl 0.01, 0.15, 0.30 M			
Salem	2021		Passive	Block	3.0	2.3	1 x 1 x 1	HE, LE	HE: muffin, chocolate, LE: banana, apple	Objects	o
VSG											
Li [m]	2019	Pictures	Passive	Block	3.0	2.00	4 x 4 x 4	HE, LE, rest	n/a	Rest	o
Hu [m]	2020	Pictures	Passive	Block	3.0	2.00	4 x 4 x 4	HE, LE, rest	n/a	Rest	o
Holsen [n]	2018	Pictures	Enhance or Regulate	Event	3.0	2.00	3.1 x 3.1 x 3.1	HE/LE, NF, blurred	Varied (HE sweet and savoury, LE)	Animals	o
									savoury e.g. hamburgers, pizza, fries, chips		

Table 2.4 Summary of the fMRI scanning protocols including task design for individual studies

Author	Year	fMRI paradigm	fMRI task	Design	Tesla scanner	TR (sec)	Voxel size (mm^3) in-plane x slice thickness	Stimulus	Food categories	Non-food category	Control fMRI task for non-specific effects BOLD signal
AGB											
Bruce [o]	2012	Pictures	Passive	Block	3.0	3.00	3 x 3 x 3	HE/LE, NF, blurred	Varied (HE sweet and savoury, LE)	Animals	o
Ness [o]	2014	Pictures	Passive	Block	3.0	3.00	3 x 3 x 3	HE/LE, NF, blurred	Varied (HE sweet and savoury, LE)	Animals	o
Bruce [o]	2014	Pictures	Passive	Block	3.0	3.00	3 x 3 x 3	HE/LE, NF, blurred	Varied (HE sweet and savoury, LE)	Animals	o
MULTIPLE											
Scholtz [p]	2013	Pictures	Appeal rating	Block	3.0	3.00	2 x 2 x 3.25	HE, LE, NF, blurred	HE: 834 ± 100 kCal, 321 ± 13 kCal/100g, 42 ± 2 % fat, 48 ± 1 % CHO, 10 ± 1 % protein e.g. sweet (cake, biscuits, panckakes etc.), savoury (burgers, pizza etc.) - 1/3 each	Objects	Yes
			(5-point Likert scale)						LE: 157 ± 18 kCal, 64 ± 5 kCal/100g, 35 ± 3 % fat, 35 ± 3 % CHO, 29 ± 3% protein e.g. vegetables, salad, fish (no fruit)		
		Auditory-motor-visual (control)	Listening to story, pressing button,	Block							
			watching checkerboard								
Goldstone [p]	2015	Pictures	Appeal rating	Block	3.0	3.00	2 x 2 x 3.25	HE, LE, NF, blurred	HE: 834 ± 100 kCal, 321 ± 13 kCal/100g, 42 ± 2 % fat, 48 ± 1 % CHO, 10 ± 1 % protein e.g. sweet (cake, biscuits, panckakes etc.), savoury (burgers, pizza etc.) - 1/3 each	Objects	Yes
			(5-point Likert scale)						LE: 157 ± 18 kCal, 64 ± 5 kCal/100g, 35 ± 3 % fat, 35 ± 3 % CHO, 29 ± 3% protein e.g. vegetables, salad, fish (no fruit)		
Faulconbridge	2016	Pictures	Passive	Block	3.0	3.00	3.4 x 3.4 x 3	HE, LE, rest	HE, LE	Rest	o
Baboumian	2019	Pictures / spoken words	Passive	Block	1.5	4.00	1.5 x 1.5 x 4	HE, LE, NF	HE: 571 ± 219 kcal, 430 ± 140 kcal/100g (>350), 44.6 ± 6.8 fat (% kcal) e.g. pepperoni pizza, fudge sundae	Office supplies	o
									LE: 23 ± 11 kcal, 50 ± 10 kcal/100g (<100), 1.1 ±0.2 fat (% kcal) e.g. raw vegetables		
Smith	2020	Gustatory	Passive	Block	3.0	2.00	3 x 3 x 3	0.4mL HF, HS, preferred, tasteless	HF: cream 33% fat, 0% sucrose	Artificial saliva	o

Table 2.4 Summary of the fMRI scanning protocols including task design for individual studies											
Author	**Year**	**fMRI paradigm**	**fMRI task**	**Design**	**Tesla scanner**	**TR (sec)**	**Voxel size (mm^3) in-plane x slice thickness**	**Stimulus**	**Food categories**	**Non-food category**	**Control fMRI task for non-specific effects BOLD signal**
									HS: skimmed milk 0% fat, 20% sucrose		
									Preferred: chosen from 0, 10, 20% sucrose +		
									skimmed milk, whole milk, half-half, cream (0, 3.4, 10, 33% fat)		

Table 2.4 Summary of fMRI paradigms
Footnotes: [I-P]: probable overlapping datasets
Abbreviations: CHO: carbohydrate, **HE**: high-energy density, **HF:** high fat, **HP:** highly palatable, **HPC:** hippocampus, **HS:** high sugar, **LE:** low-energy density, **LF:** low fat, **LS:** low sugar, **NF:** non-food, **sec:** seconds, **n/a:** not available

2.5.9 Nutritional status

Study protocols of the individual studies are summarised in **Table 2.5**, including nutritional status.

In 10 studies, (43.5%) participants were scanned only after an overnight fast (16, 44-46, 154, 161-163), or after not eating for four hours (pre-meal) (157, 159); and in six studies (26.1%), participants were just scanned when fed, shortly (0.25-1.5 hours) after a standardised fixed liquid (25, 38, 158, 173) or solid (155, 156) meal.

In five studies (21.7%) participants were scanned in two nutritional states: fasted and fed (0.5-0.75 hours after meal) states (20, 153) or pre-meal (>4 hours from last meal) and fed (immediately after consuming a 500 kcal meal) states (149-151). In only one of these five studies, were the fasted and fed visits done on different days and randomised to control for order effects (153), 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 (149-151), while in the fifth study the fed session was always after the fasted session (20).

Table 2.5 Summary of study protocols (nutritional status) in individual studies									
Author	**Year**	**State Intervention**	**Nutritional state**	**Control feeding / intervention order effects**	**Meal**	**Macronutrients (% total kcal)**	**Time since last meal (h)**	**Menstrual cycle controlled**	**Mood assessment**
RYGB									
Ochner [l]	2011	n/a	Fed	n/a	250 kcal 250 ml liquid	fat 42.8%, CHO 40.0%, protein 18.1%	1	o	o
Ochner [l]	2012	n/a	Fed	n/a	250 kcal 250 ml liquid	fat 42.8%, CHO 40.0%, protein 18.1%	1	Yes	o
Ochner [l]	2012	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	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	2018	n/a	Fed	n/a	Pre: 570 kcal male, 421 kcal female	bread roll, margarine, cheese, ham, orange juice	0.25	o	o
					Post: 174 kcal male, 107 kcal female				
Aldubaikhi	2020	n/a	Fasted	n/a	n/a	n/a	n/a	Yes	Yes
Frank	2016	n/a	Pre-meal	n/a	n/a	n/a	≥ 3 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	2018	n/a	Fed	n/a	Pre: 570 kcal male, 421 kcal female	bread roll, margarine, cheese, ham, orange juice	0.25	o	o
					Post: 174 kcal male, 107 kcal female				
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 [m]	2019	n/a	Fasted	n/a	n/a	n/a	12	o	Yes
Hu [m]	2020	n/a	Fasted	n/a	n/a	n/a	12	n/a	Yes
Holsen [n]	2018	n/a	Pre-meal	o	n/a	n/a	≥ 4	o	Yes

Table 2.5 Summary of study protocols (nutritional status) in individual studies									
Author	**Year**	**State Intervention**	**Nutritional state**	**Control feeding / intervention order effects**	**Meal**	**Macronutrients (% total kcal)**	**Time since last meal (h)**	**Menstrual cycle controlled**	**Mood assessment**
AGB									
Bruce [o]	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 [o]	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 [o]	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 [p]	2013	n/a	Fasted	n/a	Usual supper	n/a	RYGB: 16.5 (16.0-17.3)	Yes	Yes
							AGB: 16.1 (15.6-16.7)	(1st 14 days)	
							Matching-BMI: 16.4 (15.7-17.0)		
Goldstone [p]	2015	n/a	Fasted	n/a	Usual supper	n/a	16.5 (16.0-17.3)	Yes	Yes
								(1st 14 days)	
Faulconbridge	2016	n/a	Fasted	n/a	n/a	n/a	overnight	o	o
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

Table 2.5 Summary of study protocols (nutritional status)

Footnotes: [l-p]: probable overlapping datasets

CHO: carbohydrate, **kcal:** kilocalorie. **BMI**: body mass index, **n/a:** not available, **HP:** highly palatable, **HPC:** hippocampus, **HS:** high sugar, **LE:** low-energy density, **LF:** low fat, **LS:** low sugar, **NF:** non-food, **sec:** seconds, **o:** no change, **RYGB**: Roux-Y gastric bypass, **AGB**: Adjusted gastric band, **GLP-1R:** glucagon-like-peptide 1 receptor, **Ex9-39:** Exendin

Confounding factors in study protocol

Only five studies (21.7%) mentioned that groups or visits were controlled for menstrual cycle, either by advance timetabling of the date that scanning was performed to a particular phase of the menstrual cycle (16, 25, 134, 160), or showing that there was no difference between groups in timing of untimetabled scan relative to menstrual cycle (162).

Only eight studies (36.4%) included an assessment of mood using questionnares or visual analogue scales (16, 44, 45, 134, 159-162). Only three of these studies, reported a decrease in anxiety (44) and depression (45) at 1 month and 12 months after VSG

Functional MRI analysis

Summary of the fMRI analysis methodology, including statistical approaches, for individual studies is given in **Table 2.6**.

A wide variety of different approaches were used between studies, including different fMRI processing and analysis software, statistical tests, method of correction for multiple comparisons, and inclusion of covariates such as demographics, BMI, eating behaviour, appetite or food hedonic ratings, motion parameres, tissue regressors etc.

The majority of studies, 18 (78.3%), included whole brain analysis (16, 25, 33, 38, 44, 134, 149-151, 153-156, 158, 159, 161-163).

Five (21.7%) studies used small volume correction analysis (20, 45, 149, 157, 158). Four studies (17.4%) used *a priori* regions of interest (ROIs), either functional ROIs from separate cohorts performing the same fMRI task (16, 160), the study participants including both surgical and control intervention groups for food or non-food pictures (163) or Neurosynth database (163), or anatomical ROIs (46, 163).

Out of the 23 studies, two studies (8.7%) used both whole brain and SVC analyses (149, 158), while three studies (13.0%) used both whole brain and functional ROI analysis (16, 162, 163).

Three studies (13.0%) also used significant functional ROIs from initial whole brain (155, 156) or SVC (149) analyses in subsequent correlation analyses with clinical or behavioural outcomes.

The two studies that reported task-based functional connectivity performed whole brain psychophysiological interaction (PPI) analysis with significant functional ROIs from the initial food cue reactivity task from whole brain analysis used as a seed (44, 161)

Out of the 21 studies using whole brain or SVC fMRI analyses, the majority, 18 (78.3%), reported results that included an appropriate correction method for multiple comparisons (16, 20, 25, 33, 38, 44, 45, 134, 149-151, 153, 157-159, 161-163), though three studies only included uncorrected results (154-156). In addition, three studies reported only uncorrected results in secondary correlation (38, 159) or interaction (158) whole brain or SVC analyses.

Twelve studies (52.2%) included a variety of different demographic, clinical or eating behaviour covariates in their fMRI analyses (16, 25, 33, 38, 44, 45, 134, 151, 153, 158, 159, 161) **Table 2.6**

Table 2.6 Summary of the fMRI analysis methodology, including statistical approaches, for individual studies

Author	Software	Analysis methodology	Statistical test	Statistical threshold	Multiple comp correction	Covariates	Motion confound parameter in GLM	Tissue signal regressors in GLM	Motion parameter results
RYGB									
Ochner [I] 2011	SPM5	Whole brain	Paired t-test	P<0.05 uncorr. vox >20	No	Δ BMI, Δ pre-scan fullness	o	o	o
				P<0.005 uncorr. vox>135 = P<0.05 corr. using Monte Carlo sim.	Yes				
Ochner [I] 2012	SPM8	Whole brain	Paired t-test	P<0.05 uncorr.	No	Δ BMI, Δ pre-scan fullness	o	o	o
				P<0.005 uncorr. vox >152 = P<0.05 corr. using Monte Carlo sim.	Yes				
		Whole brain	Linear correlation (vs. food ratings)	P<0.05 uncorr.	No	None	o	o	
				P<0.005 uncorr. vox >152 = P<0.05 corr. using Monte Carlo sim.	Yes				
Ochner [I] 2012	SPM5	Whole brain	Paired t-test	P<0.005 uncorr. vox >145 = P<0.05 corr.	Yes	Δ BMI, Δ pre-scan fullness	o	o	o
				using Monte Carlo sim.					
Ten Kulve 2017	SPM8	SVC	RMANOVA: visit (Pre/Post),	voxel P<0.001 uncorr.	No	None	o	o	o
			treatment (placebo/Ex9-39), state (fasted/fed)	voxel FWE P<0.05 corr.	Yes				
Zoon 2018	SPM12	Whole brain	Paired t-test	P<0.001 uncorr. vox ≥8	No	None	Yes	o	o
		Within study sig. fROI (mean)	Spearman correlation (vs. weight loss, food preference/ratings/bloods)	non-GLM: P<0.05	No	None			
Aldubaikhi 2020	FSL v5.0 FEAT v6.0	Whole brain	Paired t-test	voxel Z>2.3, then cluster FWE P<0.05 corr.	Yes	None	Yes	o	Yes
		Separate cohort fROI (median)	RMANOVA: visit (Pre/Post), food (HE/LE), fROIs	non-GLM: P<0.05	Yes	None			
			Groups (RYGB/OW-LCD/) analysed separately						
Frank 2016	SPM8	Whole brain	RMANOVA: group (post-RYGB/OB), task (wanting/liking), food (HE/LE)	voxel P<0.001 uncorr., then cluster FWE P<0.05	Yes	age, BMI, hunger	Yes	o	o
		Whole brain	Linear correlation (vs. glycaemic control)	P<0.01 uncorr.	No				
Frank 2014	SPM8	Whole brain, SVC (task)	RMANOVA: group (post-RYGB/OB/NW),	main effect group: voxel FWE P<0.05	Yes	age	Yes	o	o

Table 2.6 Summary of the fMRI analysis methodology, including statistical approaches, for individual studies

Author	Software	Analysis methodology	Statistical test	Statistical threshold	Multiple comp correction	Covariates	Motion confound parameter in GLM	Tissue signal regressors in GLM	Motion parameter results
			task (memory/control), food (HE/LE)	interaction effects: uncorr. P<0.001	No	age			
Goldman 2013	SPM8	Whole brain	Unpaired t-test	P<0.01 uncorr. vox >9, then cluster FDR P<0.05	Yes	None	Yes	o	o
		Whole brain	Linear correlation (vs. weight loss)	P<0.01 uncorr. vox >9, then cluster FDR P<0.05	Yes	Time since surgery			
Zoon 2018	SPM12	Whole brain	Paired t-test	P<0.001 uncorr. vox ≥8	No	None	Yes	o	o
		Within study sig. fROI (mean)	Linear correlation (vs. weight loss, appetite)	non-GLM: P<0.05	No	None			
Wang 2016	SPM8	Whole brain	Paired t-test	voxel P<0.001 uncorr. vox >15	No	Tastant concentration	o	o	o
Salem 2021	FSL v5.0.4 FEAT v6.0	Whole brain	Unpaired t-test (pre-VLCD vs. pre-RYGB)	Mixed effects cluster-wise Z>2.3, P<0.05	Yes	o	Yes	o	o
			Paired t-test (pre- vs. post for RYGB or VLCD)	Mixed effects cluster-wise Z>2.3, P<0.05	Yes	o			
			Paired t-test (pre- vs. post for RYGB or VLCD, weight matched sub-group)	Fixed effects cluster-wise Z>2.3, P<0.05	Yes	o			
		Within study fROI (reward) or Neurosynth fROI (executive control): HE/LE food or objects > rest pre/post-RYGB/VLCD	Unpaired t-test: RYGB (Post-Pre) vs. VLCD (Post-Pre)	P<0.05	o	o			
			Unpaired t-test: pre-RYGB vs. pre-VLCD	P<0.05	o	o			
			Paired t-test (pre- vs. post for RYGB or VLCD)	P<0.05	o	o			
			Linear regression: Δ (Post-Pre) vs. Δ gut hormones (Post-Pre)	P<0.05	o	o			
			Linear regression: Δ (Post-Pre) vs. Δ DEBQ-restraint (Post-Pre)	P<0.05	Yes	o			
		aROI (hypothalamus)	Linear regression: Δ (Post-Pre) vs. % weight loss	P<0.05	n/a	o			
VSG									
Li [m] 2019	SPM12	Whole brain	RMANOVA: group (VSG/OB),	voxel P<0.001 uncorr. vox ≥100,	Yes	None	Yes	o	o
			visit (Pre/Post), food (HE/LE)	then cluster FWE P<0.05 corr.					

Table 2.6 Summary of the fMRI analysis methodology, including statistical approaches, for individual studies

Author	Software	Analysis methodology	Statistical test	Statistical threshold	Multiple comp correction	Covariates	Motion confound parameter in GLM	Tissue signal regressors in GLM	Motion parameter results
		Within study sig. fROI (peak voxel)	Partial linear correlation (vs. weight loss, eating behaviour, food rating, bloods)	non-GLM: P<0.05 Bonferroni corr.	Yes	age, sex			
		from group x visit interaction food cue reactivity							
Hu [m] 2020	SPM12	Whole brain	RMANOVA: group (RYGB/OB),	voxel P<0.001 uncorr. vox ≥50, then cluster FWE P<0.05 corr.	Yes	None	Yes	o	o
			visit (Pre/Post), food (HE/LE)						
Holsen [n] 2018	SPM8	SVC	Paired t-test	voxel P<0.05 uncorr. vox >6, then voxel FWE P<0.05 corr.	Yes	HP food desire to eat rating	Yes	o	o
						(Enhance - Regulate)			
		SVC	Linear correlation (vs. weight loss)	voxel P<0.05 uncorr. vox >6, then voxel FWE P<0.05 corr.	Yes	HP food desire to eat rating			
						(Enhance - Regulate)			
AGB									
Bruce [o] 2012	BrainVoyager QX	Whole brain	RMANOVA: visit (Pre/Post), stimulus (food/NF)	voxel P<0.001 uncorr. vox ≥3 (SVC)	No	None	o	o	o
		SVC	States (Pre-meal/Fed) analysed separately	voxel FDR P<0.05 (whole brain)	Yes				
		Within study sig. fROI (peak voxel)	Linear correlation (vs. weight loss, eating behaviour)	non-GLM: P<0.05 uncorr.	No	None			
Ness [o] 2014	BrainVoyager QX	Whole brain	Linear correlation (vs. weight loss)	voxel P<0.01 uncorr., then cluster FWE P<0.05 corr.	Yes	± age	o	o	o
Bruce [o] 2014	BrainVoyager QX	Whole brain	RMANOVA: group (AGB/LCD), visit (Pre/Post),	P<0.01 uncorr. vox >7,	Yes	None	o	o	o
			stimulus (Food/NF)	= cluster P<0.05 corr. using Monte Carlo sim.					
			States (Pre-meal/Fed) analysed separately						
MULTIPLE									
Scholtz [p] 2013	FSL v4.1, FEAT v5.98	Whole brain	Unpaired t-test	Z>2.1, then cluster FWE P<0.05	Yes	age, sex, BMI	Yes	o	Yes (no group effect)

Table 2.6 Summary of the fMRI analysis methodology, including statistical approaches, for individual studies									
Author	**Software**	**Analysis methodology**	**Statistical test**	**Statistical threshold**	**Multiple comp correction**	**Covariates**	**Motion confound parameter in GLM**	**Tissue signal regressors in GLM**	**Motion parameter results**
		separate cohort fROI (median)	ANCOVA: group (RYGB/AGB/OW)	non-GLM: P<0.05	No	age, sex, BMI			
		separate cohort fROI (median)	Pearson or Spearman correlation (vs. food rating, bloods, dumping)	non-GLM: P<0.05	No	age, sex, BMI			
Goldstone [p] 2015	FSL v4.1, FEAT v5.98	separate cohort fROI (median)	RMANOVA: treatment (Octreotide/Saline), food (HE/LE),	non-GLM: P<0.05 univariate	No	None	Yes	o	Yes
			fROI (NAcc, Caudate, Amygdala, OFC, Anterior insula) ± group (RYGB/AGB)	non-GLM: P<0.05 multivariate	Yes				(no group or treatment effect)
		separate cohort fROI (median)	Pearson correlation (vs. bloods)	non-GLM: P<0.05	No	None			
Faulconbridge 2016	FSL	aROI (mean)	RMANOVA: visit (Pre/Post), stimulus (HE/LE),	non-GLM: Holm's procedure P≤0.025	Yes	None	o	o	o
		aROI (mean)	Spearman correlation (vs. food rating, bloods)	non-GLM: P<0.05	No	None			
Baboumian 2019	SPM8	Whole brain	RMANOVA: visit (Pre/Post), condition (visual/auditory),	voxel P<0.001 uncorr. vox >29,	Yes	age, sex, Pre-BMI, Δ BMI (Post-Pre),	Yes	WM, CSF	o
			group (RYGB/VSG/LCD-CBT/OB-NT)	= cluster Monte Carlo sim. P<0.05 corr.		Pre-hunger, Δ hunger (Post-Pre), BED			
		Whole brain	Linear correlation (vs. bloods)	voxel P<0.001 uncorr. vox >10	No	Pre-hunger, Δ hunger (Post-Pre)			
Smith 2020	SPM12	SVC	Linear correlation (vs. weight loss)	?voxel FWE P<0.05 corr.	Yes	None	Yes	global	o

Table 2.6 Summary of the fMRI analysis methodology, including statistical approaches, for individual studies
Footnotes: [l-p]: probable overlapping datasets, **Δ:** change
Abbreviations: aROI: anatomical region of interest, **BMI:** body mass index, **comp.:** comparison, **CSF:** cerebrospinal flow, **DPARSFA:** Data Processing Assistant for Resting-State fMRI Advanced: rfmri.org/DPARSF, **DTI:** diffusion tensor imaging, **fALFF**: fractional amplitude of low-frequency fluctuation, **FDR:** false discovery rate, **FEAT:** fMRI Expert Analysis Tool, **FNC:** functional network connectivity, **fROI**: functional region of interest, **FSL:** FMRIB Software Library: www.fmrib.ox.ac.uk/fsl, **FEW:** family wise error, **GLM:** general linear model**,** **SVC:** small volume correction, **SPM:** statistical parametric mapping www.fil.ion.ucl.ac.uk/spm/, , **RMANOVE:** repeated measure ANOVA, **OFC:** orbitofrontal cortex, **RYGB**: Roux-Y gastric bypass, **AGB**: Adjusted gastric band, **VLCD:** very low calorie diet, **LCD:** low calorie diet, **uncorr.:** uncorrected statistics, **OB-NT**: obesity no treatment, **HE:** high energy density, **LE:** low energy density, **WM:** white matter.

2.5.10 Changes in food cue reactivity and taste/smell responses with obesity surgery

Unless specified otherwise, to save space the reported results are for passively viewing food pictures, and are significant when correcting for multiple comparisons from whole brain 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, including ventral and dorsal striatum, amygdala, hippocampus, parahippocampal gyrus, insula, ACC, paracingulate gyrus, OFC, dlPFC ('highlighted regions'), though results from all brain regions are included in the relevant tables **Table 2.7**

2.5.10.1 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) (20). However, these effects were not seen in the *fed state* (20).

In two longitudinal studies in the *fasted state,* (i) no change in BOLD signal during evaluation of HE/LE food pictures was seen ~14 weeks after surgery (n=14), nor in groups with obesity receiving a low-calorie diet, or overweight receiving no treatment (n=10-11) (162), while (ii) 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, amydala, 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) (163),

In two cross-sectional studies, (i) 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 compared to unoperated group with obesity *in pre-meal state* (n=12) (159); (ii) but no differences in BOLD signal to HE/LE foods using uncorrected statistics were seen in our highlighted regions >1 year after RYGB surgery (n=9) compared to unoperated group with obesity or normal weight group *in fed state* (158).

Commented [TG3]: Check no dlPFC or ACC when mention FP

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) (25). However, no changes in BOLD signal were reported in any of our highlighted regions in the other three longitudinal studies: (i) by the same group with identical protocol at 1 month after RYGB surgery (n=10) (33), (ii) in SVC analysis with food pictures at 1 month after RYGB surgery (n=10) including caudate, putamen, amygdala, insula, operculum and OFC (20), and (iii) in whole brain analysis at 3 months after RYGB surgery (n=19) (156).

In three 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) (20), and (ii) decreased in amygdala (but not NAcc, caudate, putamen, anterior insula, OFC) (n=14) during evaluation of HE food and LE food pictures using fROIs analysis at 14 weeks post RYGB, but not in groups with overweight receiving LCD or no treatment (n=10-11) (162) (iii) decreased at 6 months after RYGB surgery in VTA but not in NAcc, amygdala, hippocampus, insula, ACC, OFC or hypothalamus using aROI analysis (n=22) (46).

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 (16)

High-energy vs. low-energy food contrast: In four 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) (33); but (ii) did not change in a similar but smaller study (n=5) by the same group again at 1 month after RYGB (153); (iii) did not change for HE vs. LE food pictures or odours at 3 months after RYGB surgery in a larger study (n=19) (156); but (iv) 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 (38). 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 (38),

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) (159), nor >1 year after surgery *in fed state* in a food picture memory task (n=9) (158).

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) (153). This suggests that the effects of RYGB surgery on HE food cue reactivity may be greater in the fasted than fed state. Although in the *fasted* state, no change in BOLD signal to HE vs. LE foods was seen ~14 weeks after RYGB surgery in whole brain analysis, a reduction in BOLD signal during evaluation of HE vs. LE foods was seen when averaged across all reward system functional ROIs, and individually in the putamen and caudate (but not NAcc, amygdala, anterior insula nor OFC) (n=14), nor in control groups with overweight receiving LCD or no treatment (n=10-11) (162). 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 functional ROIs (46).

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 (but with a trend for decrease in insula, ACC, paracingulate gyrus, and frontal regions using uncorrected statistics) (n=10-14) (25, 33), nor at later time 3 months after RYGB surgery (n=19) (156)

In two longitudinal studies in the *fasted state*, BOLD signal to LE food (i) increased, during evaluation, in NAcc and caudate at ~14 weeks after RYGB surgery in functional ROI analysis (but not putamen, amygdala, anterior insula, OFC) (n=14) (162), and (ii) increased in the VTA (but not NAcc, thalamus, amygdala, hippocampus, hypothalamus, insula, ACC, OFC, prefrontal cortex) at ~6 months after RYGB surgery using anatomical ROIs (n=22) (46).

In a cross-sectional study in *the fasted state,* BOLD signal during evaluation of LE food was not different in those on average 8 months after RYGB surgery compared to a BMI-matched control group in either whole brain or fROI analysis (NAcc, caudate, amygdala, anterior insula, OFC) (n=20-21) {Scholtz, 2014 #15571.

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, 2018 #17707}, nor sweet taste 1 month or 12 months after RYGB surgery in the *fasted* state and during intensity and pleasantness evaluation (n=6) (154), but a decrease in BOLD signal for chocolate taste was seen 1 month after RYGB surgery in the *fasted* state in anterior insula using SVC (but not caudate, putamen, amygdala, OFC) using SVC analysis (n=10) (20).

2.5.10.2 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) (44, 161), while BOLD signal to HE vs. LE food pictures did not change at ~6 months after VSG surgery in any anatomical ROIs (VTA, NAcc, thalamus,

amygdala, hippocampus, hypothalamus, insula, ACC, OFC, prefrontal cortex) (n=22) (46).

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) (38). Furthermore, in 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 (38).

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) (44). 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) (45)

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) (44).

2.5.10.3 AGB 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 AGB surgery, but not in the *fed* state (n=10) (149). 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 AGB surgery (n=10) (149).

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 AGB surgery compared to unoperated BMI-matched control using fROI analysis (NAcc, caudate, amygdala, OFC, anterior insula) (n=20-21) (16).

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 AGB surgery compared to unoperated BMI-matched control using fROI analysis (NAcc, caudate, amygdala, OFC, anterior insula) (n=20-21) (16).

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 AGB surgery compared to unoperated BMI-matched control using fROI analysis (NAcc, caudate, amygdala, OFC, anterior insula) (n=20-21) (16).

2.5.10.4 Comparison of RYGB with AGB surgery

High-energy or low-energy food vs. non-food contrast: In a cross-sectional study comparing patients after RYGB and AGB surgery in the *fasted* state, BOLD signal during valuation of HE or LE food pictures was lower in the NAcc, caudate, putamen, subcallosal cortex, OFC in patients on average 8-9 months after RYGB than after AGB surgery (despite groups being of similar BMI), and using fROI analysis was lower in average of all reward system fROIs, and in amygdala and OFC indivdually (but not NAcc, caudate, anterior insula) (n=20-21) (16).

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 AGB 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) (16).

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 AGB surgery, but not in any

regions using fROI analysis (NAcc, caudate, amygdala, OFC, anterior insula, or average of all fROIs) (n=20-21) (16).

2.5.10.5 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) (38). In another longitudinal study in the *fasted* state, BOLD signal to HE vs. LE food pictures decreased in VTA ~6 months after RYGB surgery but not after VSG surgery, though no direct statistical comparison was made between the two surgical groups, and with no change in either group in the other anatomical ROIs (NAcc, thalamus, amygdala, hippocampus, hypothalamus, insula, ACC, OFC, prefrontal cortex) (n=18-22) (46).

2.5.11 Functional connectivity studies

Two longitudinal VSG studies with overlapping datasets, examined functional connectivity during the fMRI food picture task using whole brain psychophysiological interaction (PPI) from dlPFC seed voxels representing the region showing significant changes in BOLD signal for HE vs.LE food picture contrast after VSG surgery (44, 161). In *the fasted state,* functional connectivity for HE vs. LE food contrast increased between dlPFC and vACC at 1 month after VSG surgery (n=22-28) (44, 161), with the increase in functional connectivity positively correlated with the decrease in BMI (161).

Table 2.7 Summary of results for food cue reactivity from individual studies

Author	fMRI paradigm	Method	Nutr status	Group effect	Task contrast	Food contrast	seed for FC	ave all ROIs	NAcc /VS	Caud.	Put.	Amy.	Hippo.	PHG	VTA	Insu.	Oper	Precuneus	PCC	ACC	Paracingulate gyrus	Frontal pole	dlPFC	IFG	MFG	SFG	OFC	Pre/ post CG	Fusiform gyrus
RYGB																													
Ochner[1] 2011	Pic. / word	WB	Fed	Pre-RYGB	n/a	HE>LE	n/a		o	[↑]	o	o	o	o	o	o	o	o	o	[↑]	o	o	o	[↑] BA45	[↑]	[↑]	o	o	o
				Post-RYGB		HE>LE			o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
				Post- vs. Pre-RYGB		HE>LE			↓	o	o	o	o	o	[↓]	o	o	↓	[↓] y -52 BA23	↓ y 2 BA24 [↓] y 38 , y 32 BA32	o	*↓ BA9/8 /45 & [↓] BA10#	↓ BA9/8/45	↓ BA45	↓ BA8#	[↓] BA10#	o	Pre [↓]	o
				Post- vs. Pre-RYGB		HE>NF			o	o	o	o	o	o	o	o	o	[↓]	o	o	o	o	o	o	o	o	o	o	o
				Post- vs. Pre-RYGB		LE>NF			o	o	o	o	o	o	o	[↓] ant y 26	o	o	o	o	o	o	o	o	o	o	o	o	o
Ochner[1] 2012	Pic. / word	WB	Fed	Pre vs. Post-RYGB	n/a	HE>NF	n/a		o	o	↓	o	o	o	o	o	o	↓	↓ y -36 BA??	o	o	o	o	↓ BA6	↓ BA44#	o	o	Pre ↓ #	o
						LE>NF			o	o	o	o	o	o	o	o	o	o	o	[↓] y 46 BA10 /32	[↓] BA8/ 10#	o	o	o	o	[↓] BA6	o	o	o
Ochner[1] 2012	Pic. / word	WB	Fast	Post- vs. Pre-RYGB	n/a	HE>LE	n/a		o	o	o	o	o	o	o	↓ ant y 8	o	↓	o	o	o	↓ R 10,60, 20 L BA10 # (MFG Cluster)	↓	o	↓ R BA6#, L BA6	↓ R	o	Pre ↓# R BA6 L BA6	o
			Fed	Post- vs. Pre-RYGB		HE>LE			o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
			Fast vs. Fed	Pre-RYGB		HE>LE			o	o	o	o	o	o	o	o	o	↑	o	o	o	o	o	o	[↑] BA6#	[↑] BA8	o	o	o
			Fast vs. Fed	Post-RYGB		HE>LE			o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
Ten Kulve 2017	Pic.	SVC	Fast: Plac.	Post- vs. Pre-RYGB	n/a	HE>NF	n/a			↓	o	o				o	(↓) rol					↓ BA10#					↓ BA10		
						HE/LE> NF				↓	o	o				o	↓ rol											o		
			Fed: Plac.	Post- vs. Pre-RYGB		HE>NF				o	o	o				o	o											o		
						HE/LE> NF				o	o	o				o	o											o		
Zoon 2018	Pic.	WB	Fed	Post- vs. Pre-RYGB	n/a	HE>LE	n/a		o	o	o	o	o	o	o	o	o	[↓]	o	o	o	o	o	o	o	o	o	o	o
						HE>NF			o	o	o	o	o	o	o	o	o	[↑]	o	o	o	o	o	o	o	o	o	o	o
						HE > rest			o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o

Table 2.7 Summary of results for food cue reactivity from individual studies

Author	fMRI paradigm	Method	Nutr status	Group effect	Task contrast	Food contrast	seed for FC	ave all ROIs	NAcc /VS	Caud.	Put.	Amy.	Hippo.	PHG	VTA	Insu.	Oper	Precuneus	PCC	ACC	Paracingulate gyrus	Frontal pole	dlPFC	IFG	MFG	SFG	OFC	Pre/ post CG	Fusiform gyrus
						LE>NF			o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
						LE > rest			o	o	o	o	o	o	o	o	o	o	o	o	o	[↑] BA10[#]	o	o	o	[↑] BA10	o	o	o
						NF > rest			o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
Aldubaikhi 2020	Pic.	WB	Fast	RYGB: Post vs. Pre	n/a	HE>LE	n/a		o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
						HE>NF			o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
						LE>NF			o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
						HE/LE> NF			o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
		fROI	Fast	RYGB: Post vs. Pre		HE>LE		o	o	o	o	o				o ant											o		
						HE>NF		o	o	o	o	↓				o ant											o		
						LE>NF		o	↑	↑	o	o				o ant											o		
				Pre-RYGB		HE>LE		↑	o	o	o	o				o ant											o		
				Post-RYGB		HE>LE		o	o	o	o	o				o ant											o		
		WB	Fast	OW-LCD: Post vs. Pre	n/a	HE>LE			o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
						HE>NF			o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
						LE>NF			o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
						HE/LE> NF			o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
		fROI	Fast	OW-LCD: Post vs. Pre		HE>LE		o	o	o	o	o				o ant											o		
						HE>NF		o	o	o	o	↓				o ant											o		
						LE>NF		o	o	o	o	o				o ant											o		
				Pre-OW-LCD		HE>LE		o	o	o	o	o				o ant											o		

Table 2.7 Summary of results for food cue reactivity from individual studies

Author	fMRI paradigm	Method	Nutr status	Group effect	Task contrast	Food contrast	seed for FC	ave all ROIs	NAcc /VS	Caud.	Put.	Amy.	Hippo.	PHG	VTA	Insu.	Oper	Precuneus	PCC	ACC	Paracingulate gyrus	Frontal pole	dlPFC	IFG	MFG	SFG	OFC	Pre/ post CG	Fusiform gyrus
				Post-OW-LCD		HE>LE		o	o	o	o	o				o ant											o		
Faulconbridge [w] 2016	Pic.	aROI [f]	Fast	Post- vs. Pre-RYGB	n/a	HE>LE			o			o	o		↓	o				o							o		
				Post- vs. Pre-RYGB		HE > Rest			o			o	o		↓	o				o							o		
				Post- vs. Pre-RYGB		LE > Rest			o			o	o		↑	o				o							o		
Baboumian [w] 2019	Pic. / word	WB	Fed	Post- vs. Pre-RYGB	visual/auditory	HE>LE			o	o	o	o	o	↓	o	o	o	o	o	o	o	o	↑ BA9	o	o	o	o	o	↓
				Δ RYGB (Post-Pre) vs. Δ OB-LCD/CBT (Post-Pre)		HE>LE			o	o	o	o	o	↓	o	o	o	o	o	o	o	o	↑ BA9	o	o	o	o	o	↓
				Δ RYGB (Post-Pre) vs. Δ OB-NT (Post-Pre)		HE>LE			o	o	o	o	o	↓	o	o	o	o	o	o	o	o	↑ BA9	o	o	o	o	o	↓
Frank 2016	Pic.	WB	Pre-meal	group x food: Post-RYGB vs. OB	wanting/liking	HE>LE	n/a		o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
				main effect group: Post-RYGB vs. OB	wanting/liking	HE/LE> NF			o	o	o	o	↑	o	o	↑ ant	↑ rol	↓	o	↑ y 23 BA8	o	↑ BA46* ↓ BA9*	↑* BA46	↓ BA9* [BA46*]	↑ BA46* ↓* BA9	o	o	Pre/ post ↑	↑
				group x task: Post-RYGB vs. OB	wanting > liking	HE/LE> NF			o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
Frank 2014	Pic.	WB	Fed	group x food: Post-RYGB vs. OB	memory/control	HE>LE	n/a		o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
		SVC				HE>LE			o	o	o												o						
						LE>NF			o	o	o												o						[↓]
		WB		main effect group: Post-RYGB vs. OB	memory/control	HE/LE> NF			o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	↓
		SVC				HE/LE> NF			o	o	o												o						
		WB		group x task: Post RYGB vs. OB	memory > control	HE/LE> NF			o	o	o	o	[↓]	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
		SVC				HE/LE> NF			o	o	o												o						
		WB		group x food: Post-RYGB vs. NW	memory/control	HE>LE			o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
		SVC				HE>LE			o	o	o												o						
		WB		main effect group: Post-RYGB vs. NW	memory/control	HE/LE> NF			o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
		SVC				HE/LE> NF			o	o	o												o						

Table 2.7 Summary of results for food cue reactivity from individual studies

Author	fMRI paradigm	Method	Nutr status	Group effect	Task contrast	Food contrast	seed for FC	ave all ROIs	NAcc /VS	Caud.	Put.	Amy.	Hippo.	PHG	VTA	Insu.	Oper	Precuneus	PCC	ACC	Paracingulate gyrus	Frontal pole	dlPFC	IFG	MFG	SFG	OFC	Pre/ post CG	Fusiform gyrus
		WB		group x task: Post RYGB vs. NW	memory > control	HE/LE> NF			o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
		SVC				HE/LE> NF			o	o	o												o							
		WB		group x food: OB vs. NW	memory/control	HE>LE			o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
		SVC				HE>LE			o	o	o												o							
		WB		main effect group: OB vs. NW	memory/control	HE/LE> NF			o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	↑
		SVC				HE/LE> NF			o	o	o												o							
		WB		group x task: OB vs. NW	memory > control	HE/LE> NF			o	o	o	o	[↑]	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
		SVC				HE/LE> NF			o	o	o												o							
Goldman 2013	Pic.	WB	Pre-meal	RYGB-MS/LS	Crave	HE>NF	n/a		o	[↑]	o	o	o	o	o	↑ ant y 2	o	↓	o	o	↑ BA6/8 #	o	o	o	↑ BA6	↑ BA6/8	o	o	o
				RYGB-MS vs. RYGB-LS	Crave	HE>NF			o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
				RYGB-MS/LS	Resist	HE >NF			o	o	o	o	o	o	o	↑ ant y 14, ↓ post y -52	o	↓	o	o	↑BA 6/9 #	o	o	↑ BA 9/10 /13	↑ BA9/10 /13	↑ BA6/9	o	o	o
				RYGB-MS vs. RYGB-LS	Resist	HE >NF			o	o	o	o	o	o	o	o	o	o	o	o	o	[↑]# BA9	[↑] BA9	o	[↑] BA9	[↑] BA9	o	o	o
Scholtz [pw] 2013	Pic.	sep. cohort fROIs #	Fast	RYGB vs. OW		HE>NF		o #	o	o		o				o ant											o		
				RYGB vs. OW		LE>NF		o #	o	o		o				o ant											o		
				RYGB vs. OW		HE/LE >NF		o #	o	o		↓				o ant											o		
Zoon 2018	Pic.	WB	Fed	Post- vs. Pre-RYGB	no-go > rest	HE	n/a		o	o	o	o	o	o	o	o	[↑] inf frontal	o	[↑] y -27 BA23	o	o	'[↑] BA10# [↑] BA9#	[↑] BA9	[↑] BA9	[↑] BA10#	med [↑] BA9#	o	o	o
						LE			o	o	o	o	o	[↓]	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
Wang 2016	Gustatory	WB	Fast	1 mo Post- vs. Pre-RYGB	n/a	Sweet > ?Rinse	n/a		o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	[↓] BA1 1/47#	o	o
				12 mo Post- vs. Pre-RYGB		Sweet > ?Rinse			o	o	o	o	o	o	o	o	o	o	o	o	o	[↓] BA10#	o	o	o	o	o	o	o
				1 mo Post- vs. Pre-NW-NT		Sweet > ?Rinse			[↓]	o	o	o	o	[↓]	o	o	o	o	o	o	o	o	o	o	o	o	[↓] BA1 1/47#	o	o

Table 2.7 Summary of results for food cue reactivity from individual studies

Author	fMRI paradigm	Method	Nutr status	Group effect	Task contrast	Food contrast	seed for FC	ave all ROIs	NAcc /VS	Caud.	Put.	Amy.	Hippo.	PHG	VTA	Insu.	Oper	Precu neus	PCC	ACC	Paracingulate gyrus	Frontal pole	dlPFC	IFG	MFG	SFG	OFC	Pre/ post CG	Fusiform gyrus
				1 mo Post- vs. Pre-RYGB		Salt > ?Rinse			[↑]	[↑]	o	[↑]	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
				12 mo Post- vs. Pre-RYGB		Salt > ?Rinse			[↑]	[↑]	o	[↑]	o	o	o	[↑] ant/post	o	o	o	o	o	o	o	o	o	o	o	o	o	o
				1 mo Post- vs. Pre-NW-NT		Salt > ?Rinse			o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
Ten Kulve 2017	Gust	SVC	Fast: Plac.	Post- vs. Pre-RYGB	n/a	chocolate > tasteless	n/a			o	o	o				↓ y 2	o										o		
			Fast: Ex9-39 - Plac.	visit x treatment: Post- vs. Pre-RYGB		chocolate > tasteless				o	o	o				↑ y -7	o										o		
			Fast: Ex9-39 - Plac.	visit x treatment: Pre-RYGB		chocolate > tasteless				o	o	o				↓ y -7	o										o		
			Fast: Ex9-39 - Plac.	visit x treatment: Post-RYGB		chocolate > tasteless				o	o	o				↑ y -7	o										o		
Zoon 2018	Odor	WB	Fed	Post- vs. Pre-RYGB	n/a	HE>LE	n/a		o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
						HE>NF			o	o	o	o	o	o	o	o	o	o	o	o	o	[↓] -21 63 3 BA10[#]	o	o	o	[↓] BA10[#]	o	o	o
						HE > rest			o	o	o	o	o	o	o	o	o	[↑]	o	o	o	o	o	o	o	o	o	o	o
						LE>NF			o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
						LE > rest			o	o	o	o	o	o	o	o	o	[↑]	o	o	o	o	o	o	o	o	o	o	o
						NF > rest			o	o	o	o	o	o	o	o	o	[↑]	o	o	o	o	o	o	o	o	o	o	o
Salem 2021	Pic.	WB	Fast	Pre-RYGB vs. Pre-VLCD	n/a	HE/LE> NF		o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
				Post-RYGB vs. Post-VLCD		HE/LE> NF		o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
				Post-RYGB vs. Post-VLCD (wt loss matched, n=7 fixed effects)		HE/LE> NF		o	o	o	o	o	o	o	o	o	o	o	↓ cingulate not specified	o	o	o	o	o	o	↓	o	o	o
		fROI (reward)		Post- vs. Pre-RYGB		HE/LE > rest		o	o	o					o														
				Post- vs. Pre-VCLD		HE/LE > rest		o	o	o					o														
				RYGB (Post-Pre) vs. VLCD (Post-Pre)		HE/LE > rest	[↓]	o	o	o					o														

Table 2.7 Summary of results for food cue reactivity from individual studies

Author	fMRI paradigm	Method	Nutr status	Group effect	Task contrast	Food contrast	seed for FC	ave all ROIs	NAcc /VS	Caud.	Put.	Amy.	Hippo.	PHG	VTA	Insu.	Oper	Precuneus	PCC	ACC	Paracingulate gyrus	Frontal pole	dlPFC	IFG	MFG	SFG	OFC	Pre/ post CG	Fusiform gyrus
				RYGB (Post-Pre) vs. VLCD (Post-Pre): wt loss matched, n=7		HE/LE > rest	[↓]	[↓]	o	[↓]					o														
				Pre-RYGB vs. Pre-VLCD		HE/LE > rest		o	o	o					o														
		aROI		RYGB (Post-Pre) vs. VLCD (Post-Pre)		HE/LE > rest																							
		fROI (executive control)		Post- vs. Pre-RYGB		HE/LE > rest	o					o			o					o				o		o			
				Post- vs. Pre-VCLD		HE/LE > rest	o					o			o					o				o		o			
				RYGB (Post-Pre) vs. VLCD (Post-Pre)		HE/LE > rest	[↓]					o			o					o				o		o			
		fROI (reward/executive control)		Δ RYGB (Post-Pre): corr. vs. Δ fasting ghrelin, GLP-1, PYY, GIP (Post-Pre)		HE/LE > rest		o	o			o			o													
				Δ VLCD (Post-Pre): corr. vs. Δ fasting ghrelin, GLP-1, PYY, GIP (Post-Pre)		HE/LE > rest		o	o			o			o													
		fROI (reward/executive control)		Δ RYGB (Post-Pre): corr. vs. Δ DEBQ-restraint (Post-Pre)		HE/LE > rest		o	o	o		o			o					o						o			
				Δ VLCD (Post-Pre): corr. vs. Δ DEBQ-restraint (Post-Pre)		HE/LE > rest		o	+ve	o		o			o					+ve						o			
		aROI		Δ RYGB (Post-Pre): corr. vs. Δ weight loss		HE/LE > rest								-ve															
				Δ LVCD (Post-Pre): corr. vs. Δ weight loss		HE/LE > rest								o															
VSG																													
Li [n] 2019	Pic.	WB	Fast	group x visit: Post- vs. Pre-VSG	n/a	HE>LE	n/a		o	o	o	o	o	o	o	o	o	o	o	o	o	o	↓ BA9/46	o	o	o	o	o	o
				group x visit: Post- vs. Pre-VSG		HE > rest			o	o	o	o	o	o	o	o	o	o	o	o	o	o	↓ BA 9/46	o	o	o	o	o	o
				group x visit: Post- vs. Pre-VSG		LE > rest			o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
				group x visit: Post- vs. Pre-OB-NT		HE>LE			o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
				group x visit: Post- vs. Pre-OB-NT		HE > rest			o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o

Table 2.7 Summary of results for food cue reactivity from individual studies

Author	fMRI paradigm	Method	Nutr status	Group effect	Task contrast	Food contrast	seed for FC	ave all ROIs	NAcc /VS	Caud.	Put.	Amy.	Hippo.	PHG	VTA	Insu.	Oper	Precuneus	PCC	ACC	Paracingulate gyrus	Frontal pole	dlPFC	IFG	MFG	SFG	OFC	Pre/ post CG	Fusiform gyrus
				group x visit: Post- vs. Pre-OB-NT		LE > rest			o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
				group x visit: Pre-VSG vs. Pre-OB-NT		HE>LE			o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
	Pic.	FC: WB PPI using within study sig. fROI seed	Fast	VSG: Post vs. Pre		HE>LE	seed: dlPFC		o	o	o	o	o	o	o	o	o	o	o	↑ v	o	o	o	o	o	o	o	o	o
Hu [m] 2020	Pic.	WB	Fast	group x visit: Post- vs. Pre-VSG	n/a	HE>LE	n/a		o	o	o	o	o	o	o	o	o	o	o	o	o	o	↓ R BA10	o	o	o	o	o	o
				group x visit: Post- vs. Pre-OB-NT		HE>LE			o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
	Pic.	FC: WB PPI using		group x visit: Post- vs. Pre-VSG		HE>LE	seed: dlPFC		o	o	o	o	o	o	o	o	o	o	o	↑ v y 33 BA24	o	o	o	o	o	o	o	o	o
		within study sig. fROI seed		group x visit: Post- vs. Pre-OB-NT		HE>LE	seed: dlPFC		o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
	Pic.	FC: Using seed-voxel sig. fROI from PPI FC	Fast	Δ VSG (Post-Pre) FC: corr. vs. dec. BMI (Pre-Post)	n/a	HE>LE	n/a													+ve corr v									
	Pic.	FC: Using seed-voxel sig. fROI from PPI FC		Δ VSG (Post-Pre): corr. vs. Δ WM tract FA dlPFC-vACC	n/a	HE>LE	seed: dlPFC													+ve corr v									
Holsen [n]	Pic.	SVC	Fast	Post- vs. Pre-VSG	Enhance > Regulate	HE/LE	n/a		↓	↓	[↓]	↓			o	o ant													
				Post- vs. Pre-VSG	Regulate > Enhance	HE/LE																	↑ 36,11,49 BA8			[↑] BA8[r,t]			
Faulconbridge [w] 2016	Pic.	aROI	Fast	Post- vs. Pre-VSG		HE>LE			o			o	o		o	o				o							o		
Baboumian [w] 2019	Pic. / word	WB. (groupxvisit)	Fed	Post- vs. Pre-VSG		HE>LE			o	o	o	o	o	↓	o	o	o	o	o	o	o	o	↑ BA9	o	o	o	o	o	↓

Table 2.7 Summary of results for food cue reactivity from individual studies

Author	fMRI paradigm	Method	Nutr status	Group effect	Task contrast	Food contrast	seed for FC	ave all ROIs	NAcc /VS	Caud.	Put.	Amy.	Hippo.	PHG	VTA	Insu.	Oper	Precu neus	PCC	ACC	Paracingulate gyrus	Frontal pole	dlPFC	IFG	MFG	SFG	OFC	Pre/ post CG	Fusiform gyrus
				Δ VSG (Post-Pre) vs. Δ OB-LCD/CBT (Post-Pre)		HE>LE			o	o	o	o	o	↓	o	o	o	o	o	o	o	o	↑ BA9	o	o	o	o	o	↓
				Δ VSG (Post-Pre) vs. Δ OB-NT (Post-Pre)		HE>LE			o	o	o	o	o	↓	o	o	o	o	o	o	o	o	↑ BA9	o	o	o	o	o	↓
AGB																													
Bruce [n] 2012	Pic.	WB	Pre-meal	Post- vs. Pre-AGB	n/a	HE/LE> NF	n/a		o	o	o	o	o	o	o	o	o	o	o	o	o	o	↑ 28 61 14 BA10[#]	o	o	↑ BA10[#]	o	o	o	o
		SVC				HE/LE> NF						[o]	[o]	[o]		[o]					[↓] BA9 [#]	[o][ii]	[o][ii]	[o][ii]	[↑] BA10[#]	[↑] BA10 [↓] BA9[#]	[o]		
		WB	Fed	Post- vs. Pre-AGB		HE/LE> NF			o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o			o	o
		SVC				HE/LE> NF						[o]	[o]	[↓] BA28		[↓] ant y 18 BA47					[↓] 46 47 -9 BA10[#]	[o][ii]		[↓] BA44 4/45 [#] BA10	[↓] BA10[#]	[o][ii]	[o]		
Bruce [n] 2014	Pic.	WB	Pre-meal	group x visit: Δ AGB (Post-Pre)	n/a	HE/LE> NF			o	o	o	o	o	o	o	o	o	↓ BA19	o	o	↓[#] BA9[#][r]	o	o	o	o	↓[#] BA9[#] [r]	o	o	o
			Fed	group x visit: Δ AGB (Post-Pre)		HE/LE> NF			o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
			Pre-meal	group x visit: Δ LCD (Post-Pre)		HE/LE> NF			o	o	o	o	o	o	o	o	o	↑ BA19	o	o	↓[#] BA9[#][r]	o	o	o	o	↓[#] BA9[#] [r]	o	o	o
			Fed	group x visit: Δ LCD (Post-Pre)		HE/LE> NF			o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
Scholtz [pw] 2013	Pic.	sep. cohort fROIs [ii]	Fast	BAND vs. OW		HE>NF		o [ii]	o	o		o				o ant											o		
				BAND vs. OW		LE>NF		o [ii]	o	o		o				o ant											o		
				BAND vs. OW		HE/LE >NF		o [ii]	o	o		o				o ant											o		
MULTIPLE																													
Scholtz [n] 2013	Pic.	WB	Fast	RYGB vs. BAND	n/a	HE>NF			↓	↓	↓	o	↓	o	o	o	o	o	o	o	↓ 10 46 -8 BA10	o	o	o	o	o	↓ BA11	o	o
		sep. cohort fROIs [ii]		RYGB vs. BAND		HE>NF		↓ [ii]	o	o		o				o ant										↓		
		WB		RYGB vs. BAND		LE>NF			o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	↓ BA11/10	o	o

Table 2.7 Summary of results for food cue reactivity from individual studies

Author	fMRI paradigm	Method	Nutr status	Group effect	Task contrast	Food contrast	seed for FC	ave all ROIs	NAcc /VS	Caud.	Put.	Amy.	Hippo.	PHG	VTA	Insu.	Oper	Precuneus	PCC	ACC	Paracingulate gyrus	Frontal pole	dlPFC	IFG	MFG	SFG	OFC	Pre/ post CG	Fusiform gyrus
		sep. cohort fROIs [g]		RYGB vs. BAND		LE>NF		o [g]	o	o		o				o ant											o		
		WB		RYGB vs. BAND		HE/LE> NF			↓	↓	↓	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	↓ BA11/ 25/ 47/ [r] 49	o	o
		sep. cohort fROIs [g]		RYGB vs. BAND		HE/LE> NF		↓ [g]	o	o		↓				o											↓ BA11/2 5/47/49		
				RYGB vs. OW		HE>NF		o [g]	o	o		o				o ant											o		
				RYGB vs. OW		LE>NF		o [g]	o	o		o				o ant											o		
				RYGB vs. OW		HE/LE >NF		o [g]	o	o		↓				o ant											o		
				BAND vs. OW		HE>NF		o [g]	o	o		o				o ant											o		
				BAND vs. OW		LE>NF		o [g]	o	o		o				o ant											o		
				BAND vs. OW		HE/LE >NF		o [g]	o	o		o				o ant											o		
	Auditory-motor-visual (control)	WB	Fast	RYGB vs. BAND	Auditory-motor-visual	n/a			o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
		sep. cohort fROIs [h]		RYGB vs. BAND	Auditory-motor-visual	n/a		o [h]																				o (motor)	
Goldstone [9] 2015	Pic.	sep. cohort fROIs [i]	Fed	RYGB: Octreotide vs. Saline	n/a	HE/LE> NF		↑ [i]	↑	o		o				o ant													
				AGB: Octreotide vs. Saline		HE/LE> NF		o [i]	o	o		o				o ant													
				Δ RYGB (Octreotide-Saline) vs. Δ AGB (Octreotide vs. Saline)		HE/LE> NF		o [i]	o	o		o				o ant													
				RYGB/AGB: Octreotide vs. Saline		HE/LE> NF		↑ [i]	(↑)																				

Table 2.7 Summary of results for food cue reactivity from individual studies

Author	fMRI paradigm	Method	Nutr status	Group effect	Task contrast	Food contrast	seed for FC	ave all ROIs	NAcc /VS	Caud.	Put.	Amy.	Hippo.	PHG	VTA	Insu.	Oper	Precuneus	PCC	ACC	Paracingulate gyrus	Frontal pole	dlPFC	IFG	MFG	SFG	OFC	Pre/ post CG	Fusiform gyrus
	Pic.	sep. cohort fROIs [i]	Fed	RYGB/AGB: Corr Δ (Octreotide-Saline) vs. Δ PYY (Octreotide-Saline)	n/a	HE/LE> NF		+ve corr [i]																					
				RYGB/AGB: Corr Δ (Octreotide-Saline) vs. Δ GLP-1 (Octreotide-Saline)		HE/LE> NF		(+ve corr) [i]																					
				RYGB/AGB: Corr Δ (Octreotide-Saline) vs. Δ FGF19 (Octreotide-Saline)		HE/LE> NF		o [i]																					
	Pic.	sep. cohort fROIs [h]	Fed	RYGB: Octreotide vs. Saline	Auditory-motor-visual	n/a		o [h]																			o (motor)		
				AGB: Octreotide vs. Saline				o [h]																			o (motor)		
Faulconbridge 2016	Pic.	aROI [f]	Fast	Post- vs. Pre-RYGB	n/a	HE>LE			o			o	o		↓	o				o							o		
				Post- vs. Pre-RYGB		HE > Rest			o			o	o		↓	o				o							o		
				Post- vs. Pre-RYGB		LE > Rest			o			o	o		↑	o				o							o		
				Post- vs. Pre-VSG		HE>LE			o			o	o		o	o				o							o		
				Post- vs. Pre-OB-NT		HE>LE			o			o	o		o	o				o							o		
				Pre-RYGB vs. Pre-OB		HE>LE			o			o	o		o	o				o							o		
				Pre-VSG vs. Pre-OB		HE>LE			o			o	o		o	o				o							o		
				Pre-RYGB vs. Pre-VSG		HE>LE			o			o	o		o	o				o							o		
				Pre-RYGB/VSG/OB		HE>LE			↑			↑	o		↑	o				↑							↑		
Baboumian 2019	Pic. / words	WB	Fed	Post- vs. Pre-RYGB	visual/auditory	HE>LE			o	o	o	o	o	↓	o	o	o	o	o	o	o	o	↑ BA9	o	o	o	o	o	↓
		(group x visit)		Post- vs. Pre-VSG		HE>LE			o	o	o	o	o	↓	o	o	o	o	o	o	o	o	↑ BA9	o	o	o	o	o	↓
				Post- vs. Pre-OB-LCD/CBT		HE>LE			o	o	o	o	o	↑	o	o	o	o	o	o	o	o	o	o	o	o	o	o	↑
				Post- vs. Pre-OB-NT		HE>LE			o	o	o	o	o	↑	o	o	o	o	o	o	o	o	↓ BA9	o	o	o	o	o	↑

Table 2.7 Summary of results for food cue reactivity from individual studies

Author	fMRI paradigm	Method	Nutr status	Group effect	Task contrast	Food contrast	seed for FC	ave all ROIs	NAcc /VS	Caud.	Put.	Amy.	Hippo.	PHG	VTA	Insu.	Oper	Precuneus	PCC	ACC	Paracingulate gyrus	Frontal pole	dlPFC	IFG	MFG	SFG	OFC	Pre/ post CG	Fusiform gyrus
				Δ RYGB (Post-Pre) vs. Δ VSG (Post-Pre)		HE>LE			o	o	o	o	o	o	o	o	o	o	o	o	o	o	↑ BA9	o	o	o	o	o	o
				Δ RYGB (Post-Pre) vs. Δ OB-LCD/CBT (Post-Pre)		HE>LE			o	o	o	o	o	↓	o	o	o	o	o	o	o	o	↑ BA9	o	o	o	o	o	↓
				Δ RYGB (Post-Pre) vs. Δ OB-NT (Post-Pre)		HE>LE			o	o	o	o	o	↓	o	o	o	o	o	o	o	o	↑ BA9	o	o	o	o	o	↓
				Δ VSG (Post-Pre) vs. Δ OB-LCD/CBT (Post-Pre)		HE>LE			o	o	o	o	o	↓	o	o	o	o	o	o	o	o	↑ BA9	o	o	o	o	o	↓
				Δ VSG (Post-Pre) vs. Δ OB-NT (Post-Pre)		HE>LE			o	o	o	o	o	↓	o	o	o	o	o	o	o	o	↑ BA9	o	o	o	o	o	↓
				Δ OB-LCD/CBT (Post-Pre) vs. Δ OB-NT (Post-Pre)		HE>LE			o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o

Table 2.7 Summary of food cue reactivity results from individual studies

Footnotes: [l-p]: probable overlapping datasets, [e]: n=9 for RYGB (n=2 performed task outside scanner), [f]: VTA, NAcc, amygdala, hippocampus, PFC, ACC, OFC, insula, thalamus, hypothalamus, [g]: NAcc, caudate, amygdala, anterior insula, OFC, [h]: STG posterior division, left preCG, lingual gyrus, [i]: NAcc, caudate, amygdala, anterior insula, [j]: n=11 (different partcipants at 1 mo and 1 y), [k]: regions included in SVC masks unknown, [r]: reported in original paper as PFC, [s]: +corr in original paper but only SFG under our criteria, [t]: dmPFC in original paper, [u]: PFC in original paper, [v]: no coordinates or image in original paper, [w]: repeated in multiple surgery for between-sugery comparisons, [#]: not in original paper, added on review of coordinates, *: duplicated data in error, **Δ:** change.

Abbreviations: ACC: anterior cingulate gyrus, **AGB**: Adjusted gastric band, **ant:** anterior, **Amy:** amygdala, **aROI:** anatomical region of interest, **BA:** Broadman area, **Caud:** caudate, **CBT**: cognitive behavioural therapy, **dlPFC:** dorsolateral prefrontal cortex, **fast:** fasted state, **FC:** functional connectivity, **fROI:** functional region of interest, **HE**: high-energy density, **Hippo:** hippocampus, **Insu:** insula, **IFG:** inferior frontal gyrus, **LE:** low-energy density, **LCD:** low calorie diet, **VLCD:** very low calorie diet **Methd:** analysis methodology, **MFG:** medial frontal gyrus, **NAcc:** nucleus accumbens, **NF:** non-food, **NT**: no treatment, **NW**: normal weight (lean), **OFC:** orbitofrontal cortex, **OB**: obesity, **OB-NT**: obesity no treatment, **OW**: overweight, **Oper:** operculum **NO**: Non-obesity, **Nutr:** nutritional status, **Put:** putamen, **PHG:** parahippocampal gyrus, **PCC:** paracingulate gyrus, **VTA:** ventral tegmental area, **:PPI:** psychological-physiological interaction**, Pic:** picture, **rol:** Rolandic, **RYGB**: Roux-Y gastric bypass, **sep:** separate, **SFG:** superior frontal gyrus, **SVC:** small volume correction, **VSG**: Vertical sleeve gastrectomy, **WB:** whole brain analysis. **↑:** increased/higher BOLD signal, **↓**: decreased/lower BOLD signal, **o:** no change/difference in BOLD signal, **()** not significant, **[]** uncorrected statistics, **()** not significant

2.5.12 Correlations of fMRI measures with clinical outcomes

Results of correlations with clinical outcomes from individual studies are summarised in **Table 2.8**

Correlations of pre-operative fMRI measures with clinical outcomes

Pre-RYGB: In one longitudinal taste fMRI study in the *pre-meal* state, pre-operative BOLD signal to high fat, high sweet or preferred tastants in the VTA (but not caudate, putamen, amygdala, insula, rolandic operculum) negatively correlated with % weight loss at 6 months after RYGB surgery using SVC analysis (n=15) (157).

Pre-VSG: In contrast to the above finding with RYGB surgery, in the same longitudinal fMRI taste study in the *pre-meal* state, pre-operative BOLD signal to high fat, high sweet or preferred tastants in VTA, caudate, putamen, amygdala, insula nor rolandic operculum did not correlate with % weight loss at 6 months after VSG surgery using SVC analysis (n=17) (157).

In one longitudinal study examining active cognitive restraint in the *fasted state,* pre-operative BOLD signal during enhance > regulate contrast for highly palatable HE/LE food pictures in NAcc (but not caudate, putamen, pallidum, amygdala, VTA, anterior insula) negatively correlated with % weight loss at 12 months after VSG surgery using SVC analysis (n=18) (45).

Pre-AGB: In one longitudinal study in the *pre-meal* and *fed* states*,* pre-operative BOLD signal in PHG, insula and other frontal regions to HE/LE food pictures did not correlate with % excess weight loss at 3.5 months after AGB surgery when examining regions showing a significant change after surgery (n=10) (149).

In one longitudinal study in the *pre-meal state*, pre-operative BOLD signal to HE/LE foods in MFG and SFG positively correlated with % decrease in BMI at 3 months, and in MFG positively correlated, and in IFG negatively correlated, with % decrease in BMI at 6 months (n=16) (151). In the same stud in the *fed* state, baseline BOLD signal to HE/LE foods in MFG positively correlated with % decrease in BMI at 3 months, and in PCC at 6 months (n=16) (151).

Correlations of post-operative fMRI measures with clinical outcomes

RYGB surgery: In two longitudinal studies of RYGB surgery in the *fed* state, decrease in BMI or weight at 2 months after RYGB surgery did not correlate with change in BOLD signal to HE vs. LE food or just HE food pictures in precenues (the region showing uncorrected significant changes after surgery) (n=19) (156), nor with change in BOLD during successful inhibition of response to HE food pictures in operculum, middle cingulum, dlPFC, or other frontal regions, or to LE foods in superior temporal gyrus, PHG or hypothalamus (regions showing uncorrected significant changes after surgery) during go-nogo fMRI task (n=18) (155).

In one longitudinal study of RYGB surgery in the *fasted* state, greater weight loss at 4 weeks after RYGB surgery was associated with a greater decrease in BOLD signal to HE/LE food pictures in the hypothalamus using an anatomical ROI, but this was not seen in a control group losing weight with a VLCD (n=16-19) (163).

In one longitudinal taste fMRI study in the *pre-meal* state, the change in BOLD signal to both high fat and high sugar tastants (but not the preferred taste stimuli in VTA (but not caudate, putamen, amygdala, anterior insula, rolandic operculum) using SVC analysis positively correlated with % weight loss at 6 months after RYGB surgery (n=15) (157).

In one cross-sectional study in the *pre-meal* state, where participants performed a motivational task to crave or resist, post-operative BOLD signal to HE food pictures did not differ during crave or resist trials between those who lost more vs. less weight (where successful weight loss was defined by a mean percent of 50 weight loss) at 32 months after RYGB surgery (n=7-31), and there was no overall correlation with % excess weight loss (n=31) (134).

In one cross-sectional study in participants with T2DM in *the pre-meal* state, there was a trend for post-operative BOLD signal during evaluation of HE/LE food pictures in the OFC to be associated with a greater decrease in HbA1c at 18 months after RYGB surgery (n=12) (159).

VSG surgery: In contrast to the findings with RYGB surgery above, in one longitudinal taste

fMRI study in the *pre-meal* state, the change in BOLD signal to high fat, high sugar nor preferred tastants in VTA, caudate, putamen, amygdala, anterior insula, rolandic operculum using SVC analysis did not correlate with % weight loss at 6 months after VSG surgery (n=17) (157). Similarly, in another longitudinal study in the *fasted* state, the change in BOLD signal to HE food pictures did not correlate with the decrease in BMI at 1 month after VSG (44).

AGB surgery: No papers were found correlating fMRI findings with weight loss after AGB surgery.

Table 2.8 Correlations with clinical outcomes from individual studies

Author	Group effect	Task contrast	Food contrast	NAcc/VS	Caudate	Putamen	Amygdala	Hippocampus	PHG	Hypothalamus	VTA	Insula	Operculum	Precuneus	PCC	ACC	Paracingulate gyrus	Frontal pole	dlPFC	IFG	MFG	SFG	medial frontal cortex	OFC
RYGB																								
Zoon 2018	Δ RYGB (Post-Pre): corr. vs. dec. BMI (Pre-Post)	n/a	see fROI											o HE > LE or NF								o LE > rest		
	Δ RYGB (Post-Pre): corr. vs. weight loss (Pre-Post)		see fROI											o HE > LE or NF								o LE > rest		
Smith [w] 2020	Pre-RYGB: corr. vs. 6mo %WL		HF > NF		o	o	o				-ve corr	o	o rol											
	Pre-RYGB: corr. vs. 6mo %WL		HS > NF		o	o	o				-ve corr	o	o rol											
	Pre-RYGB: corr. vs. 6mo %WL		Pre-preferred > NF		o	o	o				-ve corr	o	o rol											
	Δ RYGB (Post-Pre): corr. vs. 6mo %WL		HF > NF								+ve corr													
	Δ RYGB (Post-Pre): corr. vs. 6mo %WL		HS > NF								+ve corr													
	Δ RYGB (Post-Pre): corr. vs. 6mo %WL		Pre-preferred > NF								o													
Frank 2016	Post-RYGB: corr. vs. Δ HbA1c (Post-Pre)	wanting/liking	HE/LE > NF	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	[-ve corr]
Goldman 2013	Post-RYGB-MS/LS: corr. vs. %EWL or current BMI	Crave	HE > NF	o	o	o	o	o	o	o	o	[-ve] BMI post y -7	o	o	o	[-ve] BMI y 35 BA32	o	o	o	o	o	o	o	o
	Post-RYGB-MS/LS: corr. vs. %EWL or current BMI	Resist	HE > NF	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
Zoon 2018	Δ RYGB (Post-Pre): corr. vs.dec. BMI or weight loss (Pre-Post)	no-go > rest	HE										o		o			o	o	o	o	o		
			LE						o	o														
Zoon 2018	Δ RYGB (Post-Pre): corr. vs. dec. BMI (Pre-Post)	n/a	see fROI											o HE or LE > rest				o HE > NF				o HE > NF		
	Δ RYGB (Post-Pre): corr. vs. weight loss (Pre-Post)		see fROI											o HE or LE > rest				o HE > NF				o HE > NF		
Salem 2021	Δ RYGB (Post-Pre): corr. vs. Δ weight loss		HE/LE > rest							-ve														
	Δ LVCD (Post-Pre): corr. vs. Δ weight loss		HE/LE > rest							o														
VSG																								
Li [m] 2019	Δ VSG (Post-Pre): corr. vs. dec. BMI (Pre-Post)	n/a	HE > LE																o					
	Δ VSG (Post-Pre): corr. vs. dec. BMI (Pre-Post)	n/a														+ve corr v								
	Pre-VSG: corr. vs. Pre-BMI															-ve corr v								
Smith [w] 2020	Pre-VSG: corr. vs. 6mo %WL		HF > NF		o	o	o				o	o	o rol											

Table 2.8 Correlations with clinical outcomes from individual studies

Author	Group effect	Task contrast	Food contrast	NAcc/VS	Caudate	Putamen	Amygdala	Hippocampus	PHG	Hypothalamus	VTA	Insula	Operculum	Precuneus	PCC	ACC	Paracingulate gyrus	Frontal pole	dlPFC	IFG	MFG	SFG	medial frontal cortex	OFC
	Pre-VSG: corr. vs. 6mo %WL		HS > NF		o	o	o				o	o	o rol											
	Pre-VSG: corr. vs. 6mo %WL		Pre-preferred > NF		o	o	o				o	o	o rol											
	Δ VSG (Post-Pre): corr. vs. 6mo %WL		HF > NF																					
	Δ VSG (Post-Pre): corr. vs. 6mo %WL		HS > NF																					
	Δ VSG (Post-Pre): corr. vs. 6mo %WL		Pre-preferred > NF																					
Hu [m] 2020	Δ VSG (Post-Pre) FC: corr. vs. dec. BMI (Pre-Post)	n/a	HE > LE													+ve corr v								
	group x visit: Post- vs. Pre-VSG	n/a	n/a													↑ vACC-dlPFC			↑ vACC-dlPFC					
	group x visit: Post- vs. Pre-OB-NT															o vACC-dlPFC			o vACC-dlPFC					
	Δ VSG (Post-Pre): corr. vs. Δ WM tract FA dlPFC-vACC	n/a	HE > LE													+ve corr v								
Holsen [n] 2018	Pre-VSG: corr. vs. %WL	Enhance > Regulate	HE/LE	-ve corr	o	o	o			-ve corr	o	o ant												
	Pre-VSG: corr. vs. %WL	Regulate > Enhance	HE/LE																o			o[†]		
AGB																								
Bruce [o] 2012	Pre-AGB: corr. vs. %EWL	n/a	HE/LE > NF						o			o ant								o	o	o	o	
	Pre-AGB: corr. vs. %EWL		HE/LE > NF						o			o ant								o	o	o	o	
Ness [o] 2014	Pre-LABG: corr. vs. % dec. BMI (Pre-3mo)	n/a	HE/LE > NF	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	+ve corr BA6	+ve corr BA6	o	o
	Pre-LABG: corr. vs. % dec. BMI (Pre-3mo) incl. age		HE/LE > NF	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	+ve corr BA6	o	o
	Pre-LABG: corr. vs. % dec. BMI (Pre-6mo)		HE/LE > NF	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	-ve corr 43 49 -1 BA10[p]/47	+ve corr BA6 BA8[a]	o	o	o
	Pre-LABG: corr. vs. % dec. BMI (Pre-6mo) incl. age		HE/LE > NF	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	+ve corr 34 9 25 BA9/44[a]	o	o	o	o
	Pre-LABG: corr. vs. % dec. BMI (Pre-3mo)		HE/LE > NF	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
	Pre-LABG: corr. vs. % dec. BMI (Pre-3mo) incl. age		HE/LE > NF	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
	Pre-LABG: corr. vs. % dec. BMI (Pre-6mo)		HE/LE > NF	o	o	o	o	o	o	o	o	o	o	o	+ve corr y -43 -1 -43 0 BA31	o	o	o	o	o	o	o	o	o

Table 2.8 Correlations with clinical outcomes from individual studies

Author	Group effect	Task contrast	Food contrast	NAcc/VS	Caudate	Putamen	Amygdala	Hippocampus	PHG	Hypothalamus	VTA	Insula	Operculum	Precuneus	PCC	ACC	Paracingulate gyrus	Frontal pole	dlPFC	IFG	MFG	SFG	medial frontal cortex	OFC
	Pre-LABG: corr. vs. % dec. BMI (Pre-6mo) incl. age		HE/LE > NF	o	o	o	o	o	o	o	o	o	o	-ve corr BA7/31	o	o	o	*-ve corr - 24 43 20 BA10	o	o	o	-ve corr BA10	o	o
MULTIPLE																								
Smith 2020	Pre-RYGB: corr. vs. 6mo %WL		HF > NF		o	o	o				-ve corr	o	o rol											
	Pre-RYGB: corr. vs. 6mo %WL		HS > NF		o	o	o				-ve corr	o	o rol											
	Pre-RYGB: corr. vs. 6mo %WL		Pre-preferred > NF		o	o	o				-ve corr	o	o rol											
	Δ RYGB (Post-Pre): corr. vs. 6mo %WL		HF > NF								+ve corr													
	Δ RYGB (Post-Pre): corr. vs. 6mo %WL		HS > NF								+ve corr													
	Δ RYGB (Post-Pre): corr. vs. 6mo %WL		Pre-preferred > NF								o													
	Pre-VSG: corr. vs. 6mo %WL		HF > NF		o	o	o				o	o	o rol											
	Pre-VSG: corr. vs. 6mo %WL		HS > NF		o	o	o				o	o	o rol											
	Pre-VSG: corr. vs. 6mo %WL		Pre-preferred > NF		o	o	o				o	o	o rol											
	Δ VSG (Post-Pre): corr. vs. 6mo %WL		HF > NF																					
	Δ VSG (Post-Pre): corr. vs. 6mo %WL		HS > NF																					
	Δ VSG (Post-Pre): corr. vs. 6mo %WL		Pre-preferred > NF																					

Table 2.8 Correlations with clinical outcomes from individual studies

Footnotes: [I-P]: probable overlapping datasets, [#]: not in original paper, added on review of coordinates, **Δ:** change.

Abbreviations: ACC: anterior cingulate gyrus, **AGB**: Adjusted gastric band, **ant:** anterior, **Amy:** amygdala, **aROI:** anatomical region of interest, **BA:** Broadman area, **CBT**: cognitive behavioural therapy, **corr:** correlation, **dlPFC:** dorsolateral prefrontal cortex, **fast:** fasted state, **FC:** functional connectivity, **fROI:** functional region of interest, **HE**: high-energy density, **IFG:** inferior frontal gyrus, **LE:** low-energy density, **LCD:** low calorie diet, **VLCD:** very low calorie diet **Methd:** analysis methodology, **MFG:** medial frontal gyrus, **mo:** months, **NAcc:** nucleus accumbens, **NF:** non-food, **NT**: no treatment, **NW**: normal weight (lean), **n/a:** not available, **OFC:** orbitofrontal cortex, **OB**: obesity, **OB-NT**: obesity no treatment, **OW**: overweight, **NO**: Non-obesity, **PHG:** parahippocampal gyrus, **PCC:** paracingulate gyrus, **VTA:** ventral tegmental area, **:PPI:** psychological-physiological interaction**, Pic:** picture, **rol:** Rolandic, **RYGB**: Roux-Y gastric bypass, **sep:** separate, **SFG:** superior frontal gyrus, **SVC:** small volume correction, **VSG**: Vertical sleeve gastrectomy, **WB:** whole brain analysis. **o:** no significant correlation with BOLD signal, **-ve corr:** negative correlation with BOLD signal, **+ve corr:** positive correlation with BOLD signal

2.5.13 Eating behaviour measurements and correlations with fMRI outcomes

Results of eating behaviour measurements from individual studies are summarised in **Table 2.9-A and 2.9-B**. Results of correlations of fMRI findings with behavioural outcomes from individual studies are summarised in **Table 2.10**

Twelve (54.5%) studies reported *appetite ratings*: hunger, fullness, desire/volume to eat, thirst, pleasantness to eat (16, 20, 44, 150, 153, 155-160, 162). Nine (40.9%) studies reported *food wanting* (16, 25, 33, 44, 45, 156, 159, 160, 162). Eight studies (36.4%) reported *food liking* (16, 25, 46, 154, 156, 157, 159, 162). Three (13.6%) studies reported *food preference*: MTPRT (156), taste intensity (154), LFPQ (162). Two (9.1%) studies reported food intake. ad libitum test meal, ad libtum ice-cream and 3-day food diary (16, 162). Six (27.3%) studies reported *eating behaviour questionnaires*: TFEQ (45, 158, 159), YFAS (44), EI (149), BED, EDEQ, and DEBQ (16). Four (18.2%) studies reported nausea and dumping syndrome (16, 20, 160, 162). Nine (40.9%) studies reported *mood*: BDI-II depression (16, 45, 159) CESD-10 (134, 149) HAMD and HAMA (44), STAI anxiety (45), PANAS-positive/negative (16, 160).
ADD eating behaviour questionnaires

RYGB surgery

Hunger: In the *fasted* state, hunger rating decreased in three longitudinal studies at 1 month after RYGB surgery (20, 153, 157), and were lower in one cross-sectional study at >1 year after RYGB surgery in *fed* state compared to participants with normal weight or obesity (158), but did not differ in another study in *pre-meal* state at 18 months after RYGB surgery, compared to an unoperated group with obesity (159). Hunger did not differ in the *fasted* state between groups ~8 months after RYGB surgery and AGB surgery, despite their differences in food cue reactivity but both were lower than BMI-matched participants with overweight (16).

Volume wanting to eat: In a longitudinal study in *fasted* state**,** volume wanting to eat' decreased at 1 months after RYGB surgery (20). In a cross-sectional study, 'volume wanting to eat' was lower at >1 year after RYGB surgery compared to unoperated group with obesity (158). Acute intravenous infusion of the GLP-1 antagonist Exendin9-39 decreased **'**volume wanting to eat' at 1 months after RYGB surgery (20).

Fullness: In three longitudinal studies, fullness rating either did not change at one month after RYGB surgery in *fed and fasted* states (153), or increased (155) or did not change (156) at two months in *fed* state after RYGB surgery. In a cross-sectional study in *fed* state, fullness ratings 2 months after RYGB surgery were greater than unoperated group with obesity (158); while fullness in *fasted* state or in *fed* state after an *ad libitum* meal did not differ between groups after RYGB and AGB surgery. despite their differences in food cue reactivity (16).

Wanting/liking/appeal rating: In three longitudinal studies in *fed state,* desire to eat HE food (25, 33) and wanting/liking of HE food odours (156) decreased at 1 month and 2 months respectively after RYGB surgery, but it did not change for LE food in any of the studies.

Furthermore, in longitudinal studies in *fasted* state: (i) liking for HE and HE/LE food decreased at six months after RYGB surgery, but it did not change for LE food (46), while (ii) the appeal rating of HE food was greater than LE food pre-operatively but was similar at ~14 weeeks after RYGB surgery, while LCD diet had no effect on HE or LE food ratings in overweight (162).

In one cross sectional study in *fasted* state, appeal ratings for HE food (collected simultaneously with fMRI, and seen for chocolate, sweet and savoury HE food categories) and ice-cream palatability was both lower at ~8 months after RYGB surgery compared to after~8 months AGB surgery or BMI-matched group; while LE food appeal was similar between all three groups (16). However ice cream intake in *fasted* state did not differ between the post-RYGB and post-AGB groups, though there was a lower percentage of energy intake from fat calculated from home food diaries in the RYGB compared to AGB groups (16).

In two cross-sectional studies, HE/LE food wanting and liking were lower at 18 months after RYBG surgery compared to unoperated group with obesity (159).

Eating behaviour questionnaires: In a longitudinal study, at 4 weeks after RYGB, restraint-related eating behaviour assessed by Dutch Eating Behaviour Questionnaire (DEBQ) decreased and emotional-eating decreased in RYGB group compared to VLCD group; however, there was no difference between RYGB group and VLCD group in emotional eating (163).

In a cross-sectional study, only disinhibition-related eating assessed by Three Factor Eating Behaviour Questionnaire TFEQ was lower at 18 month after RYGB surgery, but no change in hunger- and restraint- related eating compared to unoperated group with obesity (159). Furthermore, only restraint and external eating behaviour (not emotional) was lower in RYGB group compared to partcicipants with overweight on average 8-9 months (16). This was not seen in another cross-sectional study where neither disinhibition-, nor hunger or restraint-related eating related eating were different in those who at >1 year after RYGB surgery compared to unoperated group with obesity (158).

In a longitudinal study, emotional- and external- related eating (assessed by TFEQ and DEBQ) decreased, restraint-related eating (when assessed by TFEQ but not DEBQ) increased at at 1 year after VSG surgery (45)

In a longitudinal study, restraint (assessed by eating inventory questionnaire) while disinhibition and hunger decreased at 3.5 months after AGB surgery (n=10) (149). However, there was no difference in any domains in DEBQ (restraint, emotional and external) on average 8-9 months after AGB surgery (16).

Higher restraint scores (but not emotional nor external) at average 8-9 months were seen after after AGB surgery compared to RYGB surgery (16).

***VSG* surgery**

Hunger: In two longitudinal studies in *fasted* state, hunger ratings either decreased (157) or did not change (44) at 4 weeks and 1 month respectively after VSG surgery.

Desire to eat: In a longitudinal study in *fasted* state, desire to eat highly palatable food decreased at 12 months after VSG surgery during trials when they were instructed to enhance their craving but not during trials were they were instructed to suppress their craving (45).

Wanting/liking rating: In two longitudinal studies in the *fasted state*, cravings for HE food (44) and liking of HE food (46) decreased at 1 and ~6 months after VSG surgery, but did not change for LE food.

Eating behaviour questionnaires:

AGB surgery

Hunger: In one longitudinal study in *pre-meal and fed* states, hunger ratings did not change at 3.7 months after AGB surgery compared after LCD (150).

Correlations of fMRI measures with behavioural outcomes

Post-operative fMRI meaures with appetite ratings: In a longitudinal RYGB study in the *fed* state, decrease in ratings of hunger, volume able to eat, or desire to eat did not correlate with changes in BOLD signal during successful motor response inhibition to HE food cues in any of the regions showing a significant (but uncorrected for multiple comparisons) change at 2 months after RYGB surgery (including PHG, hypothalamus, operculum, dlPFC, and other frontal and temporal regions) in a Go-NoGo fMRI paradigm, though a greater increase in fullness was associated with a greater decrease in BOLD signal to LE food pictures in PHG (n=18) (155).

Post-operative fMRI measures with food hedonics: In longitudinal studies of RYGB and VSG surgery: (i) in the *fed* state, a greater decrease in liking of HE food was associated with a greater decrease in BOLD signal to HE food cues in caudate, lentiform nucleus, thalamus, ACC and frontal lobe (dlPFC, MFG, SFG) at 1 month after RYGB surgery (n=14) (25); (ii) in the *fed* state, a greater decrease in preference for HE food from a ranking task was associated with a greater uncorrected decrease in BOLD signal to HE vs. LE food pictures (but not odours) in the precuneus (region showing significant change after surgery), but this was not seen with decreases in ratings of wanting or liking of HE foods (for the pictures or odours used in fMRI task) at 2 months after RYGB surgery (n=19) (156); (iii) in the *fasted* state, the change in BOLD signal to HE vs. LE food pictures in the VTA (the only anatomical ROI showing significant change after surgery) did not correlate with the decrease in liking ratings of HE vs. LE food pictures at ~7 months after RYGB or LVSG surgery (n=18-22) (46); (iv) in the *fasted* state a greater decrease in craving for HE food was associated with a greater decrease in BOLD signal to HE food pictures in the dlPFC (region showing signficant change after surgery) at 1 month after VSG (n=22) (44).

In a cross-sectional study in the *fasted* state, a lower taste pleasantness rating of ice cream outside the scanner was associated with a lower BOLD signal during valuation of HE foods averaged across the reward system fROIs (NAcc, caudate, amygdala, anterior insula, OFC) at average 8 months after RYGB surgery, with a similar trend after AGB surgery (n=20-21) (16).

Pre-operative fMRI measures with eating behaviour questionnaires: In a longitudinal study, a lower BOLD signal to HE/LE food pictures at baseline in IFG (but not in any of the other regions showing a significant change after surgery: insula, PHG, MFG, SFG, medial FG) in the *fed* (but not *pre-meal*) state was associated with a greater decrease in disinhbited eating (but not with the increase in dietary restraint or decrease in hunger-related eating) at 3 months after AGB surgery, when examining regions showing a significant change after surgery (n=10) (149).

Post-operative fMRI measures with eating behaviour questionnaires: Three longitudinal studies investigated correlations of changes in eating behaviour questionnaires with change in or post-operative fMRI findings after different surgeries: (i) after RYGB in the *fasted* state, the increase in DEBQ-restraint eating did not correlate with the change in BOLD signal to HE/LE food pictures in any fROI (NAcc, caudate, putamen, amygdala, hippocampus, anterior insula, paracingulate gyrus, vmPFC, parietal lobule) at 4 weeks after RYGB surgery, but was associated with the increase in BOLD signal to HE/LE food pictures in the caudate and parahippocampal gyrus at 4 weeks after VLCD (n=16-19) (163); (ii) at 1 month after VSG in the *fasted* state, the decrease in YFAS score was not associated with the decrease in BOLD signal to HE food pictures in dlPFC (the region showing significant change after surgery) after VSG surgery (n=22) (44); (iii) at 3.5 month after AGB surgery in the *fed* state, a greater decrease in disinhibited eating and hunger-related eating tended to be associated with a lower post-operative BOLD signal to HE food pictures in the IFG and MFG respectively (fROI analysis), whilst a greater increase in dietary restraint tended to be associated with a lower post-operative BOLD signal to HE food pictures in IFG, when examining regions showing a significant change after surgery (n=10) (149)

Table 2.9-A Results of eating behaviour measurements from individual studies

Author	Appetite			Food Wanting			Food Liking			Food Preference		
	Test	Comparison	Result	Test	Comparison	Result	Test	Comparison	Result	Test	Comparison	Result
RYGB												
Ochner [i] 2011				Desire to eat	Pre-RYGB: HE vs. LE	↑						
					Post-RYGB: HE vs. LE	o						
					HE: Post- vs. Pre-RYGB	↓						
					LE: Post- vs. Pre-RYGB	o						
Ochner [i] 2012				Desire to eat	Pre-RYGB: HE vs. LE	↑	Liking	Pre-RYGB: HE vs. LE	o			
					Post-RYGB: HE vs. LE	o		Post-RYGB: HE vs. LE	o			
					HE: Post- vs. Pre-RYGB	↓		HE: Post- vs. Pre-RYGB	o			
					LE: Post- vs. Pre-RYGB	o		LE: Post- vs. Pre-RYGB	o			
					HE-LE: Post- vs. Pre-RYGB	↓		HE-LE: Post- vs. Pre-RYGB	↓			
Ochner [i] 2012	Hunger	Fasted: Post- vs. Pre-RYGB	↓									
		Fed: Post- vs. Pre-RYGB	o									
	Fullness	Fasted: Post- vs. Pre-RYGB	o									
		Fed: Post- vs. Pre-RYGB	o									
Ten Kulve 2017	Hunger, volume,	Placebo: Post- vs. Pre-RYGB	↓									
	appetite sweet & savoury	Ex9-39: Post- vs. Pre-RYGB	↓									
		Pre-RYGB: Ex9-39 vs. Placebo	o									
		Post-RYGB: Ex9-39 vs. Placebo	o									
	Fullness	Placebo: Post- vs. Pre-RYGB	o									
		Ex9-39: Post- vs. Pre-RYGB	o									
		Pre-RYGB: Ex9-39 vs. Placebo	o									
		Post-RYGB: Ex9-39 vs. Placebo	o									
Zoon 2018	Hunger	Fed: Post- vs. Pre-RYGB	o	Picture Wanting	HE: Post- vs. Pre-RYGB	↓	Picture Liking	HE: Post- vs. Pre-RYGB	↓	MTPRT	LE/savoury: Post- vs. Pre-RYGB	↓

Table 2.9-A Results of eating behaviour measurements from individual studies												
Author	**Appetite**			**Food Wanting**			**Food Liking**			**Food Preference**		
	Test	Comparison	Result	Test	Comparison	Result	Test	Comparison	Result	Test	Comparison	Result
	Fullness	Fed: Post- vs. Pre-RYGB	o		LE: Post- vs. Pre-RYGB	o		LE: Post- vs. Pre-RYGB	o		HF/sweet: Post- vs. Pre-RYGB	↑
	Volume to eat	Fed: Post- vs. Pre-RYGB	↓		NF: Post- vs. Pre-RYGB	o		NF: Post- vs. Pre-RYGB	(↓)			
	Desire to eat	Fed: Post- vs. Pre-RYGB	o									
	Thirst	Fed: Post- vs. Pre-RYGB	↓									
Frank 2016	Hunger	pre/post-fMRI: RYGB vs. OB	o	Wanting	HE/LE: Post-RYGB vs. OB	↓	Liking	HE/LE: Post-RYGB vs. OB	↓			
Frank 2014	Hunger	RYGB vs. OB	↓*									
		RYGB vs. NW	↓*									
		OB vs. NW	o									
	Fullness	RYGB vs. OB	↑ *									
		RYGB vs. NW	↑									
		OB vs. NW	o									
	Volume to eat	RYGB vs. OB	↓*									
		RYGB vs. NW	↓*									
		OB vs. NW	o									
Goldman 2013												
Zoon 2018	Hunger	Post-meal: Post- vs. Pre-RYGB	↓									
	Fullness	Post-meal: Post- vs. Pre-RYGB	↑									
	Volume to eat	Post-meal: Post- vs. Pre-RYGB	↓									
	Desire to eat	Post-meal: Post- vs. Pre-RYGB	↓									
Wang 2016							Taste pleasantness	Sweet: Post- vs. Pre-RYGB (1mo or 12mo)	o	Taste intensity	Sweet: Post- vs. Pre-RYGB (1mo or 12mo)	o
								Salt: Post- vs. Pre-RYGB (1mo or 12mo)	o		Salt: Post- vs. Pre-RYGB (1mo or 12mo)	o
Zoon 2018				Odor wanting	HE: Post- vs. Pre-RYGB	↓	Odor liking	HE: Post- vs. Pre-RYGB	↓			
					LE: Post- vs. Pre-RYGB	o		LE: Post- vs. Pre-RYGB	o			

Table 2.9-A Results of eating behaviour measurements from individual studies

Author	Appetite			Food Wanting			Food Liking			Food Preference		
	Test	Comparison	Result	Test	Comparison	Result	Test	Comparison	Result	Test	Comparison	Result
					NF: Post- vs. Pre-RYGB	o		NF: Post- vs. Pre-RYGB	↓			
Salem 2021							VAS-pleasantness to eat	Pre: RYGB vs. VLCD	o			
								Post: RYGB vs. VLCD	o			
VSG												
Li [m] 2019	Hunger	Fasted: Post- vs. Pre-RYGB	o	Craving	HE: Post vs. Pre-VSG	↓						
	Hunger	Fasted: Post- vs. Pre-OB-NT	o		LE: Post vs. Pre-VSG	o						
					Pre-VSG: HE vs. LE	↑						
					Post-VSG: HE vs. LE	↓						
					HE: Post vs. Pre-OB	o						
					LE: Post vs. Pre-OB	o						
					Pre-OB or Post-OB: HE vs. LE	↑						
Holsen [n] 2018				Food desire to eat	Enhance: Post- vs. Pre-VSG	↓						
				Food desire to eat	Regulate: Post- vs. Pre-VSG	o						
AGB												
Bruce [o] 2014	Hunger	Pre-meal: Post-AGB vs. Post-LCD	o									
		Fed: Post-AGB vs. Post-LCD	o									
MULTIPLE												
Scholtz [p] 2013	Hunger, Volume to eat,	Fasted: RYGB vs. AGB	o	Appeal rating	HE: RYGB vs. AGB	↓	Ice cream palatability	RYGB vs. AGB	↓			
	Pleasantness to eat	Δ Post-*ad libitum* ice cream: RYGB vs. AGB	o		LE: RYGB vs. AGB	o						
		Fasted: RYGB vs. OW	↓		HE: RYGB vs. OW	↓						
		Fasted: AGB vs. OW	↓		LE: RYGB vs. OW	o						
	Fullness	Fasted: RYGB vs. AGB	o		HE: AGB vs. OW	o						
		Δ Post-*ad libitum* ice cream: RYGB vs. AGB	o		LE: AGB vs. OW	o						
		Fasted: RYGB vs. OW	o									

Table 2.9-A Results of eating behaviour measurements from individual studies												
Author	**Appetite**			**Food Wanting**			**Food Liking**			**Food Preference**		
	Test	Comparison	Result	Test	Comparison	Result	Test	Comparison	Result	Test	Comparison	Result
		Fasted: AGB vs. OW	o									
Goldstone [P] 2015	Hunger, Pleasantness to eat, Volume to eat, Fullness	RYGB: Octreotide vs. Saline	o [e]	Appeal rating	HE/LE: RYGB Octreotide vs. Saline	↑ [e]						
		AGB: Octreotide vs. Saline	o		HE/LE: AGB Octreotide vs. Saline	o						
					HE/LE: Δ RYGB (Octreotide-Saline) vs. Δ AGB (Octreotide vs. Saline)	o						
Faulconbridge							Liking Fasted	HE or HE-LE: Post- vs. Pre-RYGB	↓			
								HE or HE-LE: Post- vs. Pre-VSG	↓			
								HE or HE-LE: Post- vs. Pre-OB	o			
								LE: Post- vs. Pre-RYGB	o			
								LE: Post- vs. Pre-VSG	o			
								LE: Post- vs. Pre-OB	o			
Smith	Hunger	Fasted: Post- vs Pre-RYGB	↓				Taste liking	10 or 20% sucrose: Post- vs. Pre-RYGB/VSG	↓			
	Hunger	Fasted: Post- vs Pre-VSG	↓					3.4% fat: Post- vs. Pre-RYGB/VSG	↓			
	Hunger	Fasted: Pre-RYGB vs. Pre-VSG	o					10 or 33% fat: Post- vs. Pre-RYGB/VSG	o			
Smith							Pre-RYGB liking: 0% fat, 20% sucrose	6mo % WL Post RYGB	+ve corr			
							Pre-RYGB liking: 3.4% fat, 20% sucrose	6mo % WL Post RYGB	+ve corr			
							Pre-RYGB liking: 10% fat, 10% sucrose	6mo % WL Post RYGB	+ve corr			
							Δ RYGB (2w Post-Pre) liking: 33% fat, 0% sucrose	6mo % WL Post RYGB	-ve corr			
							Pre-VSG liking: 0% fat, 20% sucrose	6mo % WL Post VSG	o			
							Pre-VSG liking: 3.4% fat, 20% sucrose	6mo % WL Post VSG	o			
							Pre-VSG liking: 10% fat, 10% sucrose	6mo % WL Post VSG	o			
							Δ VSG (2w Post-Pre) liking: 33% fat, 0% sucrose	6mo % WL Post VSG	o			

Table 2.9-A Results of eating behaviour measurements from individual studies

Footnotes: [l-p]: probable overlapping datasets, [e]: n=9 for RYGB (n=2 performed task outside scanner), [#] (pre-MRI but not post-MRI). **Δ:** change.
Abbreviations: comp: comparison, **RYGB**: Roux-Y gastric bypass, **VSG**: Vertical sleeve gastrectomy, **AGB**: Adjusted gastric band, **CBT**: cognitive behavioural therapy, **HE**: high-energy density, **LE:** low-energy density, **LCD**: low-calorie diet, **VLCD:** very low calories diet, **NF:** non-food, **NT**: no treatment, **NW**: normal weight (lean), **MTPRT:** macronutrient and taste preference ranking task, **OB**: obesity, **OW**: overweight, **NO**: Non-obesity, **w:** weeks, **WL:** weight loss, **VAS:** visual analogue scale, **↑:** increased/higher, **↓**: decreased/lower, **o:** no change/difference.

Table 2.9-B Results of eating behaviour measurements from individual studies												
Author	**Food intake**			**Eating behaviour**			**Nausea and Dumping Syndrome**			**Mood**		
	Test	Comparison	Result	Test	Comparison	Result	Test	Comp.	Result	Test	Comparison	Result
RYGB												
Ten Kulve 2017							Nausea	Placebo: Post vs. Pre	↑			
								Ex9-39: Post vs. Pre	↑			
								Pre: Ex9-39 vs. Placebo	o			
								Post: Ex9-39 vs. Placebo	o			
Frank 2016				TFEQ-disinhibition	post-RYGB vs. OB	↓				BDI-II depression	post-RYGB vs. OB	o
				TFEQ-hunger	post-RYGB vs. OB	o						
				TFEQ-restraint	post-RYGB vs. OB	o						
				PFS	post-RYGB vs. OB	↓						
Frank 2014				TFEQ-disinhibition	RYGB vs. OB	o						
					RYGB vs. NW	o						
					OB vs. NW	↑						
				TFEQ-hunger	RYGB vs. OB	o						
					RYGB vs. NW	o						
					OB vs. NW	↑						
				TFEQ-restraint	RYGB vs. OB	o						
					RYGB vs. NW	(↑)						
					OB vs. NW	(↑)						
Goldman 2013										CESD-10 depression	RYGB-MS vs. RYGB-LS	o
Salem 2021				DEBQ-restraint	RYGB: Post- vs. Pre	↑	VAS-nausea	Pre: RYGB vs. VLCD	o			
					VLCD: Post vs pre	o		Post: RYGB vs. VLCD	o			

Table 2.9-B Results of eating behaviour measurements from individual studies												
Author	**Food intake**			**Eating behaviour**			**Nausea and Dumping Syndrome**			**Mood**		
	Test	Comparison	Result	Test	Comparison	Result	Test	Comp.	Result	Test	Comparison	Result
					RYGB (Post-Pre) vs. VLCD (Post-Pre)	o						
				DEBQ-emotional	RYGB (Post-Pre) vs. VLCD (Post-Pre)	o						
				DEBQ-external	RYGB (Post-Pre) vs. VLCD (Post-Pre)	↓						
VSG												
Li [m] 2019				YFAS	Post vs. Pre-RYGB	↓				HAMD	RYGB: VSG Post vs. Pre	o
				YFAS	Post vs. Pre-OB	o					OB: Post vs. Pre	o
										HAMA	RYGB: VSG Post vs. Pre	↓
											OB: Post vs. Pre	o
Hu [m] 2020										HAMD	RYGB: VSG Post vs. Pre	o
											OB: Post vs. Pre	o
										HAMA	RYGB: VSG Post vs. Pre	o
											OB: Post vs. Pre	o
											No sig. interaction group x time effects in HAMA and HAMD	
Holsen [n] 2018				TFEQ-uncontrolled	Post- vs. Pre-VSG	↓				BDI-II depression	Post vs. Pre-VSG	↓
				TFEQ-emotional	Post- vs. Pre-VSG	↓				STAI anxiety	Post vs. Pre-VSG	o
				TFEQ-restraint	Post- vs. Pre-VSG	↑						
				DEBQ-restraint	Post- vs. Pre-VSG	o						
				DEBQ-emotional	Post- vs. Pre-VSG	↓						
				DEBQ-external	Post- vs. Pre-VSG	↓						
				PFS	Post- vs. Pre-VSG	↓						
AGB												
Bruce [o]				EI-restraint	Post vs. Pre-AGB	↑				CES-D depression	Post vs. Pre-AGB	o

Table 2.9-B Results of eating behaviour measurements from individual studies												
Author	**Food intake**			**Eating behaviour**			**Nausea and Dumping Syndrome**			**Mood**		
	Test	Comparison	Result	Test	Comparison	Result	Test	Comp.	Result	Test	Comparison	Result
2012												
				EI-disinhibition	Post vs. Pre-AGB	↓						
				EI-hunger	Post vs. Pre-AGB	↓						
MULTIPLE												
Scholtz [p] 2013	*ad libitum* ice cream intake	RYGB vs. AGB	o	BED (prevalence)	Pre-RYGB vs. Pre-AGB vs. OW	o	Nausea VAS	Fasted: RYGB vs. AGB	↑	PANAS-positive	RYGB vs. AGB vs. OW	o
	3 day food diary	% fat: RYGB vs. AGB	↓		Post-RYGB vs. Post-AGB vs. OW	o		Δ Post-*ad libitum* ice cream: RYGB vs. AGB	o	PANAS-negative	RYGB vs. AGB vs. OW	o
		% CHO: RYGB vs. AGB	o	EDEQ-restraint	RYGB vs. AGB	↓		Fasted: RYGB vs. OW	o	BDI-II depression	RYGB vs. AGB vs. OW	o
		% protein: RYGB vs. AGB	o	DEBQ-restraint	RYGB vs. AGB	o		Fasted: AGB vs. OW	o	BAS-drive	RYGB vs. AGB vs. OW	o
				DEBQ-emotional	RYGB vs. AGB	o	Sleepiness VAS	Δ Post-*ad libitum* ice cream: RYGB vs. AGB	o	BAS-reward responsiveness	RYGB vs. AGB vs. OW	o
				DEBQ-external	RYGB vs. AGB	o	Blood pressure, pulse	Δ Post-*ad libitum* ice cream: RYGB vs. AGB	o	BAS-fun skeeking	RYGB vs. AGB vs. OW	o
				EDEQ-restraint	RYGB vs. OW	↓	Dumping syndrome	Post-meal: RYGB vs. AGB	↑	BIS	RYGB vs. AGB vs. OW	o
				DEBQ-restraint	RYGB vs. OW	o	(retrospective Arts and Sigstad)			Barratt impulsivity	RYGB vs. AGB vs. OW	o
				DEBQ-emotional	RYGB vs. OW	o						
				DEBQ-external	RYGB vs. OW	↓						
				EDEQ-restraint	AGB vs. OW	o						
				DEBQ-restraint	AGB vs. OW	o						
				DEBQ-emotional	AGB vs. OW	o						
				DEBQ-external	AGB vs. OW	o						
Goldstone [p] 2015							Nausea VAS	RYGB: Octreotide vs. Saline	o [e]	PANAS-positive	RYGB: Octreotide vs. Saline	o [e]
								AGB: Octreotide vs. Saline	o		AGB: Octreotide vs. Saline	o
							Sleepiness VAS	RYGB: Octreotide vs. Saline	o [e]	PANAS-negative	RYGB: Octreotide vs. Saline	o [e]

Table 2.9-B Results of eating behaviour measurements from individual studies												
Author	**Food intake**			**Eating behaviour**			**Nausea and Dumping Syndrome**			**Mood**		
	Test	Comparison	Result	Test	Comparison	Result	Test	Comp.	Result	Test	Comparison	Result
								AGB: Octreotide vs. Saline	o		AGB: Octreotide vs. Saline	o
							Blood pressure, pulse	RYGB: Δ meal (Post-Pre) Octreotide vs. Saline	o [e]	Stress, Anxiety VAS	RYGB: Octreotide vs. Saline	o
								AGB: Δ meal (Post-Pre) Octreotide vs. Saline	o			

Table 2.9-B Summary of eating behaviour measurements from individual studies

Footnotes: [l-p]: probable overlapping datasets, [e]: n=9 for RYGB (n=2 performed task outside scanner), [#] (pre-MRI but not post-MRI). **Δ:** change.

Abbreviations: comp: comparison, **RYGB**: Roux-Y gastric bypass, **VSG**: Vertical sleeve gastrectomy, **AGB**: Adjusted gastric band, **CBT**: cognitive behavioural therapy, **CHO:** carbohydrates, **BED:** binge eating disorder, **BIS:** behavioural inhibitory scale, **BDI-II:** Beck Depression Inventory II**, DEBQ:** Dutch Eating Behaviour Questionnaire, **EI:** eating inventory, **EDEQ: HAMA:** Hamilton Anxiety Rating Scale, **HAMD**: Hamilton Depression Rating Scale, **HE**: high-energy density, **LE:** low-energy density, **LCD**: low-calorie diet, **TFEQ:** Three Factor Eating Questionnaire, **VLCD:** very low calories diet, **NF:** non-food, **NT**: no treatment, **NW**: normal weight (lean), **OB**: obesity, **OW**: overweight, **NO**: Non-obesity, **WL:** weight loss, **VAS:** visual analogue scale, **PFS:** power of food scale, **YFAS:** Yale Food Addiction Scale , **↑:** increased/higher, **↓**: decreased/lower, **o:** no change/difference, **()** not significant

Table 2.10 Correlations of fMRI findings with behavioural outcomes from individual studies

Author	Group effect	Task contrast	Food contrast	average all ROIs	NAcc	Caudate	Putamen	Lent n.	Thalamus	Amygdala	Hippo	PHG	VTA	Insula	Precuneus	ACC	Paracingulate gyrus	Frontal pole	dlPFC	IFG	MFG	SFG	vmPFC	OFC
RYGB																								
Ochner [l] 2012	Δ RYGB (Post-Pre): corr. vs. Δ liking (Post-Pre)	n/a	HE > LE		o	+ve corr	o	+ve corr	+ve corr	o	o	o	o	o	o	+ve corry 28 BA32	o	o	o[3]	o	+ve corr BA8[p]	+ve corr BA8	o	o
	Δ RYGB (Post-Pre): corr. vs. Δ desire to eat (Post-Pre)		HE > LE		o	o	o	o	o	o	o	o	o	o	+ve corr	o	o	o	o	o	o	o	o	o	o
Zoon 2018	Δ RYGB (Post-Pre): corr. vs. Δ pref. HE/HS vs. LE/LS (Post-Pre)	n/a	see fROI												+ve corr HE > LE							o LE > rest		
	Δ RYGB (Post-Pre): corr. vs. Δ liking or wanting (Post-Pre)		see fROI												o HE > LE or NF							o LE > rest		
Zoon 2018	Δ RYGB (Post-Pre): corr. vs. Δ hunger, fullness, volume, desire to eat (Post-Pre)	no-go > rest	HE															o	o	o	o	o		
			LE									fullness - ve corr												
Zoon 2018	Δ RYGB (Post-Pre): corr. vs. Δ pref. LE/LS vs. HE/HS (Post-Pre)	n/a	see fROI												o HE or LE > rest			o HE > NF				o HE > NF		
	Δ RYGB (Post-Pre): corr. vs. Δ liking, wanting or intensity (Post-Pre)		see fROI												o HE or LE > rest			o HE > NF				o HE > NF		
Faulconbridge [w] 2016	Δ RYGB (Post-Pre): corr. vs. Δ liking HE-LE (Post-Pre)		HE > LE										o											
Salem 2021	Δ RYGB (Post-Pre): corr. vs. Δ DEBQ-restraint (Post-Pre)		HE/LE > rest		o	o	o			o	o			o			o						o	
	Δ VLCD (Post-Pre): corr. vs. Δ DEBQ-restraint (Post-Pre)		HE/LE > rest		o	+ve	o			o	o			o			+ve						o	
Scholtz [ew] 2013	Post-RYGB: corr. vs. ice cream pleasantness	n/a	HE > NF	+ve corr [g]																				
	Post-RYGB: corr. vs. Arts or Sigstad dumping scores			o [g]						o														o
VSG																								
Li [m] 2019	Δ VSG (Post-Pre): corr. vs. Δ YFAS (Post-Pre)	n/a	HE > LE																o					
	Δ VSG (Post-Pre): corr. vs. Δ craving HE-LE (Post-Pre)		HE > LE																+ve					
Faulconbridge [w] 2016	Δ VSG (Post-Pre): corr. vs. Δ liking HE-LE (Post-Pre)		HE > LE										o											
AGB																								
Bruce [o]	Pre-AGB: corr. vs. Δ EI-restraint, -disinhibition or -hunger (Post-Pre)	n/a	HE/LE > NF									o		o ant						o	o	o	o	

Table 2.10 Correlations of fMRI findings with behavioural outcomes from individual studies

Author	Group effect	Task contrast	Food contrast	average all ROIs	NAcc	Caudate	Putamen	Lent n.	Thalamus	Amygdala	Hippo	PHG	VTA	Insula	Precuneus	ACC	Paracingulate gyrus	Frontal pole	dlPFC	IFG	MFG	SFG	vmPFC	OFC
	Pre-AGB: corr. vs. Δ EI-restraint (Post-Pre)		HE/LE > NF									o		o ant						o	o	o	o	
	Pre-AGB: corr. vs. Δ EI-disinhibition (Post-Pre)		HE/LE > NF									o		o ant						+ve BA45	o	o	o	
	Pre-AGB: corr. vs. Δ EI-hunger (Post-Pre)		HE/LE > NF									o		o ant						o	o	o	o	
	Post-AGB: corr. vs. Δ EI-restraint, -disinhibition or -hunger (Post-Pre)	n/a	HE/LE > NF									o		o ant						o	o	o	o	
	Post-AGB: corr. vs. Δ EI-restraint (Post-Pre)		HE/LE > NF									o		o ant						-ve BA45	o	o	o	
	Post-AGB: corr. vs. Δ EI-disinhibition (Post-Pre)		HE/LE > NF									o		o ant						o	+ve BA47	o	o	
	Post-AGB: corr. vs. Δ EI-hunger (Post-Pre)		HE/LE > NF									o		o ant						+ve BA45	o	o	o	
Scholtz [ow]	post-AGB: corr. vs. ice cream pleasantness		HE > NF	(+ve corr) [#]																				
MULTIPLE																								
Scholtz [p]	Post-RYGB: corr. vs. ice cream pleasantness	n/a	HE > NF	+ve corr [#]																				
	Post-AGB: corr. vs. ice cream pleasantness		HE > NF	(+ve corr) [#]																				
	Post-RYGB: corr. vs. Arts or Sigstad dumping scores			o [#]						o														o
Faulconbridge	Δ RYGB (Post-Pre): corr. vs. Δ liking HE-LE (Post-Pre)		HE > LE										o											
	Δ VSG (Post-Pre): corr. vs. Δ liking HE-LE (Post-Pre)		HE > LE										o											
	Δ OB (Post-Pre): corr. vs. Δ liking HE-LE (Post-Pre)		HE > LE										o											
	Δ RYGB/VSG/OB (Post-Pre): corr. vs. Δ liking HE-LE (Post-Pre)		HE > LE										o											

Table 2.10 Correlations of fMRI findings with behavioural outcomes from individual studies

Footnotes: [I-p]: probable overlapping datasets, [#]: not in original paper, added on review of coordinates, **Δ:** change.

Abbreviations: ACC: anterior cingulate gyrus, **AGB**: Adjusted gastric band, **ant:** anterior, **BA:** Broadman area, **CBT**: cognitive behavioural therapy, **corr:** correlation, **EI:** eating inventory, **dlPFC:** dorsolateral prefrontal cortex, **fROI:** functional region of interest, **HE**: high-energy density, **HS:** high sugar, **IFG:** inferior frontal gyrus, **LE:** low-energy density, **LS:** low sugar **LCD:** low calorie diet, **VLCD:** very low calorie diet, **MFG:** medial frontal gyrus, **NAcc:** nucleus accumbens, **NF:** non-food, **OFC:** orbitofrontal cortex, **OB**: obesity, **PHG:** parahippocampal gyrus, **Pref:** preference, **VTA:** ventral tegmental area, **RYGB**: Roux-Y gastric bypass, **SFG:** superior frontal gyrus, **VSG**: Vertical sleeve gastrectomy **o:** no significant correlation with BOLD signal, **-ve corr:** negative correlation with BOLD signal, **+ve corr:** positive correlation with BOLD signal

2.5.14 Mechanistic studies and correlations with fMRI outcomes

Results of hormonal and metabolic measurements from individual studies are summarised in **Table 2.11**. Findings from interventional and association studies examining relationships between potential mechanistic mediators of the effects of obesity surgery from individual studies are summarised in Table **2.12**.

Measurements of hormonal mediators

Results of hormonal mediators measurements from individual studies are summarised in **Table 2.11**

Tweleve studies out of 23 (52.5%) 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 (20), total ghrelin at 3 months (156), acyl ghrelin at 6 months (46) concentrations, but there was an increase in fasting PYY at 14 weeks post-RYGB (162). 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 AGB surgery and BMI-matched unoperated controls, while *fasting* PYY was higher after RYGB surgery than after AGB surgery though not BMI-matched controls (16).

As expected, in the *fed state*, in longitudinal studies post-prandial plasma GLP-1 increased at 1 months (20), and both plasma GLP-1 and PYY at 14 weeks (162) 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 fMTRI findings (163).

In cross-sectional studies plasma GLP-1, PYY and bile salts, but not FGF-19, were higher at ~8 months after RYGB than AGB surgery, while fasting insulin was similar between the surgical groups (16, 160).

***Post-VSG**:* In longitudinal studies, *fasting* total or acyl ghrelin at 1 (44), 6 (46),and (45)12 months, glucose at 12 months (45), leptin and insulin at 1 months (44, 45) 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 (38)

***Post-AGB**:* Hormonal changes were not assessed in any longitudinal studies after AGB 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 AGB surgery from BMI-matched controls (16).

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, Exendin9-39, 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 4 weeks after RYGB surgery compared to pre-operatively in the fasted state, but not 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) (20). Similarly, in this study in the *fasted* state, Exendin9-39 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) (20). However acute intravenous infusion of Exendin9-39, did not change appetite for savoury and sweet foods after RYGB surgery (20).

In a cross-sectional study in the *fed state,* the acute administration of the somatostatin analogue, Octreotide, abolished the higher post-prandial plasma GLP-1 and PYY concentrations after RYGB compared to AGB surgery, by lowering both plasma concentrations (160). 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 AGB surgery (n=7-9). Furthermore, a greater suppression of plama 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/AGB groups (160). Likewise, in a separate cohort of patients after RYGB surgery, acute Octreotide administration increased motivation to earn sweets using a progressive ratio task (160), with motivation previously shown to decrease after RYGB surgery (174)

Table 2.11 Hormonal mediators measurements from individual studies

Author	Ghrelin			GLP-1			PYY			Leptin			Insulin			Glucose			Others		
	Test	Comparison	Result	Test	Comparison	Result	Test	Comparison	Result	Test	Comparison	Result	Test	Comparison	Result	Test	Comparison	Result	Test	Comparison	Result
RYGB																					
Ten Kulve 2017				Total amidated GLP-1	Fasted: Post vs. Pre-RYGB	o										Glucose	Fasted: Post vs. Pre	o			
					Fed: Post vs. Pre-RYGB	↑											Fed: Post vs. Pre	↑			
					Pre-RYGB: Ex9-39 vs. Placebo	o											Pre: Ex9-39 vs. Placebo	↑			
					Post-RYGB: Ex9-39 vs. Placebo	o											Post: Ex9-39 vs. Placebo	↑			
Zoon 2018	Pre-meal total ghrelin	Post vs. Pre-RYGB	o																Endocannabinoids		
																			Pre-meal anandamide	Post vs. Pre	↑
																			Pre-meal 2-AG, DHEA, DLE, OEA, PEA, SEA,	Post vs. Pre	o
Frank 2016																HbA1c	Post-RYGB vs. OB	↓			
Frank 2014																Pre-meal capillary glucose	RYGB vs. OB	o			
																	RYGB vs. NW	o			
																	OB vs. NW	o			
VSG																					
Li [m] 2019	Fasted total ghrelin	Post- vs. Pre-VSG	↓							Fasted leptin	Post- vs. Pre-VSG	↓	Fasted	Post- vs. Pre-VSG	↓						
										Fasted leptin/BMI	Post- vs. Pre-VSG	↓									
Holsen [n] 2018	Fasted acyl ghrelin	Post- vs. Pre-VSG	↓							Fasted leptin	Post- vs. Pre-VSG	↓	Fasted	Post- vs. Pre-VSG	↓	Fasted glucose	Post vs. Pre	↓			
AGB																					
No studies																					

MULTIPLE																					
Scholtz [P] 2013	Acyl ghrelin	Fasted: Post-RYGB vs. Post-AGB	o	GLP-$1_{1\text{-}36,\ 7\text{-}36,\ 9\text{-}36}$ amide	Fasted: Post-RYGB vs. Post-AGB	o	$PYY_{1\text{-}36,\ 3\text{-}36}$	Fasted: Post-RYGB vs. Post-AGB	↑				Insulin	Fasted: Post-RYGB vs. Post-AGB	↓	Total bile acids	Fasted: Post-RYGB vs. Post-AGB	o	Total bile acids	Fasted: Post-RYGB vs. Post-AGB	↑
		Δ Post-*ad libitum* ice cream: Post-RYGB vs. Post-AGB	o		Δ Post-*ad libitum* ice cream: Post-RYGB vs. Post-AGB	↑		Δ Post-*ad libitum* ice cream: Post-RYGB vs. Post-AGB	↑					Δ Post-*ad libitum* ice cream: Post-RYGB vs. Post-AGB	o		Δ Post-*ad libitum* ice cream: Post-RYGB vs. Post-AGB	↑		Δ Post-*ad libitum* ice cream: Post-RYGB vs. Post-AGB	↑
		Fasted: Post-RYGB vs. OW	o		Fasted: Post-RYGB vs. OW	o		Fasted: Post-RYGB vs. OW	o					Fasted: Post-RYGB vs. OW	o		Fasted: Post-RYGB vs. OW	o		Fasted: Post-RYGB vs. OW	o
		Fasted: Post-AGB vs. OW	o		Fasted: Post-AGB vs. OW	o		Fasted: Post-AGB vs. OW	o					Fasted: Post-AGB vs. OW	o		Fasted: Post-AGB vs. OW	↓		Fasted: Post-AGB vs. OW	o
Goldstone [P] 2015				Fed: GLP-$1_{7\text{-}36\ amide,\ 9\text{-}36\ amide}$	RYGB: Octreotide vs. Saline	↓ *	Fed: $PYY_{1\text{-}36,\ 3\text{-}36}$	RYGB: Octreotide vs. Saline	↓ *				Fed insulin	RYGB: Octreotide vs. Saline	o *	Fed glucose	RYGB: Octreotide vs. Saline	↑ *	Fed FGF19	RYGB: Octreotide vs. Saline	↓ *
					AGB: Octreotide vs. Saline	↓		AGB: Octreotide vs. Saline	↓				Post-prandial: Saline RYGB > BAND	AGB: Octreotide vs. Saline	o		AGB: Octreotide vs. Saline	o		AGB: Octreotide vs. Saline	o
					Δ RYGB (Octreotide-Saline) vs. Δ AGB (Octreotide vs. Saline)	↓ *		Δ RYGB (Octreotide-Saline) vs. Δ AGB (Octreotide-Saline)	↓ *					Δ RYGB (Octreotide-Saline) vs. Δ AGB (Octreotide vs. Saline)	o *		Δ RYGB (Octreotide-Saline) vs. Δ AGB (Octreotide vs. Saline)	↑ *		Δ RYGB (Octreotide-Saline) vs. Δ AGB (Octreotide vs. Saline)	↓ *
					Saline: RYGB vs. AGB	↑ *		Saline: RYGB vs. AGB	↑ *					Saline: RYGB vs. AGB	↑ *		Saline: RYGB vs. AGB	o *		Saline: RYGB vs. AGB	o
					Octreotide: RYGB vs. AGB	o *		Octreotide: RYGB vs. AGB	o *					Octreotide: RYGB vs. AGB	↑ *		Octreotide: RYGB vs. AGB	↑ *		Octreotide: RYGB vs. AGB	o *
Faulconbridge 2016	Fasted total ghrelin	Post- vs. Pre-RYGB	o																		
		Post- vs. Pre-VSG	↓																		
		OB: Post vs. Pre	(↑)																		
Baboumian 2019				Fed total GLP-1	RYGB: Post vs. Pre	↑															
					VSG: Post vs. Pre	↑															
					LCD-CBT: Post vs. Pre	o															
					OB: Post vs. Pre	o															
					RYGB vs. VSG: Δ Post-Pre	o															
					RYGB vs. LCD-CBT or OB: Δ Post-Pre	↑															
					VSG vs. LCD-CBT or OB: Δ Post-Pre	↑															
					LCD-CBT vs. OB: Δ Post-Pre	o															

Table 2.11 Hormonal mediators measurements from individual studies

Footnotes: [I-P]: probable overlapping datasets, [#]: not in original paper, added on review of coordinates, **Δ:** change.

Abbreviations: AGB: Adjusted gastric band, **CBT**: cognitive behavioural therapy, **GLP-1:** glucagon-like-peptide-1, **LCD:** low calorie diet, **OB**: obesity, **OW**: overweight, **↑:** increased/higher BOLD signal, **RYGB**: Roux-Y gastric bypass, **VSG**: Vertical sleeve gastrectomy, **↓**: decreased/lower BOLD signal, **o:** no change/difference in BOLD signa

Table 2.12 Findings from interventional and association studies examining relationships between potential mechanistic mediators of the effects of obesity surgery from individual studies

Author	State	Group effect	Food contrast	average all ROIs	NAcc/VS	Caudate	Putamen	Subcallosal cortex	Amygdala	Hippocampus	PHG	VTA	Insula	Operculum	Precuneus	Paracingulate gyrus	Frontal pole	dlPFC	IFG	MFG	SFG	OFC
RYGB																						
Ten Kulve 2017	Fasted: Placebo	Post- vs. Pre-RYGB	HE > NF			↓	o		o				o	(↓) rol			↓ BA10[#]					↓ BA10
			HE/LE > NF			↓	o		o				o	↓ rol								o
	Fed: Placebo	Post- vs. Pre-RYGB	HE > NF			o	o		o				o	o								o
			HE/LE > NF			o	o		o				o	o								o
	Fasted: Ex9-39	Post- vs. Pre-RYGB	HE > NF			(↑)	o		o				o	o								o
			HE/LE > NF			↑	o		o				o	o								o
	Fed: Ex9-39	Post- vs. Pre-RYGB	HE > NF			o	o		o				o	o								o
			HE/LE > NF			o	o		o				o	o								o
Zoon 2018	Fed	Δ RYGB (Post-Pre): corr. vs. Δ ghrelin (Post-Pre)	see fROI												o HE > LE or NF						o LE > rest	
		Δ RYGB (Post-Pre): corr. vs. Δ eCBs (Post-Pre)	see fROI												o HE > LE or NF						o LE > rest	
Zoon 2018	Fed	Δ RYGB (Post-Pre): corr. vs. Δ ghrelin (Post-Pre)	see fROI												o HE or LE > rest		o HE > NF				o HE > NF	
		Δ RYGB (Post-Pre): corr. vs. Δ eCBs (Post-Pre)	see fROI												o HE or LE > rest		o HE > NF				o HE > NF	
Salem 2021		Δ RYGB (Post-Pre): corr. vs. Δ fasting ghrelin, GLP-1, PYY, GIP (Post-Pre)	HE/LE > rest		o	o			o	o			o									
		Δ VLCD (Post-Pre): corr. vs. Δ fasting ghrelin, GLP-1, PYY, GIP (Post-Pre)	HE/LE > rest		o	o			o	o			o									
Scholtz [#] 2013	Fasted	Post-RYGB: corr. vs. fasted GLP-1, PYY, bile acids	HE/LE > NF	o [¥]					o													o
			HE > NF	o [¥]					o													o
			LE > NF	o [¥]					o													o
		Post-RYGB: corr. vs. post-ice cream GLP-1, PYY, bile acids	HE/LE > NF	o [¥]					o													o
			HE > NF	o [¥]					o													o
			LE > NF	o [¥]					o													o

Table 2.12 Findings from interventional and association studies examining relationships between potential mechanistic mediators of the effects of obesity surgery from individual studies

Author	State	Group effect	Food contrast	average all ROIs	NAcc/VS	Caudate	Putamen	Subcallosal cortex	Amygdala	Hippocampus	PHG	VTA	Insula	Operculum	Precuneus	Paracingulate gyrus	Frontal pole	dlPFC	IFG	MFG	SFG	OFC
VSG																						
Li [m] 2019	Fasted	Δ VSG (Post-Pre): corr. vs. Δ fasted total ghrelin (Post-Pre)	HE > LE															+ve				
		Δ VSG (Post-Pre): corr. vs. Δ fasted insulin or leptin (Post-Pre)	HE > LE															o				
AGB																						
No studies																						
MULTIPLE																						
Scholtz [p] 2013	Fasted	Post-RYGB: corr. vs. fasted GLP-1, PYY, bile acids	HE/LE HE/NF LE/NF	o [g]					o													o
		Post-RYGB: corr. vs. post-ice cream GLP-1, PYY, bile acids	HE/LE HE/NF LE/NF	o [g]					o													o
Goldstone [p] 2015	Fed	Post-RYGB: Octreotide vs. Saline	HE/LE > NF	↑ [i]	↑	o			o				o ant									
		Post- AGB: Octreotide vs. Saline	HE/LE > NF	o [i]	o	o			o				o ant									
		Δ RYGB (Octreotide-Saline) vs. Δ AGB (Octreotide vs. Saline)	HE/LE > NF	o [i]	o	o			o				o ant									
		Post-RYGB/AGB: Octreotide vs. Saline	HE/LE > NF	↑ [i]	(↑)																	
	Fed	RYGB/AGB: corr. Δ (Octreotide-Saline) vs. Δ PYY (Octreotide-Saline)	HE/LE > NF	+ve corr [i]																		
		RYGB/AGB: Corr Δ (Octreotide-Saline) vs. Δ GLP-1 (Octreotide-Saline)	HE/LE > NF	(+ve corr) [i]																		
		RYGB/AGB: Corr Δ (Octreotide-Saline) vs. Δ FGF19 (Octreotide-Saline)	HE/LE > NF	o [i]																		
	Fed	Post-RYGB: Octreotide vs. Saline	Auditory-motor-visual	o [h]																		o (motor)
		Post-AGB: Octreotide vs. Saline		o [h]																		o (motor)
Faulconbridge 2016	Fasted	Δ RYGB (Post-Pre): corr. vs. Δ fasted total ghrelin (Post-Pre)	HE > LE									+ve corr										
		Δ VSG (Post-Pre): corr. vs. Δ fasted total ghrelin (Post-Pre)	HE > LE									+ve corr										

Table 2.12 Findings from interventional and association studies examining relationships between potential mechanistic mediators of the effects of obesity surgery from individual studies

Author	State	Group effect	Food contrast	average all ROIs	NAcc/VS	Caudate	Putamen	Subcallosal cortex	Amygdala	Hippocampus	PHG	VTA	Insula	Operculum	Precuneus	Paracingulate gyrus	Frontal pole	dlPFC	IFG	MFG	SFG	OFC
		Δ OB (Post-Pre): corr. vs. Δ fasted total ghrelin (Post-Pre)	HE > LE									o							o	o	o	
Baboumian 2019	Fed	Δ RYGB (Post-Pre): corr. vs. Δ peak fed - fasted total GLP-1 (Post-Pre)	HE > LE		o	o	o	o	o	o	o	o	o	o	o	[+ve corr]# BA10#	[+ve corr]# BA10#	o	o	o	o	o
		Δ VSG (Post-Pre): corr. vs. Δ peak fed - fasted total GLP-1 (Post-Pre)	HE > LE		o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o

Table 2.12 Findings from interventional and association studies examining relationships between potential mechanistic mediators of the effects of obesity surgery from individual studies

Footnotes: ᴸᴾ: probable overlapping datasets, #: not in original paper, added on review of coordinates, **Δ:** change.

Abbreviations: AGB: Adjusted gastric band, **ant:** anterior, **BA:** Broadman area, **CBT**: cognitive behavioural therapy, **corr:** correlation, **dlPFC:** dorsolateral prefrontal cortex, **GLP-1:** glucagon-like-peptide-1, **LCD:** low calorie diet, **HE**: high-energy density, **IFG:** inferior frontal gyrus, **LE:** low-energy density, **MFG:** medial frontal gyrus, **NAcc:** nucleus accumbens, **NF:** non-food, **SFG:** superior frontal gyrus, **OB**: obesity, **OW**: overweight, **↑:** increased/higher BOLD signal, **RYGB**: Roux-Y gastric bypass, **VSG**: Vertical sleeve gastrectomy, **VTA:** ventral tegmental area, **o:** no significant correlation with BOLD signal, **-ve corr:** negative correlation with BOLD signal, **+ve corr:** positive correlation with BOLD signal

Correlations of post-operative fMRI measures with hormonal measures

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) (156); (ii) in the *fasted* state*,* a greater decrease in BOLD signal to HE vs. LE food in the VTA (the only anatomical ROI 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 (46); (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 seum insulin or leptin) (44); (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) (163).

In three longitudinal studies of correlation with satiety gut hormones: (i) in the *fasted* state, a greater decrease in BOLD signal during evaluation of HE food and LE food pictures in the OFC fROI (but not amygdala) at ~14 weeks after RYGB surgery was associated with a greater increase in post-prandial plasma PYY after surgery with a similar trend for plasma GLP-1 (n=11) (162); (ii) 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 (38); (iii) 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 overall changes in gut hormones were not reported (n=16-19) (163).

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) (16).

2.5.15 Correlations of post-operative fMRI measures with aversive measures

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 amgydala alone at ~8 months after RYGB surgery with retrospective dumping syndrome scores in the three months following surgery (n=21) (16). There were also no differences in fasting or post-prandial nausea ratings between the RYGB and AGB surgery despite differences in food cue reactivity and appeal between the groups (16).

In a longitudinal study in the *fasted* state, changes in BOLD signal during valuation of HE foods in amygdala or OFC , at ~14 weeks after RYGB surgery did not correlate with the changes in fasting or post-prandial nausea at ~14 weeks after surgery or changes in dumping syndrome early after surgery (162). While two other longitudinal studies reported either increases (20) or no change (163) in nausea ratings after RYGB surgery, no correlations with fMRI finding were made.

2.5 Discussion

This systematic review aimed to review the literature for fMRI studies that investigated changes in food cue reactivity, and taste and odour responses assessed by changes in BOLD signal or 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 studies 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 23 studies were in general highly variable between studies 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 **Figure 2.3 .** Furthermore, confounding factors were infrequently reported that may contribute to variability in results e.g. menstrual cycle (175), motion in scanner, mood assessment (176).

Unfortunately, the low number of studies when dividing by study design (longitudinal, cross-sectional), surgery type (RYGB, VSG, AGB), 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 **Figure 2.4.**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.

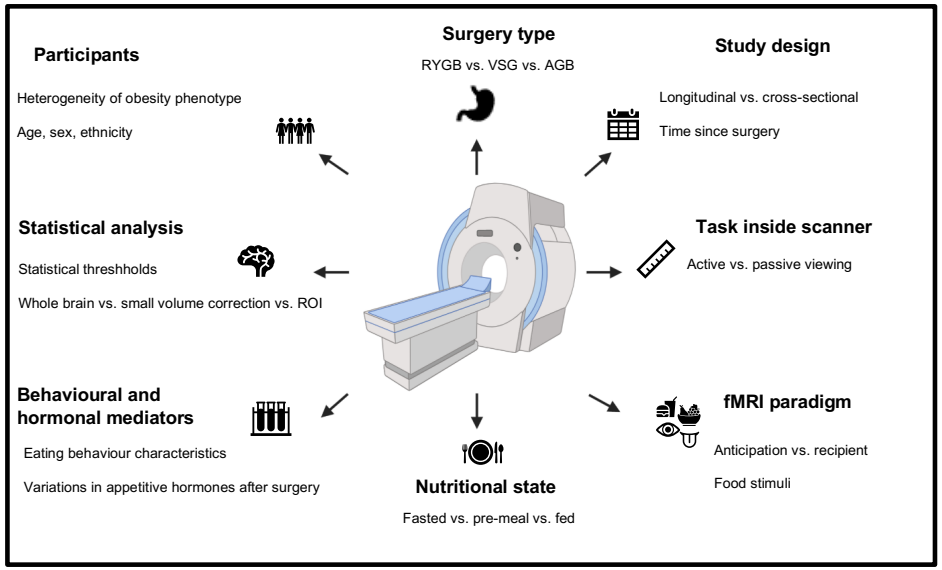

Figure 2.3 Schematic representation of factors contributing to variability in fMRI studies

Abbreviations: **RYGB**: Roux-Y gastric bypass, **VSG**: Vertical sleeve gastrectomy, **AGB**: Adjusted gastric band, **SVC:** small volume correction**, fROI:** functional region of interest

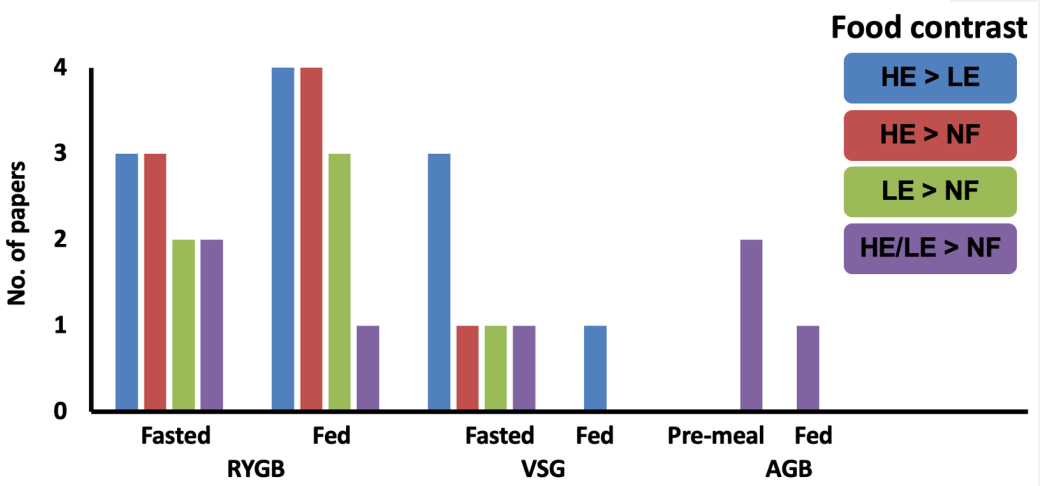

Figure 2.4 summary of longitudinal studies by nutritional state and fMRI paradigm

2.5.1 Collated results of 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 (177, 178), food liking/wanting (179), food intake (127, 136), healthier eating behaviours (145) after surgery that will contribute to the marked weight loss. This will also enable sustained weight loss when compared to dietary interventions (180, 181). Consistent with this literature, this was also seen in many studies that also included fMRI with reduced food cue reactivity in brain regions that are 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. Although it is difficult to prove from fMRI studies (i.e reduced food cue reactivity to HE vs. object *but not* LE vs. object, or HE vs. LE food pictures) since these contrats were not consistenly tested, but it has been seen in other measures (such as food preference rating)

For example, subcortical (caudate, nucleus accumbens, putamen, pallidum) and limbic regions (amygdala, hippocampus, PHG), insula and cingulate cortexes defined by BA 6/8/9/10/19/23/24/32 are regions in the brain that are 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 cue reactivity to HE or HE/LE food pictures. Overall the fMRI findings after RYGB/VSG surgery were in agreement with this hypothesis. Food cue reactivity either decreaed (20, 25, 33, 38, 46, 153, 162, 163), or did not change (44, 155, 156, 161). Even no change in food cue reactivity may be interpreted as a relative decrease, since non-surgical or non-pharmacological weight loss might be expected to increase food cue reactivity (26, 34, 37, 182). Only in one cross-sectional study, did those who had RYGB surgery have higher HE/LE food cue reactivity in the insula, hippocampus, and cingulate cortex compared to a control unoperated group with obesity (159). 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 patable food picture, compared to passive picture viewing in most studies. However, an active evaluation task did not preclude reductions in food cue reactivity being seen both cross-sectionally and longitudinally in other studies (16, 162).

These findings from longitudinal studies, while variable, suggest a general tendency for a unidirectional reduction in food cue reactivity, unlike life-style and dietary interventions where food cue reactivity in reward implicated regions tend to increase (26, 34, 37, 182). Higher BOLD signal in ventral striatum to a food incentive delay task was reported after successful and unsuccesful weight loss at six months after dietary intervention (34). 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 (26), indicating a counteract effect of brain response to food after lifestyle intervention.

Food preference was further examined by gustatory stimuli in two longitudinal studies. Decrease in BOLD signal to chocolate tastant in insula, the primary gustatory cortex, was reported in one study (20). 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 (157). While evidence on taste detection threshholds after RYGB surgery is variable, a recent systematic review on tase 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 for food preference alteration in a subgroup of patients (183).

2.5.2 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 (16, 25, 33, 46, 156, 159) and VSG (44-46) surgeries. However, fMRI correlations were rarely examined between decrease in BOLD signal to HE foods and decreases in food hedonics (25, 156), 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 (44), (ii) lower 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 AGB surgery, with both HE food cue reactivity and pleasantness being lower after RYGB than AGB surgery (16).

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 AGB using 3-day food diary (16). However, the literature on dietary measures, specifically food intake after obesity surgery consistenly indicates lower total energy intake, but have not consistently reported differential food preference away from HE towards LE (low fat and low sugar) foods (122, 128). While most studies focused on HE food consumption, liking and wanting, little is known about preferentially reduced HE responses or intake (33). The available evidence indicates that change in food preference might serve as an additional function of RYGB surgery and implicates better weight loss outcomes (128, 184). 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) (38, 44, 46, 153, 161, 173), suggesting a selective reduction in food preference to HE food mediated by reduced food cue reactivigty 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 (20, 33, 153, 155, 157) only after RYGB surgery when measured by VAS. 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.

Personality (psychological) traits are important contributors in shaping eating behaviour. The most frequently used eating behaviour questionares are TFEQ and DEBQ across studies, aimed to measure dietary restraint (tendency to restrain from food intake to prevent weight gain or loose 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 AGB surgery (16) or did not differ compared to unoperated controls (158, 159), or longitudinally increased after RYGB (163), VSG (45), and AGB surgeries (149). 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 (185), insula (186) and dlPFC (187) in *fasted state*, and in putamen, caudate (186), OFC, dlPFC (186) in *fed state* ; or (ii) a *negative correlation* with BOLD signal in dlPFC (188) NAcc, caudate, putamen in *fasted state* (186), and in amygdala in *fed state* (186), or no effect with BOLD signal in *fastedd state* (189, 190).

Finally, disinhibited eating was lower than unoperated controls (159) or did not change after RYGB surgery (158), and decreased after AGB surgery (149), but correlations with changes in food cue reactivity were either not examined or not significant (149). Disinhibited eating has been associated with enhanced food cue reactivity(191-193), enhanced insula and NAcc responses to palatable food taste (194, 195), and altered functional connectivity between inhibitory control and reward brain regions (196, 197).

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 6/8/9/10/11/13/25/44/45/46/47 (frontal pole, dlPFC, dmPFC, IFG, MFG, SFG) had variable changes and often 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 (198). In addition, the OFC is essential in subjective reward evaluation (199).

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 cogenitive-inhibitory circuit recruitment to food cues as they may hold a lower reward value or salience after surgery; whilst, 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 picture in dlPFC after VSG surgery suggesting an enhanced inhibitory effect (44, 161). BOLD signal in other frontal regions (IFG, MFG, SFG) decreased (25, 33, 153, 159) or increased (134, 155, 159) after RYGB surgery.

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 (37). 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 (182)

2.5.3 Comparison of different obesity surgery procedures

Across **AGB** studies, food cue reactivity to HE food pictures was only decreased in clusters within the frontal pole BA9/10 in two longitudinal studies (149, 150), and in paracingulate gyrus and precuneus in participants after AGB surgery and LCD group in one study (150). In both of these studies, reduction in BOLD signal was more pronounced in the pre-meal state but not fed state (149, 150). The comparable affect on food cue reactivity in participants after AGB surgery and LCD group in the latter study suggests a similar of this surgery to dietary interventions. Furthermore, when participants after AGB 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 behviour questionnaires (16). Evidence from a systematic review of dietary intake after AGB surgery support these findings (200). In a longitudinal study, increased energy intake from high fat and high sugar foods was reported

after AGB surgey compared to RYGB surgery at 1 year (124). 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 AGB surgery.

Only two studies directly compare food cue reactivity longitudinally in RYGB vs. VSG (38) or cross-sectionally in RYGB vs. AGB (16), suggesting an inhanced BOLD signal to HE vs. LE food picture in dlPFC after RYGB compared to VSG surgery (38), and reduced BOLD signal to HE food picture in regions implicated in reward processing regions (NAcc, caudate, putamen) after RYGB compared to AGB surgery (16) .The available literature was mostly investigating RYGB surgery accounting for 73.9% of included studies compared to 26.1% and 21.7% for VSG and AGB surgeries respectively. Behavioural non-fMRI studies have shown a comparable effect of RYGB and VSG surgeries on eating behaviour (specifically food intake and food preference) (123, 127), and their superior effect to AGB surgery in terms of sustained weight loss (201) and changes in hunger, fullness, and food prefrences (136). 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 AGB) 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 (202). 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 AGB surgeries.

2.5.4 Quality of studies

Based on a recent published article for best practice in nutrition-related fMRI studies (147), the reviewed literature lacks some of the mandatory, highly recommended, and recommended requirements, with only 64.9%, 58.3%, and 40.7%, respectively of these requirements being met across studies **Figure 2.5 and Appendix 2**. The important practices that are likely to aid reproducibility, replication and optimisation of interpretation of fMRI findings but 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 four longitudinal studies of RYGB and VSG surgery included a control group with obesity (matched-BMI), whom either received no treatment to control for order effects (46), or dietary/lifestyle intervention and weight loss itself (38, 162, 163). Overall, food cue reactivity to HE/LE food pictures in control groups was either unchanged (162), or changed in the opposite direction to the RYGB/VSG surgery groups. However, in one RYGB surgery longitudinal study when a sub-group of participants after RYGB surgery and VLCD were matched for weight loss (n=7), no difference between groups of matched weight loss in BOLD signal to HE/LE food pictures in fROI analysis for regions implicated in reward (NAcc, caudate, putamen, amygdala, insula, OFC). While these findings may suggest that reduction in food cue reactivity is mediated by weight loss, it was examined in a very small sample size (n=7), and reductions in BOLD signal in these regions were not seen after RYGB surgery in this study. This was not the same for an AGB surgery study, where despite a trend for greater weight loss in the dietary intervention group than AGB surgery group, HE food cue reactivity decreased in both groups within BA9 (paracingulate gyrus and SFG), though did change in opposite directions between groups in BA19 (precuneus) (150). However the degree of weight loss was not always comparable between surgical and non-surgcial groups. As a result, this lack of inclusion or adequate control groups is a major limitation when interpreting fMRI studies of obesity surgery.

Since females represent most of the study participants, it is cruicial to account for phase of menstrual cycle effect at time of scanning. Early and late follicular phase have differential effect on fMRI food cue reactivity in brain regions implicated in salience and reward processing (203, 204).

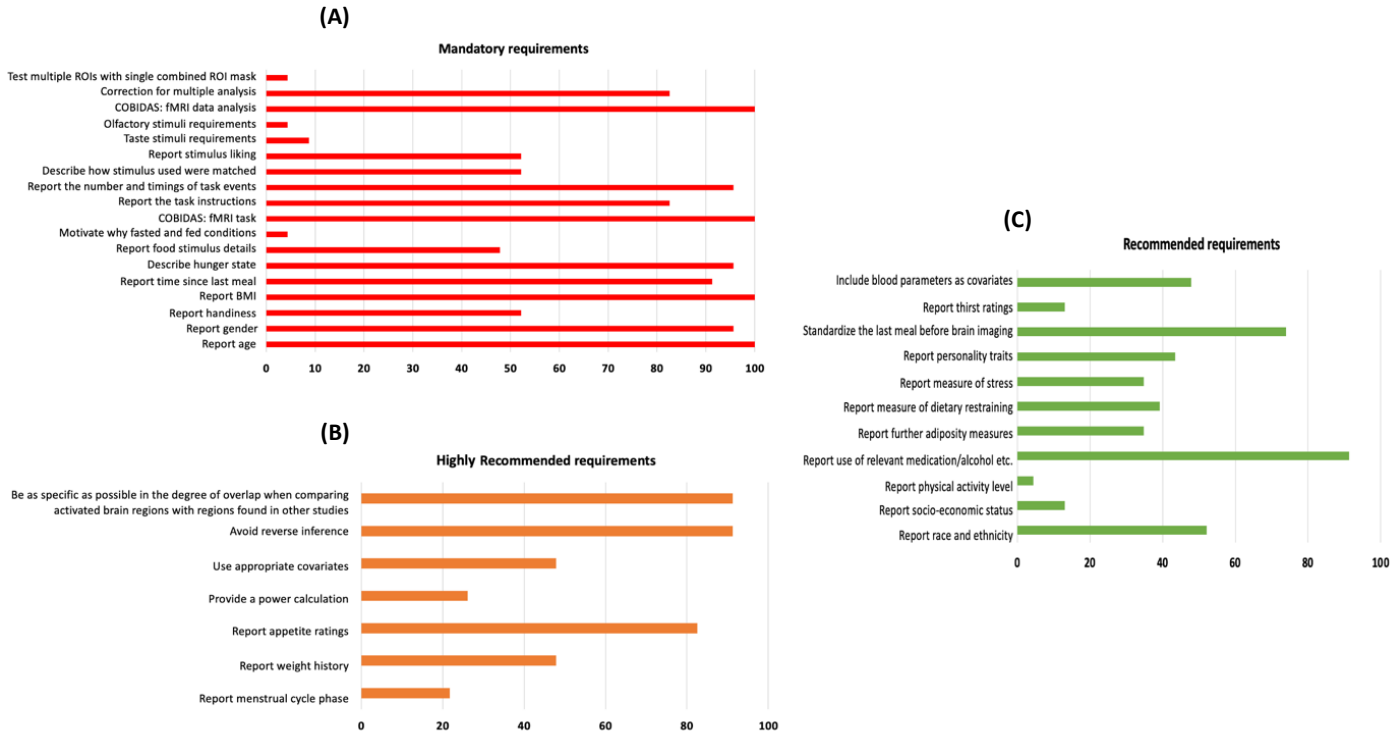

Figure 2.5 Quality assessment for individual studies by mandatory, highly recommended, and recommended requirements percentages

A quality assessment criteria was adapted from Smeet *et al* (147) to evaluate study design, analysis, and reporting of fMRI findings. (A) mandatory requirements, (B) highly recommended requirements, and (C) recommended requirements

2.5.5 Heterogeniety between studies

Participants characteristics

Within participants characteristics across the 23 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 (205). 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 (206).

Ethnicity did vary between studies, but there is no evidence of ethnic difference in obesity surgery outcomes (207), and 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 (208, 209).

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 (210). In contrast, another cross-sectional study showed *higher* BOLD signal to favorite-food cue in amygdala, insula, putamen and PHG in participants with obesity and insulin resistance compared to participants with normal weight (71). Additional studies have found correlations of direct measures of insulin resistance with food cue reactivity **(This is examined further in Chapter 5).**

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 (20), putamen (25), and at 4 months in amygdala (162), and at 6 months in VTA (46). 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 reactvity with fMRI. Although differences in food cue reactivity have been compared between successful vs. unsuccesful weight loss after RYGB surgery, the latter group did not distinguish between weight regain and poor initial weight loss response (134).

Commented [TG4]: were there no later timepoint longitudinal studies?
The latest is 6 months in Faulconbridge:decrease in VTA
Comparing both time differences and cross-sectional/longitudinal studies is difficult

for example Ghadah's study where HE food cue reactivity did not decrease at ~14 weeks
in the table BOLD signal to HE decreased in amygdala in fROI analysis

OK so I deleted all findings for HE vs. LE and HE/LE, and cross-sectional studies b/c the contrast is HE/LE or HE vs. LE or GOLDMAN included active task (crave and resist)

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 (33, 153) and VSG (44, 161) surgeries, while there is a later increase in BOLD signal to HE vs. LE food in dlPFC at 4 months after RYGB surgery (38) and 1 year after VSG surgery (45). 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 perphaps also food aversion or post-surgery discomfort), but over time increased engagement of these inhibitory circuits is needed to sustain weight loss.

Nutritional status

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 (211-216)

Since post-prandial satiety hormone responses such as PYY and GLP-1 are exaggerated after RYGB surgery, 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, HE, 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 (20, 153). 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, precunues, cingulate and other regions in frontal, parietal and occipital lobes after RYGB surgery than unoperated controls with obesity (159), whilst no differences in food cue reactivity wee seen in the fed state (158).

This is most likely explained by a floor effect, whereby food cue recativity is already suppressed to some degree in the pre-operative fed state (not only through increases in anorexigenic PYY and GLP-1, but also increases in plasma glucose (217), insulin (70) and decreases in orexigenic hormone ghrelin (43, 216), depending on the size and satiating effects of the meal), and so cannot get any lower post-operatively when 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 ghrelin after RYGB surgery could also be important here, though the literature on the effects of RYGB on the ghrelin system are highly variable (218).

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 equal across HE and LE food categories, or indeed might 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 (25, 33, 156) or VSG surgery (44), though one longitudinal RYGB surgery study found an increase in LE food cue reactivity after RYGB surgery which contributed to a decrease in HE vs. LE food reactivity (though without any increase in HE food cue reactivity) (162). As investigated further in Chapter 4, this raises the intriguing possibility that the LE food cue reactivity may be as, or even more, important than HE food reactivity in obesity and its treatment.

Most of the fMRI studies used paradigms involving food pictures or occasionally other cues such as spoken or visual food words, and many (39.1%) 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 (16, 160, 162), liking/wanting ratings (159), craving or resisting of desire for the food (45, 134)), and other tasks e.g. inhibited a motor response in a Go-NoGo task (155), or performed a 1-back memory task (158) will be problematic because of the different cognitive proxess and regional brain engagement that this will involve. This is also seen when comparing longitudinal effects of obesity surgery on reponses to anticipatory food cues and gustatory fMRI studies (20, 154). 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 (219).

fMRI analysis and interpretation

Most of the studies that performed exploratory analyses of associations of fMRI findings with clinical, hormonal and behavioural outcomes perfomed numerous correlations without any correction for multiple comparisons (155, 156).

Different analytical and statistical methods including neuroimaging processing software and pipelines, and choices of whole brain, SVC, fROI and 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 analysied by 70 independent teams testing the same hypothesis, showed substantial variability in findings (220).

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 (25, 33, 38, 45, 153). As a result, their inclusion may have attenuated the ability to detect changes in food cue reactvity or taste responses in that particular study, since they would not have been orthogonal to the primary fMRI outcome. This includes longitudinal studies which used covariates such as change in BMI (25, 33, 38, 153), desire to eat rating (45), and hunger rating (38). 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 regions. Additionally, there was great heterogeneity in the method of determination between studie, 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 particular changes in eating behaviour measures may be helpful in this regard.

Associations of fMRI findings with clinical outcomes

Changes in BOLD signal after RYGB did not correlate with the change in weight loss after RYGB (134, 155, 156) and VSG surgeries (44). Although interpretation is difficult because of the small number of such studies and small sample sizes, there is no evidence available that differences in food reward processing or inhibitory control as assessed by fMRI explain variability in weight loss after RYGB and VSG surgeries. Greater weight loss after RYGB surgery has been associated with greater reductions in motivation to receive sweets using a preogressive ratio task (174).

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 (157). 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 (45). Pre-operatively, greater BOLD signal in MFG and lower BOLD signal in IFG to HE/LE food picture was associated with greater weight loss after AGB surgery (151). 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 1 month of low-calorie diet was associated with more weight loss at 6 months of intervention (26). BOLD signal to HE vs. LE food or HE/LE foods did not change between groups of high and medium protein intake during a 2 year weight maintenance study (221). 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 (221). 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 (222).

Improvements in glycaemic control after RYGB surgery including reductions in HbA1c, fasting glucose or T2DM prevalence were reported in six studies (16, 20, 45, 159, 160, 163). Changes

in prevailing glucose may also influence functional MRI outcomes given influence on brain responses to food cue reactivity (217).

2.5.6 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 (52, 223-225). Acute PYY infusion in participants with normal weight decreased BOLD signal at rest in OFC, caudate, and insula (223). 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-adminsitration of the GLP-1 receptor antagonist, exendin9-39 (226). Co-infusion of PYY_{3-36} and GLP-1 was associated with decreased BOLD signal in insula (52). Futhermore, ghrelin is a stomach-derived orexigenic hormone that promotes food intake (227), and increases food cue reactivity in reward processing regions (228),and HE food appeal, mimicking the effects of endogenous hyperghrelinaemia produced by fasting (216) (ref).

Associations between decreases in orexigenic plasma ghrelin and decreases in BOLD signal to HE food pictures in dlPFC were seen after VSG surgery (44), and in VTA after RYGB but not VSG surgery, despite only VSG surgery showing a decrease in plasma ghrelin (46).

From the current review, no associations between plasma GLP-1 (38) and ghrelin (156) in *fed state* and BOLD signal to HE vs. LE at 4 and 3 months after RYGB, respectively. Similarly after an average 8-9 month in a cross-sectional study, no associations between BOLD signal to HE and HE/LE food picture in *fasted state* and GLP-1 after RYGB surgery (16). However, a recent study from our group found that greater post-prandial increases in plasma PYY (and a tendency for GLP-1) were associated with greater reductions in HE and LE food cue reactvity in the OFC after RYGB surgery (162).

This role for PYY and GLP-1 is supportd 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 (20). Acute suppression of post-prandial 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 AGB surgery (160). 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 resward region (160).

These findings suggest a potential role for satiety gut hormones GLP-1 and PYY in reduced food cue reactivity after RYGB surgery but not VSG or AGB surgeries.

2.6 Future directions and summary conclusion

In the light of findings from this systematic review, the following recommendations are suggested to optimize future fMRI studies

- Establishment of multi-centre collaborations to allow for greater sample sizes, hence minimizing effects of participant variability and maximizing effect size.
- Standardising fMRI paradigms and protocols (including food pictures, nutritional state, time since surgery), this will allow combination of multiple datasets.
- Inclusion of control group (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.
- Inclusion of other eating behavioural measures to support and correlate with fMRI findings, including appetite, food hedonics (e.g. liking, wanting and prefeence), food intake, eating behaviour questionnaires.
- Further evaluation of whether there are different changes in HE food and LE food cue reactivity, which likely need larger studies to identify.
- Further direct comparison of different surgical procedures to identify differential effects on food cue reactivity and eating behavioir, which might aid more personalised selection of surgical interventions based on baseline characteristics.
- Further inclusion of appetitive hormonal measures to correlate with fMRI and behavioural outcomes, to identify potential mediators of the changes after obesity surgery, and identify potential explanations for differences between various surgical procedures.

Conclusions

- The large methodological variation across studies, often with small numbers, with variable results of changes in food cue reactivity after obesity surgery, limits conclusions.
- 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 are infrequently included.
- Obesity surgery can affect responses in reward processing regions and restraint and cognitive control regions
- Lower BOLD signal in striatum, limbic and OFC regions to food often seen after RYGB and VSG surgery in limbic and striatal regions in longitudinal and cross-sectional studies.
- Variable directions of change in BOLD signal in dlPFC and regions implicated in restraint and cognitive control.
- Little evidence from fMRI results of preferential reduction in HE vs. LE food cue reactivity, despite often being seen with other non-fMRI measures, though not always studied and likely underpowered.
- Although uncommonly studied, greater weight loss after RYGB and VSG surgeries not correlated with change in food cue reactivity, though suggestions that baseline reactivity may predict weight loss in some circumstances.
- Large variability in eating behavioural measures studied, and usually indirect such as questionnaires, and although consistently show a shift to healthier eating behavours after surgery, correlations with fMRI outcomes were uncommonly reported, variable and inconsistent.
- Some consistent evidence for potential role for satiety gut hormones GLP-1 and PYY in reduced food cue reactivity after RYGB surgery.

Chapter 3 Methods

3.1 Participants /Cohorts

For chapters 4 and 5, three separate cohorts from pre-existing data sets, all of whom have undergone an identical study protocol including food evaluation fMRI paradigm (16, 216) after an overnight fast [cohorts (A) and (B)] or small snack [cohort (C)], *ad libitum* lunch for measuring food intake and taste ratings, eating behaviour questionnaires and appetite ratings. Main differences between cohorts are summarized in **Table 3.1.** Throughout thesis, **cohort A** will be followed by (*pre-RYGB/Endobarrier)* to indicate that participants in this cohort were patients with obesity who were recruited to take part in either RYGB or Endobarrier clinical trial, **cohort B** *(nOB/OB)* to indicate that participants in this cohort included participants with and without obesity, and **cohort C** *(OB)* to indicate that this cohort included only patients with obesity who were taking part in GHADD clinical trial.

3.1.1 Cohort A *(pre-RYGB/Endobarrier)*

A total of 48 participants with obesity studied before scheduled RYGB surgery or at baseline in the NIHR Endobarrier clinical trial (comparing insertion of the duodenal-jejunal bypass liner with standard medical management for obesity with T2DM) (https://www.journalslibrary.nihr.ac.uk/eme/eme07060) (229). Participants who were on waiting list for obesity surgery, were following Tier 3 dietary advice, and participants from Endobarrier clinical trial were on diet for diabetes control. Participants in this cohort were divided into two groups based on BMI and HOMA-IR levels. In chapter 4, participants were divided into either non-severe obesity or severe-obesity group, where those with BMI < 40 kg/m^2 were considered in non-severe obesity group and those with BMI ≥ 40 kg/m^2 were considered in severe obesity group. In chapter 5, same participants were divided based on whether average of HOMA-IR levels was < or ≥ 2.5.

3.1.2 Cohort B *(nOB/OB)*

A total of 96 participants with varying BMI levels across lean, overweight, and obesity were recruited by public advertisement and from hospital obesity clinics. Participants in this cohort were divided into two groups based on BMI and HOMA-IR levels. In chapter 4, participants were divided into lower- or higher-BMI group, based on median split of 26.8 kg/m^2. In chapter 5, same participants were divided based on whether average of HOMA-IR levels was < or ≥ 2.5.

3.1.3 Cohort C (OB)

A total of 26 participants with obesity studied from Gut Hormones in ADDiction Study (GHADD) (https://clinicaltrials.gov/ct2/show/NCT02690987), a double-blinded, randomised placebo-controlled, cross-over study using intravenous GLP-1 analogue, Exenatide or desacyl ghrelin (DAG), and saline infusions in adults with obesity who are dieting. Only participants with obesity during saline visit were included for the analysis. They were divided into two groups based on BMI and HOMA-IR levels. In chapter 4, participants were divided into either non-severe obesity or severe-obesity group, where those with BMI < 40 kg/m^2 were considered in non-severe obesity group and those with BMI ≥ 40 kg/m^2 were considered in severe obesity group. In chapter 5, same participants were divided based on whether average of HOMA-IR levels was < or ≥ 2.5.

	Cohort A *(pre-RYGB/EB)*	**Cohort B** *(nOB/OB)*	**Cohort C** *(OB)*
Participant's recruitment	on waiting list for RYGB surgery, or taking part in Endobarrier study	from multiple observational and interventional studies	taking part in GHADD study
Visit number when data were collected	first visit	first visit	visits 1, 2 or 3 (Saline infusion)
Obesity status	obesity	normal weight, overweight and obesity	obesity and actively dieting
T2DM status	many with T2DM	few with T2DM	none with T2DM
Smoking status	ex-smokers eligible	ex-smokers eligible	never smoked
Nutritional status	Fasted overnight ~15 hours	Fasted overnight ~15 hours	small snack of 150 kcal ~2.5 hours before scanning
Image acquisition parameters*	intermediate TR higher voxel size	highest TR smaller voxel size	smallest TR (multiband) higher voxel size
Food picture in fMRI paradigm	HE and LE food pictures	HE and LE food pictures	HE food pictures

Table 3.1 Main methodological differences between cohorts
EB: Endobarrier, **HE:** high energy, **LE:** low energy, **nOB:** non-obesity, **OB:** obesity, **RYGB:** Roux-En Y gastric bypass, **T2DM:** type 2 diabetes mellitus. *Differences in image acquisition between cohorts are summarized in **Table 3.2**

3.2 Inclusion and Exclusion criteria

Inclusion and exclusion criteria differed between cohorts, depending on the aim of the proposed study for each cohort. See **Table 3.2** for inclusion and exclusion criteria for each cohort.

	Cohort A *(pre-RYGB/EB)*	**Cohort B** *(nOB/OB)*	**Cohort C** *(OB)*
Inclusion criteria	male or female		
	age 18-60 years old		
	35.0 < BMI < 55.0 kg/m^2	18.0 < BMI < 55.0 kg/m^2	35.0 < BMI < 55.0 kg/m^2
	awaiting RYGB surgery or entering Endobarrier Trial		actively dieting
Exclusion criteria	Previous obesity surgery		
	current smoker		current or ex-smokers
	neurological disease, serious mental illness, current or previous drug dependence (other than nicotine)		
			on anti-depressants
	pregnancy or breast feeding		
		outside days 1-14 menstrual cycle	
	type 1 diabetes mellitus		type 1 or 2 diabetes mellitus
	on insulin or GLP-1 analogues		
	shoulder width above 58cm		
	inability to use keypad with right hand		
	claustrophobia		
	MRI contraindications such as metal implants or pacemakers		
	vegetarian or vegan, gluten or lactose intolerance or non-Western diet		

Table 3.2 Inclusion and exclusion criteria for cohorts
BMI: body mass index, **EB:** Endobarrier, **GLP-1:** glucan-like peptide 1, **nOB:** non-obesity, **OB**: obesity, **RYGB:** Roux-En Y gastric bypass, **T2DM:** type 2 diabetes mellitus

3.3 Methodologies for fMRI studies

3.3.1 Scanning visit protocol

Nutritional status: in cohort A *(pre-RYGB/Endobarrier)* and B *(nOB/OB):* Participants were asked to refrain from alcohol and strenuous exercise, to eat their usual supper at 8:00 pm, and then attain the Imperial Clinical Research Facility in the morning while fasted.

While participants in cohort C *(OB):* were given a snack consisting of two biscuits (McVities™ plain digestive biscuits, providing 142 kcal, 40.6% (total energy intake) fat, 52.4% total carbohydrate (18.6g), 14.1% sugars, 6.2% protein) and a 116g fruit-flavoured jelly (Hartley's no added sugar jelly, providing 6 kcal, 0% fat, 100% total carbohydrate, 100% sugars, 0% protein).

Menstrual cycle control: only female participants from *cohort A and cohort C*, were scanned during the first half of their menstrual cycle (1-13 days) to minimize variation in reward-sensitive responses (175).

Anthropometric measurements: Upon their arrival, measurements of height, weight, percentage body fat by bio-electrical impedance analysis were measured by Bodystat 1500 Isle of Man, UK in *cohort B*, and (BC-418 or MC-780 P, Tanita) in *cohort A and cohort C.*

Appetite ratings: Participants were asked to complete visual analogue scales VAS to measure hunger and fullness (maximum 100 mm) anchored from [not at all to extremely]. Scanning visit protocol for all cohorts illustrated in **Figure 3.1**

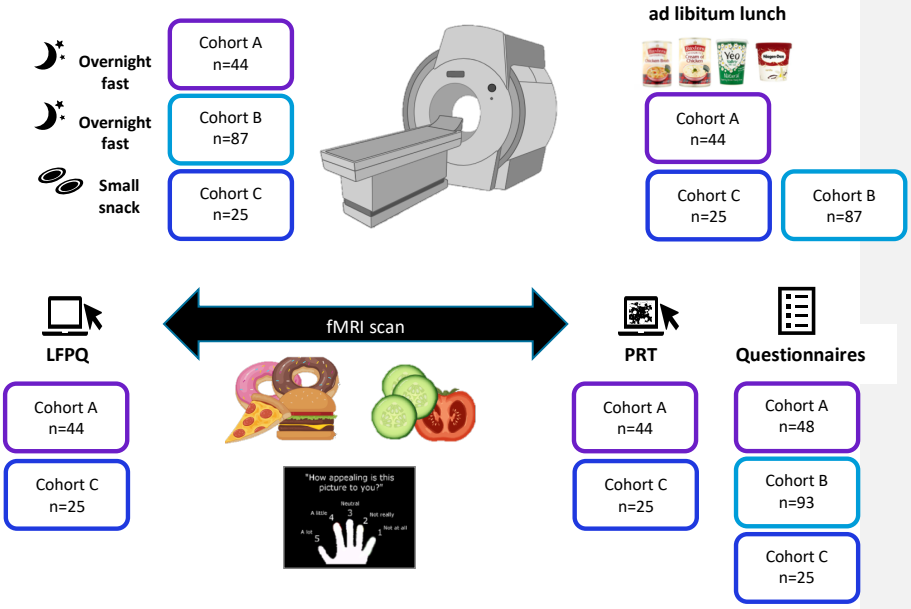

Figure 3.1 Scanning visit protocol and fMRI paradigm for cohorts

Following an overnight fast, participants underwent a 1hr MRI scanning session at ~11am to noon, with 2 runs of 9 minute fMRI food evaluation task from +95 min. Subjects were required to rate the appeal (on a scale of 1-5 using a keypad) of pictures of high-energy (HE) or low energy (LE) density foods and objects. Other eating behaviour measures that took place in scanning visit included: Leeds Food Preference Questionnaire, Progressive ratio task, eating behaviour questionnaires, *ad libitum* lunch meal.

3.3.2 Functional MRI protocol

Scanning session lasted 90 minutes starting between 11:00 am and noon in which participants could respond to the display instructions and images seen on a computer screen via an angled mirror using a handheld 5-button or single button keypad (214). Tasks were programmed using E-Prime Professional v2.0 (Psychology Software Tools, Pittsburgh, USA).

Prior to scanning sessions, participants had a practice picture evaluation task. Four types of colourful pictures were presented during scanning session in a block design paradigm across 2 runs, each run lasted 9 minutes. Pictures included:
60 low-calorie foods (e.g., fish, vegetables, salads),
60 high-calorie foods (e.g. chocolate, cakes, pizza),
60 non-food related household objects (e.g. furniture, clothing),
180 Gaussian blurred images of the other pictures (as a low-level baseline), similar to those used previously (214, 216).
Food pictures were selected to represent familiar foods that are typical to the modern Western diet. Pictures were obtained from freely available websites and the International Affective Picture System (IAPS, NIMH Center for the Study of Emotion and Attention, University of Florida, Gainesville, FL, USA). Food and object pictures were of similar luminosity and resolution.

Each run contained different pictures in 5 blocks each of high-calorie and low-calorie foods and objects interleaved with 31 blocks of blurred pictures (6 pictures per 18 secs) using one of four pseudorandom block orders with a randomized picture order within each block. Every image was displayed for 2500 ms, followed by a 500 ms inter-stimulus interval of a fixation cross. Each high-calorie food block consisted of equal numbers of foods containing chocolate, non-chocolate sweet and savory non-sweet foods (2 of each).

Participants were given a hand held keypad within the scanner to rate the appeal of the food on a scale of 1-5 (1 = “not at all”, 5 = “a lot”). To allow image registration, a T1 weighted structural scan was then carried out, followed by an ad libitum meal outside the scanner.

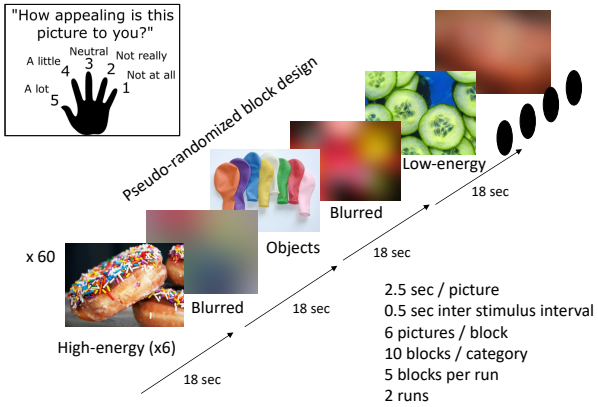

Figure 3.2 Diagram of fMRI picture evaluation task.
During the fMRI picture evaluation task, high-energy and low-energy food, and neutral pictures were evaluated using a 5-button box

3.3.3 fMRI acquisition

See **Table 3.3** for fMRI acquisition parameters for each cohort.

	Cohort A *(pre-RYGB/EB)*	**Cohort B** *(nOB/OB)*	**Cohort C** *(OB)*
Tesla scanner	3.0T Seimens Verio MRI scanner	3.0T Philips Achieva MRI scanner	3.0T Seimens Verio MRI scanner
Location	Clinical Imaging Centre, Hammersmith Hospital	Robert Steiner MRI Unit, Hammersmith Hospital	Invicro Clinical Imaging, Hammersmith Hospital
Head coil	32 channel	8 channel	32 channel
Repition time (TR)	2250 ms	3000 ms	1500 ms
Echo time (TE)	30 ms	30 ms	30 ms
Voxel size (mm^2)	3.0 x 3.0 mm	2.0 x 2.0 mm	3.0 x 3.0 mm
Image acquisition	80° flip angle	90° flip angle	80° flip angle
Slice thickness	39 ascending interleaved contiguous 3.0 mm	44 ascending interleaved contiguous 3.25 mm	54 ascending contiguous 3.0 mm
Field of view (FOV)	192x192	190x219	192x192
Number of volume for food picture evaluation	252 for each of 2 runs	189 for each of 2 runs	378 for each of 2 runs

Table 3.3 fMRI acquisition for cohorts
BMI: body mass index, **EB:** Endobarrier, **GLP-1**: glucan-like peptide 1, **nOB**: non-obesity, **OB:** obesity, **RYGB:** Roux-En Y gastric bypass, **T2DM:** type 2 diabetes mellitus

3.3.5 fMRI processing and analysis

fMRI Expert Analysis Tool v.5.98 was used for fMRI data processing and analysis (http://www.fmrib.ox.ac.uk/fsl*).* For pre-processing the following steps were used:

(i) motion-correction was applied using MCFLIRT (230),
(ii) fieldmap based echoplanar imaging (EPI) unwarping (231),
(iii) non-brain tissue removal using brain extraction tool (BET) (232),
(iv) spatial smoothing using a 6mm full width half maximum (FWHM) Guassian kernel,
(v) grand mean intensity normalization of the entire 4D dataset by a single multiplicative factor and highpass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma 100.0 sec (food task)

Time-series statistical analysis was done using FILM with local autocorrelation correction including event onsets as explanatory variables within the context of the general linear model (GLM) on a voxel-by-voxel basis (stick functions convolved with the haemodynamic response function) for the relevant contrast. Motion parameters were included as part of the GLM (233).

For the food evaluation fMRI tasks, the GLM was also used to measure BOLD signal **to (i) high-energy or (ii) low-energy compared to objects or (iii) high vs. low-energy food.**

Registration to high resolution T1 structural images was carried out using FLIRT, including boundary-based registration (BBR) (234, 235). Registration from high resolution structural to standard space was then further refined using FNIRT non-linear registration. For the food evaluation, the two runs for each visit were averaged using higher-level fixed effects analysis for each contrast.

Functional regions of interest (fROIs) for the following 6 areas involved in reward, emotional and motivation processing: anterior insula, amygdala, OFC, caudate, putamen, and nucleus accumbens were determined from *cohort B* participants with varying BMI level. Median BOLD signal was extracted from predetermined *a priori* fROIs, using Featquery software, to compare between groups within each cohort, voxel-wise false discovery rate (FDR) corrected $P<0.05$. These areas were chosen based on previous fMRI studies examine alterations in reward pathway.

Whole brain mixed effects analysis was preformed to compare BOLD signal between groups within each cohort using unpaired t-tests with a cluster threshold Z>2.6, corrected P<0.05 including visit number as a covariate for cohort C only. Correlations between BMI and HOMA-IR levels and BOLD signal were also examined by calculating demeaned BMI and HOMA-IR. Coordinates within significant clusters were then determined by using FSLeyes Harvard-Oxford Cortical Structural Atlas and Sallet Dorsal Frontal connectivity-based parcellation.

Participants had to be excluded from all datasets due to various problems with their scanning visits. Reasons included: (i) poor compliance with the task, measured by an inability to give an appeal rating response during the task to either food or object pictures >15% of the time, (ii) signal dropout, (iii) average relative motion during the 2 runs of the food picture evaluation fMRI task >0.5 mm/scan volume.

3.3.6 fMRI confounders

Confounders including (i) absolute and relative motion; (ii) menstrual cycle; (iii) visual analogue scales of anxiety, stress, and sleepiness; (iv) fasting duration; (v) hours slept night before; (vi) Positive Affect and Negative Affect Schedule (PANAS)(94)

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3.5 Leeds food preference questionnaire (LFPQ)

Cohort A (pre-RYGB/Endobarrier)

Participants completed the Leeds Food Preference Questionnaire (LFPQ) while fasted overnight, and before the MRI scanning session. This questionnaire aimed to examine implicit wanting and explicit liking using combinations of different of low fat (LF)/ high fat (HF) and savoury (sv)/sweet (sw) foods picture. To measure explicit liking, the participants were asked the following question for each single picture "How pleasant would it be to taste this food right now?", then they had to answer using a 100-mm VAS. To measure implicit wanting, the participants were asked the following question "Which food do you most want to eat now?", participants had to choose between two food pictures based on their preferred option. All pictures were presented randomly. The mean response times for each food category were calculated. Analysis was preformed in collaboration with Graham Finlayson, University of Leeds, UK (236).

3.6 Taste ratings

Cohort A *(pre-RYGB/Endobarrier)* and ***cohort C*** *(OB)*

Before consuming *ad libitum* lunch, participants were first asked to rate the taste of a teaspoon of each presented item in the meal with emphasis on the following taste sensations:

(i) Creaminess intensity: including all 4 dishes, LF and HF soup, yoghurt and ice cream;

(ii) Pleasantness: including all 4 dishes;

(iii) Sweetness intensity: only deserts yoghurt and ice cream.

Taste intensity ratings were measured by asking participants "How close the creaminess/sweetness of this taste to your ideal creaminess/sweetness?" with the term "just right or ideal" anchored at 50mm mark. A rating of ideal creaminess or sweetness above 50mm is considered creamier or sweeter than ideal and vice versa.

Ratings were performed using the Sussex Ingestion Pattern Monitor (SIPM) system general linear scale rating computer software (www.sipm.co.uk, Martin Yeomans, University of Sussex, UK).

3.7 ad libitum lunch and energy intake

3.7.1 Cohort A (pre-RYGB/Endobarrier)

Participants were presented with an ad libitum lunch meal provided in excess consisting of a choice of chicken broth (low-fat (LF) savoury, tinned Baxters Favourites), cream of chicken soup with added cream (high-fat (HF) savoury, tinned Baxters Favourites), natural yoghurt (LF sweet, Yeo Valley); vanilla ice-cream (HF sweet, Haagen DazsAt) at ~40 minutes after the end of the MRI session at ~ 13:10. If participants did not like chicken soups, they were instead given tomato broth and cream of tomato soup (Baxters Favourites). See **Table 3.3** for nutritional composition of the dishes served.

Participants were instructed to eat until comfortably full while the investigators were outside the room. Each item was weighed before and after to determine total macronutrient (fat, carbohydrate, protein) energy intake. Energy intake was then calculated in three ways: (i) absolute kilocalories, (ii) percentage of estimated 24 hour resting energy expenditure (REE), calculated using the Cunningham equation: [REE = 501 + (21.6 x lean body mass (LBM) (kg)] in kcal per 24h, equating LBM with fat free mass determined by bio-electrical impedance analysis (237), (iii) percentage of total meal energy intake.

Composition	Cream of Chicken	Chicken Broth	Cream of Tomato [a]	Tomato Broth [a]	Yoghurt	Ice Cream
Energy Density (kcal/100g)	104	31	111	31	82	251
Fat (g/100g)	8.25	0.27	8.01	0.89	4.20	17
of which saturated (g/100g)	4.58	0.09	4.40	0.18	2.70	10.4
Carbohydrates (g/100g)	5.46	5.24	6.44	4.44	6.50	20.2
of which sugars (g/100g)	1.29	1.16	5.11	3.56	6.50	14.3
Fibre (g/100g)	0.09	0.89	0.36	0.53	0.00	0.00
Protein (g/100g)	2.07	1.51	1.18	1.16	4.60	4.20
Salt (g/100g)	0.63	0.53	0.63	0.36	0.18	0.15
Amount served (g)	900	900	900	900	500	500
Amount served (kcal)	833	249	890	249	410	1255

Table 3.3 Composition of ad libitum lunch meal.
[a] alternatives to chicken.

3.7.2 Cohort B (nOB/OB)

Participants were presented with an *ad libitum* savoury lunch meal provided in excess and were instructed to "eat as much as they wanted until they felt comfortably full". The lunch meal was macaroni and cheese (per 100 g: 205 kcal, 6.5 g protein, 18.9 g carbohydrate, and 11.5 g fat), or if this meal was not liked at least moderately on a VAS at their screening visit, an alternative of chicken *Tikkamasala* (per 100 g: 150 kcal, 6.6 g protein, 13 g carbohydrate, and 8 g fat). Men were presented with 2000 g, and women were presented with 1500 g, of lunch together with ad libitum water. Participants were then asked to rate pleasantness and tastiness of that dish.

3.7.3 Cohort C (OB)

Participants were presented with an *ad libitum* lunch meal provided in excess consisting of a choice of tomato broth (low-fat (LF) savoury, Sainsbury's Tomato and Basil), cream of tomato soup with added cream (high-fat (HF) savoury, Baxters cream of tomato), natural yoghurt (LF sweet, Yeo Valley); vanilla ice-cream (HF sweet, Haagen Dazs) at ~40 minutes after the end of the MRI session at ~ 13:10. If participants did not like chicken soups, they were instead given tomato broth and cream of tomato soup (Baxters Favourites). See **Table 3.3** for nutritional composition of the dishes served.

Participants were instructed to eat until comfortably full while the investigators were outside the room. Each item was weighed before and after to determine total macronutrient (fat, carbohydrate, protein) energy intake. Energy intake was then calculated in three ways: (i) absolute kilocalories, (ii) percentage of estimated 24 hour resting energy expenditure (REE), calculated using the Cunningham equation: [REE = 501 + (21.6 x lean body mass (LBM) (kg)] in kcal per 24h, equating LBM with fat free mass determined by bio-electrical impedance analysis (237).

3.8 Progressive ratio task

Progressive ratio (PRT) task was performed to assess appetitive motivation for HE sweets (appetitive food reward). A bowl filled with 20 M&M crispy sweets (Mars UK Ltd.) was placed in front of participants. Each M&M was only 4 kcal (43.7% sugar, 44.1% fat). The following instruction was given to all participants: "Press as little or as much as you like. When you no longer want to continue, press the space bar." A practice trial run was done to ensure participants understand the task. Then, participants were left alone in the room to complete the exercise. On a laptop, pparticipants were instructed to press a computer mouse in an exponentially increasing manner to receive each sweet (160, 174). For example, pressing 10 times would earn the participant a single M&M sweet. To earn another, they must press 20 more times, then 40, and so on until they press the space bar indicating completion.

This task evaluates the breakpoint of effort to achieve the HE food. The task took place ~2-3 hours after the start of the *ad libitum* lunch meal in the satiated state.

The total amount of clicks and number of remaining candies are included in the analysis.

3.9 Eating behaviour and psychological trait questionaries

Participants from all cohorts were asked to complete severeal eating behaviour and psychological questionaries using an iPad to assess eating behaviour, attitudes, and personality traits. Questionnaires were completed on site, or at home. Scores were automatically calculated and generated to an Excel spreadsheet for further statistical analysis.

Three Factor Eating Behaviour Questionnaire (TFEQ) to evaluate three domains of eating behaviour: (i) cognitive restraint: refers to conscious restraint in order to control body weight; (ii) hunger: refers to susceptibility to hunger cues; (iii) disinhibited eating: refers to loss of control during eating (238).

Dutch Eating Behaviour Questionnaire (DEBQ) to evaluate three domains of overeating behaviours: (i) restraint eating: refers to overeating after a strict cognitive control; (ii) emotional eating: refers to eating in response to an emotional status (such as fear, anger, or anxiety); (iii) external eating: refers to eating in response to an external food cue (such as the

smell of food). A higher score indicates a higher tendency to the measured eating behaviour (239).

Eating Disorders Examination Questionnaire (EDEQ) to assess an existing eating disorders: (i) dietary restraint, (ii) preoccupation with weight and shape, and (iii) binge eating (240).

Beck depression inventory (BDI-II) to assess depression severity. It consists of 21 questions with a maximum rating of 63 points (92). A Score between 0-13 indicates minimal depression, 14-19 mild depression, 20-28 moderate depression, and 29-63 severe depression (92).

Barratt Impulsivity Scale (BIS) to assess impulsivity, a personality trait in which an individual decides choices without rational thinking. It consists of 30 items cumulating into a total impulsiveness score. A higher score indicates a higher impulsivity rate (241).

Binge Eating Scale (BES) to assess the current presence of binge eating behaviour e.g. binging or purging food, as well as cognitive indicators of binging, such as fear, guilt, and an inability to stop (242).

3.9 Statistical analysis

Analysis was conducted using SPSS v24 (IBM), and graphs made using Prism 8 (GraphPad Software Inc.). Statistical significance was taken as $P<0.05$, with $P=0.5$. The following statistical tests were used:

3.9.1 Mixed model analysis

Fixed effects mixed model repeated measures ANOVA, with post-hoc Fisher LSD test was preformed to measure differences in BOLD signal, *ad libitum* lunch intake and taste ratings between-groups and within-group in three cohorts. The model included fixed effects for groups (depending on BMI or HOMA-IR levels) and their corresponding interaction as well as a random intercept effect for each participant. Between group comparisons in *cohort A* and *cohort C*: participants with non-severe obesity vs. severe obesity groups; *cohort B*: participants with lower-BMI vs. higher-BMI (based on median split).

Food cue reactivity analysis: Participants who attended scanning visit and did not have a signal dropout were included in food cue reactivity analysis. Based on the mixed model approach, six functional ROIs (amygdala, insula, OFC, putamen, NAcc and caudate) and energy density (HE and LE) were included in the model. To examine the effect of group, energy density and fROI on BOLD signal, interaction (group*ED*ROI) and post-hoc tests were reported for significant interaction and individual ROI exploratory results. The effect of BMI was further examined as a continuous variable and for interactions of BMI*ED*ROI, BMI* ROI, BMI*ED.

***Ad libitum* meal analysis:** Participants who had lunch and completed taste ratings were included in *ad libitum* lunch analysis. Based on the mixed model approach, fat (low fat and high fat) and sugar (savoury and sweet) content of each dish were included in the model. To examine the effect of group, sugar and fat on energy intake and taste ratings, interactions (group*fat*sugar) and post-hoc tests were reported for significant interactions.

Analysis results are presented in the form of type-III test results of fixed effect (p-values) and their subsequent post-hoc tests (mean difference, SEM, effect size, lower and upper confidence intervals).

3.9.2 Repeated measure ANOVA

RMANOVA was performed to examine the difference between groups in *cohort A* for explicit liking and implicit wanting from Leeds Food preference Questionnaire LFPQ data. Fat (low fat and high fat) and sugar (savoury and sweet) categories of food pictures were included in the model. To examine the effect of group, sugar, and fat on explicit liking and implicit wanting, interactions (group*fat*sugar) and post-hoc tests were reported for significant interactions.

Food cue reactivity analysis for combined cohorts: RMANOVA was also used to examine the effect of severe obesity on food cue reactivity when three cohorts were combined in one model. Only participants with obesity from cohort B was included to this model.

3.9.3 Unpaired t-tests or Mann-Whitney

For energy intake and taste ratings (pleasant and tasty), Mann-Whitney test was performed to compare mean ranks between lower and higher BMI participants in *Cohort B*.

Confounders for fMRI data including i) absolute and relative motion; ii) menstrual cycle; iii) visual analogue scales of anxiety, stress, and sleepiness; iv) fasting duration; v) hours slept night before; vi) mood (positive and negative PANAS) were examined by unpaired t-test to compare means between groups in each cohort.

3.9.4 Correlations

Spearman's correlation was performed to assess the association between BMI and HOMA-IR levels and different outcomes measures (food cue reactivity BOLD data, energy intake, taste ratings, and eating behavior questionnaires).

Chapter 4 Food cue reactivity and eating behaviour and BMI in obesity

4.1 Introduction

Functional magnetic resonance imaging has been used in the context of obesity and eating behaviour in humans to expand our understanding of reward-based eating through examining brain responses to food cues (visual, olfactory, gustatory or auditory). Previous fMRI studies have predominantly used visual HE food cues during scanning and reported higher food cue reactivity in regions involved in reward processing (including the striatum, amygdala, insula, nucleus accumbens, and orbitofrontal cortex), when comparing participants with obesity and those with normal weight (243, 244). However, this finding is not consistent within the literature, where sometimes BOLD signal is either lower in the reward system regions or higher in other regions of the brain of patients with obesity (245-247). Moreover, the BOLD signal in regions involved in restraint and cognitive control (e.g. dorsolateral prefrontal cortex) is variable across studies, where it is either higher (248) or lower (249) in patients with obesity. Since it cannot be confirmed what neural responses to food cues reflect, it was further interpreted that patients with obesity may have higher responsivity and lower cognitive control to high palatable food, resulting in more high palatable food intake and weight gain.

The major problem with neuroimaging studies in obesity is the significant variability in areas showing higher or lower BOLD signal to food cues and the direction of the BOLD signal. Moreover, interpreting neuroimaging findings and linking them to specific behaviours may lead to confusion. Obesity is a heterogeneous condition, and patients with obesity do not necessarily share similar eating phenotypes, limiting interpretation only from scanning.

In an attempt to further explain the discrepancy in neuroimaging studies, combining the findings with other eating behaviour measures will help understand the mechanism underlying pathological overeating, including measures of actual food intake, food preferences tasks, personality traits and behavioural questionnaires. Obesity is associated with eating behaviours that promote overeating, and with higher liking for highly palatable foods (243).

While BMI is a crude measure for a heterogeneous disease, it is an important marker for obesity and a potential determinant of pathological overeating. This chapter aims to analyze

data from three cohorts, including participants with obesity who underwent a similar fMRI paradigm and investigate the effect of BMI on food cue reactivity and other eating behaviour measures in obesity.

4.2 Objectives

The main aim of this chapter is to examine the following objectives in three cohorts and examine whether findings are replicated in all cohorts

1. Examine the relationship between BMI and neural activation in response to food cues via region of interest (ROI) and whole brain analysis including brain regions implicated in reward processing.
2. Examine the relationship between BMI and food intake using *ad libitum* lunch and taste ratings
3. Examine the relationship between BMI and measures of eating behaviour using questionnaires (DEBQ, TFEQ, EDEQ)

4.3 Hypothesis

1. Higher BMI is associated with higher cue reactivity in brain reward systems to HE food and/or lower reactivity to LE foods, as well as similar differences in food appeal
2. Higher BMI is associated with increased food intake, especially high fat and sweet/ or lower low fat and savoury food
3. Higher BMI is associated with increased appetite and unhealthier eating behaviour

4.4 Results

4.4.1 Participants characteristics

Participants characteristics from three cohorts based on their BMI levels are summarized in **Table 4.1-A**. There was a significant difference between groups (severe vs. non-severe obesity) in gender in *cohort A* and white ancestry distribution in *cohort C*. There were no significant differences between groups (lower- and higher-BMI) in age, gender and white ancestry distribution in *cohort B*. There was a significant difference between groups (severe vs non-severe obesity, and lower vs. higher BMI) in HOMA-IR levels *in cohors A and cohort B*. Participants characteristics when three cohorts were combined, including only participants with obesity, for food cue reactivity analysis are summarized in **Table 4-1-B**

	Cohort A (pre-RYGB/EB)				Cohort B (nOB/OB)				Cohort C (OB)			
Variable	***All***	***non-severe obesity non-SO***	***severe obesity SO***	***P#***	***All***	***BMI < median [c]***	***BMI > median [c]***	***P##***	***All***	***non-severe obesity non-SO***	***severe obesity SO***	***P#***
n	48	26	22		96	46	50		26	17	9	
Female n (%)	30 (62.5%)	11 (42.3%)	19 (86.4%)	0.003[d]	60 (61.2%)	26 (56.5%)	34 (68.0%)	0.29[d]	18 (69.2%)	12 (70.6%)	6 (66.7%)	1.00 [d]
Age (years) (range)	49.6 ± 8.8 (31-64)	50.5 ± 7.5 (31-64)	48.6 ± 10.2 (31-63)	0.45[e]	33.6 ± 10.2 (19-55)	32.5 ± 10.5 (20-55)	34.7 ± 9.8 (19-54)	0.29[e]	42.8 ± 11.3 (24-60)	43.2 ± 11.4 (28-60)	42.0 ± 11.8 (24-57)	0.80 [e]
Caucasian n (%)	27 (56.3%)	15 (57.7%)	12 (54.5%)	1.00 [d]	61 (62.2%)	32 (69.6%)	29 (58.0%)	0.29 [d]	17 (65.4%)	8 (47.1%)	9 (52.9%)	0.009 [d]
BMI kg/m^2 (range)	39.8 ± 6.2 (30.6-55.5)	35.2 ± 2.9 (30.6-39.8)	45.3 ± 4.1 (40.3-55.5)	<0.001 [e]	28.6 ± 6.7 (19.1-53.1)	23.8 ± 2.1 (19.1-26.6)	33.1 ± 6.3 (26.7-53.1)	<0.001[e]	37.0 ± 4.7 (29.6-46.3)	34.22 ± 2.8 (29.6-39.9)	42.3 ± 2.3 (40.8-46.3)	<0.001[e]
Type 2 diabetes millitus n (%)	37 (77.1%)	23 (62.2%)	14 (37.8%)	0.82[d]	3 (3.1%)	1 (33.3%)	2 (66.7%)	1.00[d]	0	0	0	
HOMA-IR [quartiles], (range)	1.61 [a] [1.24,2.25], (0.80-22.16)	1.49 [1.24-2.06], (0.83-3.33)	1.83 [1.09-2.56], (0.80-22.16)	<0.001 [f]	1.1 [b] [0.71-1.74], (0.33-9.02)	0.80 [0.56-1.06], (0.33-2.37)	1.62 [1.13-2.22], (0.47-9.02)	<0.001[f]	1.7 [0.97-2.88], (0.28-9.13)	1.75 [0.93—2.90], (0.44-9.13)	1.33 [0.94-3.12], (0.28-4.9)	0.89 [f]
HOMA- IR > 2.5	38/47 (80.9%)	22 (57.9%)	16 (42.1%)		11/93 (46.2%)	0 (0)	11 (100%)			5 (62.5%)	3 (37.5%)	

Table 4.1-A Participants characteristics in cohorts

Data presented as mean SD, median [interquartile range] (minimum-maximum), or n (%). *P<0.05

[a] n=47, [b] n=93, [c] median=26.85 kg/m^2, [d] P value for fisher's exact test, [e] P value for unpaired t-test, [f] P value for Mann-whitney test, [#] P value for the difference between SO vs. non-SO groups, [##]P value for the difference between lower vs. higher BMI.

Abbreviations: EB: Endobarrier, **SO:** severe obesity, **non-SO:** non-severe obesity bnon-obesity, **OB:** obesity, n**OB:** non-obesity **HOMA-IR:** homeostasis model of assessment-insulin resistance, **RYGB:** Roux-En Y gastric bypass, **T2DM:** type 2 diabetes mellitus, **BMI:** body mass index

	Combined cohorts for food cue reactivity analysis			
Variable	***All***	***non-severe obesity non-SO***	***severe obesity SO***	***P#***
n	92	57	35	
Female n (%)	64 (69.6%)	33 (57.9%)	31 (88.6%)	0.64 [b]
Age (years) (range)	44.0 ± 11.4 (20-64)	44.4 ± 11.0 (21-64)	43.5 ± 12.0 (20-63)	0.60 [a]
Caucasian n (%)	54 (58.7%)	31 (54.4%)	23 (65.7%)	[b]
BMI kg/m^2 (range)	34.3 ± 2.7 (30.0-39.9)	34.3 ± 2.7 (30.0-39.9)	44.6 ± 3.9 (40.3-55.5)	0.028 [a]
Type 2 diabetes millitus n (%)	24 (42.1%)	24 (3142.1%)	11 (31.4%)	0.38 [b]
HOMA-IR [quartiles], (range)	2.7 [a] [1.5,4.1], (0.3-912.0)	2.7 [a] [1.7,4.1], (0.40-9.9)	2.8 [1.4-4.1], (0.3-12.0)	0.95 [c]

Table 4.2-B Participants characteristics in combined cohorts analysis
Data presented as mean SD, median [interquartile range] (minimum-maximum), or n (%). *P<0.05
[a] P value for unpaired t-test, [b] P value for fisher's exact test, , [c] P value for Mann-whitney test, [#] P value for the difference between SO vs. non-SO groups,
Abbreviations: SO: severe obesity, **non-SO:** non-severe obesity, **HOMA-IR:** homeostasis model of assessment-insulin resistance, **T2DM:** type 2 diabetes mellitus, **BMI:** body mass index.

4.4.2 Food-pictures cue reactivity

Functional regions of interest analysis

Cohort A (pre-RYGB/EB) **n=44**: for BOLD signal during evaluation of HE and LE food pictures (vs. objects), there was no significant interaction effects for: (i) group*ED*ROI [F(1,44)= 0.61, P=0.81 Greenhouse-Geisser correction], However, there was a significant interaction effect for (ii) group*ROI (independent of energy density) [F(1,44)= 2.66, P=0.004], (iii) group*ED (across average 6 ROIs) [F(1,484)= 13.09, P<0.001], and (iv) overall effect of group [F(1,44)= 4.24, P=0.05], in mixed model RMANOVA analysis. Further post-hoc analysis for group*ED interaction showed lower BOLD signal to LE food picture in average 6 ROIs in participants with severe obesity compared to participants with non-severe obesity **Table 4.2 and 4.3.** Spearman's correlation between BMI levels and BOLD signal in 6 fROIs to HE and LE food pictures revealed negative correlation between BMI and BOLD signal to LE food picture in average 6 ROIS, amygdala, caudate and putamen **Table 4.5 Figure 4.2**

This was not consistent in *cohort B (nOB/OB)* **n=87**, where for BOLD signal during evaluation of HE and LE food pictures (vs. objects), there was no significant interaction effects for: (i) group*ED*ROI [F(10,957)= 0.73, P=0.70 Greenhouse-Geisser correction], (ii) group*ED (across average 6 ROIs) [F(1,957)= 2.76, P=0.10], nor (iii) overall effect of group [F(1,87)= 0.27, P=0.60]. However, there was a significant interaction effect for (iv) group*ROI (independent of energy density) [F(10,957)= 4.45, P<0.001], in mixed model RMANOVA analysis. **Table 4.2 and 4.3.** Spearman's correlation between BMI levels and BOLD signal in 6 fROIs to HE and LE food pictures revealed negative correlation between BMI and BOLD signal to LE food picture in OFC **Table 4.5 Figure 4.2**

nor cohort C (OB) **n=25**, where for BOLD signal during evaluation of HE food pictures (vs. objects), there was no significant interaction effects for: (i) group*ROI [F(5,125)= 0.88, P=0.50] Greenhouse-Geisser correction, nor (ii) overall effect of group [F(1,25)= 0.27, P=0.61], in mixed model RMANOVA analysis **Table 4.2 and 4.3.** Spearman's correlation between BMI levels and BOLD signal in 6 fROIs to HE food picture revealed no correlation between BMI and BOLD signal to HE food picture in any fROI **Table 4.5 Figure 4.2**

When participants with obesity from three cohorts were combined (n=92), i) participants from *cohort A and cohort B* were included for LE food BOLD data: no significant interaction effect for group*ROI [F(1,87)= 0.70, P=0.58]; however there was a trend for overall group effect [F(1,63)= 3.80, P=0.056] in RMANOVA. Exploratory individual ROI analysis also revealed a significant lower BOLD signal to LE food picture in participants with severe obesity compared to participants with non-severe obesity in insula and caudate **Table 4.4**. Similar results were seen when spearman's correlation was performed, a negative correlation between BMI and LE food BOLD signal in insula, caudate and putamen **Table 4.6.**

	Cohort A [a] *(pre-RYGB/EB)* n=44		Cohort B [b] *(nOB/OB)* n=87		Cohort C [a] *(OB)* n=25		Combined cohorts [b] *(OB)* n=67	
Interaction	**(df) F**	**P**	**(df) F**	**P**	**(df) F**	**P**	**(df) F**	**P**
group*ED*ROI	(1,44) 0.61	0.81	(10,957) 0.73 [a]	0.70	-	-	0.06 (5,2.21)	0.10
group*ROI	(1,44) 2.66	0.004	(10,957) 4.45	**<0.001******	(5,125) 0.88	0.50	0.84 (5,241.16)	0.50
group*ED	(1,484) 13.09	**<0.001******	(1,957) 2.76	0.10	-	-	1.55 (1,63)	0.22
group	(1,44)4.24	**0.045***	(1,87) 0.27	0.60	(1,25) 0.28	0.61	(1,63) 3.80	0.056
BMI*ED*ROI	(5,484) 0.89	0.49	(5,957) 0.98	0.43	-	-	-	-
BMI*ROI	(5,484) 4.15	**0.001*****	(5,957) 5.17	**<0.001******	0.54 (5,125)	0.75	-	-
BMI*ED	(1,484) 24.62	**<0.001******	(1,957) 0.21	0.65	-	-	-	-
BMI	(1,44) 4.27	**0.045***	(1,87) 0.26	0.62	0.18 (1,25)	0.67	-	-

Table 4.3 Mixed model RMANOVA for effect of severe obesity group (categorical and continuous variable) on food cue reactivity

Results from mixed model RMANOVA for BOLD signal for group (non-SO:non-severe vs. SO:severe obesity or lower vs. higher-BMI) as between-subject factor or BMI, and ED energy density (low and high energy food picture) and average six fROI region of interest (insula, amygdala, OFC, NAcc, putamen and caudate) as within subject factors. [a] no energy density within subject factor because fMRI paradigm in this cohort only included HE picture, [b] results for combined cohort A and cohort B. Significant results in bold *P<0.05, ****P<0.001

Abbreviations: ED: energy density, **BMI:** body mass index. **ROI:** region of interest, **EB**: Endobarrier, **OB:** obesity, n**OB:** non-obesity, **RYGB:** Roux-En Y gastric bypass.

Cohort A *(pre-RYGB/EB)*			**95% confidence interval**				
	Post-hoc contrast	**Mean ± SEM**	**lower**	**upper**	**df**	**F**	**P**
	LE: SO vs. non-SO	-0.097 ± 0.029	-0.155	-0.04	(1,64.15)	11.42	**0.001*****
	HE: SO vs. non-SO	-0.011 ± 0.029	-0.068	0.047	(1,64.15)	0.13	0.72
	non-SO: HE vs. LE	0.026 ± 0.016	-0.005	0.057	(1, 484)	2.76	0.10
	SO: HE vs. LE	0.113 ± 0.018	0.077	0.148	(1, 484)	39.04	**<0.001******
Cohort B *(nOB/OB)*							
	LE: higher vs. lower BMI	-0.025 ± 0.024	-0.072	0.022	(1,111.28)	1.12	0.29
	HE: higher vs. lower BMI	0.002 ± 0.024	-0.045	0.049	(1,111.28)	0.01	0.94
	Lower BMI: HE vs. LE	0.01 ± 0.011	-0.013	0.033	(1,957)	0.75	0.39
	Higher BMI: HE vs. LE	0.037 ± 0.011	0.015	0.059	(1,957)	10.49	**0.001*****
Cohort C[a] *(OB)*							
	HE: non-SO	0.041 ± 0.029	-0.020	0.102	25	-	-
	HE: SO	0.069 ± 0.043	-0.020	0.157	25	-	-

Table 4.4 Post-hoc analysis for effect of severe obesity group on food cue reactivity
Results from post-hoc pairwise comparisons for group*ED interaction. Between-subject factor (non-SO: non-severe vs. SO: severe obesity or lower vs. higher-BMI), and within-group factor ED energy density (LE: low energy and HE:high energy food picture). [a] estimates for BOLD signal in non-SO and SO groups. Significant results in bold ***P<0.001.
EB: Endobarrier, **nOB:** non-obesity, **OB:** obesity, **RYGB:** Roux-En Y gastric bypass, **HE:** high energy, **LE:** low energy, **df:** degree of freedom.

Cohort A *(pre-RYGB/EB)* **Cohort B** *(nOB/OB)* *n=67*							
LE vs. Object			**95% confidence interval**				
	Post-hoc contrast	**Mean ± SEM**	**lower**	**upper**	**df**	**F**	**P**
ant. Insula	SO vs. non-SO	-0.080 ± 0.034	-0.146	-0.013	(1,63)	5.63	**0.021****
Amygdala	SO vs. non-SO	-0.080 ± 0.062	-0.204	0.044	(1,63)	1.66	0.20
OFC	SO vs. non-SO	-0.041 ± 0.044	-0.129	0.048	(1,63)	0.84	0.36
Caudate	SO vs. non-SO	-0.106 ± 0.051	-0.208	-0.005	(1,63)	4.40	**0.040***
Putamen	SO vs. non-SO	-0.072 ± 0.042	-0.156	0.012	(1,63)	2.93	0.09
NAcc	SO vs. non-SO	-0.023 ± 0.047	-0.117	0.070	(1,63)	0.25	0.62
Cohort A *(pre-RYGB/EB)* **Cohort B** *(nOB/OB)* **Cohort C** *(OB)* *n=92*							
HE vs. Object			**95% confidence interval**				
	Post-hoc contrast	**Mean ± SEM**	**lower**	**upper**	**df**	**F**	**P**
ant. Insula	SO vs. non-SO	-0.010 ± 0.026	-0.062	0.043	(1,86)	0.14	0.71
Amygdala	SO vs. non-SO	-0.015 ± 0.050	-0.114	0.085	(1,86)	0.09	0.77
OFC	SO vs. non-SO	0.023 ± 0.340	-0.045	0.092	(1,86)	0.47	0.49
Caudate	SO vs. non-SO	-0.027 ± 0.040	-0.107	0.053	(1,86)	0.44	0.51
Putamen	SO vs. non-SO	-0.021 ± 0.036	-0.094	0.051	(1,86)	0.35	0.56
NAcc	SO vs. non-SO	-0.013 ± 0.045	-0.102	0.076	(1,86)	0.09	0.77
Cohort A *(pre-RYGB/EB)* **Cohort B** *(nOB/OB)* *n=67*							
HE vs. LE			**95% confidence interval**				
	Post-hoc contrast	**Mean ± SEM**	**lower**	**upper**	**df**	**F**	**P**
LE	SO vs. non-SO	-0.067 ± 0.034	-0.136	0.002	(1,63)	3.80	0.06
HE	SO vs. non-SO	-0.029 ± 0.031	-0.092	0.033	(1,63)	0.88	0.35
Non-SO	HE vs. LE	0.028 ± 0.018	-0.007	0.064	(1,63)	2.51	0.12
SO	HE vs. LE	0.066 ± 0.025	0.017	0.115	(1,63)	7.20	**0.009*****

Table 4.5 Post-hoc analysis for effect of severe obesity group on food cue reactivity in all cohorts combined (n=67 for LE vs. object and HE vs. LE analysis, and n=92 for HE vs. object analysis)
Results from post-hoc pairwise comparisons for group*ED interaction. Between-subject factor (non-SO: non-severe vs. SO: severe obesity), and within-group factor ED energy density (LE: low energy and HE:high energy food picture). Significant results in bold *P<0.05,**P<0.005, ***P<0.003.
Abbreviations: **EB:** Endobarrier, **nOB:** non-obesity, **OB:** obesity, **RYGB:** Roux-En Y gastric bypass, **HE:** high energy, **LE:** low energy, **df:** degree of freedom, **OFC:** orbitofrontal cortex, **ant:** anterior, **NAcc:** nucleus accumbens.

		Cohort A *(pre-RYGB/EB)*		***Cohort B*** *(nOB/OB)*		***Cohort C*** *(OB)*	
Energy density	**fROI**	**r**	**P**	**r**	**P**	**r**	**P**
High-energy pictures	av 6 ROIs	-0.07	0.64	-0.04	0.73	0.07	0.75
	ant. insula	-0.05	0.76	-0.10	0.38	0.11	0.62
	amygdala	0.05	0.74	0.09	0.39	0.07	0.73
	OFC	0.08	0.61	-0.07	0.54	0.36	0.08
	caudate	-0.10	0.54	-0.12	0.27	0.06	0.79
	putamen	-0.07	0.67	-0.01	0.95	0.02	0.93
	NAcc	-0.03	0.83	0.03	0.78	-0.21	0.31
Low-energy pictures	av 6 ROIs	-0.44	**0.003*****	-0.09	0.43	-	-
	ant insula	-0.25	0.11	-0.17	0.11	-	-
	amygdala	-0.30	**0.046***	0.09	0.41	-	-
	OFC	-0.20	0.19	-0.31	**0.003****	-	-
	caudate	-0.34	**0.025****	-0.15	0.16	-	-
	putamen	-0.45	**0.002*****	-0.001	0.99	-	-
	NAcc	-0.28	0.063	0.01	0.91	-	-

Table 4.6 Spearman's correlation between BMI levels and BOLD signal to HE and LE food picture in all cohorts

Spearman's Correlations between BMI levels and BOLD signal in averaged across all 6 fROIS, anterior insula, amydala, OFC, caudate, putamen, nucleus accumbens to HE food vs. objects and LE foods vs objects. Data presented as r Spearman correlation coefficient, *P<0.05, **P<0.01,***P<0.005,***P<0.001.

Abbreviations: av 6 ROIs: average of six functional regions of interest; **ant:** anterior; **OFC:** orbitofrontal cortex; **NAcc**: nucleus accumbens

		Cohort A** (pre-RYGB/EB) **Cohort B** (nOB/OB) **Cohort C** (OB) **n=92	
Energy density	**fROI**	**r**	**P**
High-energy	av 6 ROIs	-0.06	0.60
	ant. insula	-0.06	0.56
	amygdala	0.06	0.59
	OFC	0.17	0.11
	caudate	-0.15	0.16
	putamen	-0.10	0.36
	NAcc	-0.12	0.26
	fROI	***Cohort A** (pre-RYGB/EB) **Cohort B** (nOB/OB) **n=67***	
Low-energy	av 6 ROIs	-0.31	**0.011****
	ant insula	-0.29	**0.016****
	amygdala	-0.18	0.15
	OFC	-0.18	0.14
	caudate	-0.28	**0.022****
	putamen	-0.29	**0.016****
	NAcc	-0.15	0.22

Table 4.7 Spearman's correlation between BMI levels and BOLD signal to HE and LE food picture in participants with obesity from three cohorts

Spearman's correlations between BMI levels and BOLD signal in averaged across all 6 fROIS, anterior insula, amydala, orbitofrontal cortex, caudate, putamen, nucleus accumbens to HE food vs. objects and LE foods vs objects. Data presented as r Spearman correlation coefficient, *P<0.05, **P<0.01,***P<0.001.
Abbreviations: av 6 ROIs: average of six functional regions of interest; **ant:** anterior; **OFC:** orbitofrontal cortex; **NAcc**: nucleus accumbens

Exploratory analysis for individual fROIs

Difference in BOLD signal amygdala, anterior insula, orbitofrontal cortex, NAcc, putamen, caudate was examined between groups within each cohort for HE and LE food pictures vs. objects

Cohort A (pre-RYGB/EB): for BOLD signal during evaluation of HE and LE food pictures (vs. objects), there was a significant interaction effect for group*ED in amygdala, caudate, and putamen [F(1,44)= 4.28, P=0.04], [F(1,44)= 6.50, P=0.014], and [F(1,44)= 3.99, P=0.05] respectively. BOLD signal to LE vs. object food pictures was lower in amygdala, caudate, putamen in severe compared to non-severe obesity group. Pairwise comparison between groups and within groups for HE and LE food pictures are summarized in **Table 4.7 Figure 4.1-A.**

Cohort B (nOB/OB): for BOLD signal during evaluation of HE and LE food pictures (vs. objects), there was no significant interaction effects for group*ED in any individual ROI. BOLD signal to LE vs. objects food pictures was lower in OFC in participants with lower BMI compared to participants with higher BMI. Pairwise comparison between groups and within groups for HE and LE food pictures are summarized in **Table 4.8 Figure 4.1-B.**

cohort C (OB): BOLD signal to HE vs. object food pictures was not different between groups in any individual ROI. Pairwise comparison between groups for HE food pictures are summarized in **Table 4.9 Figure 4.1-C**.

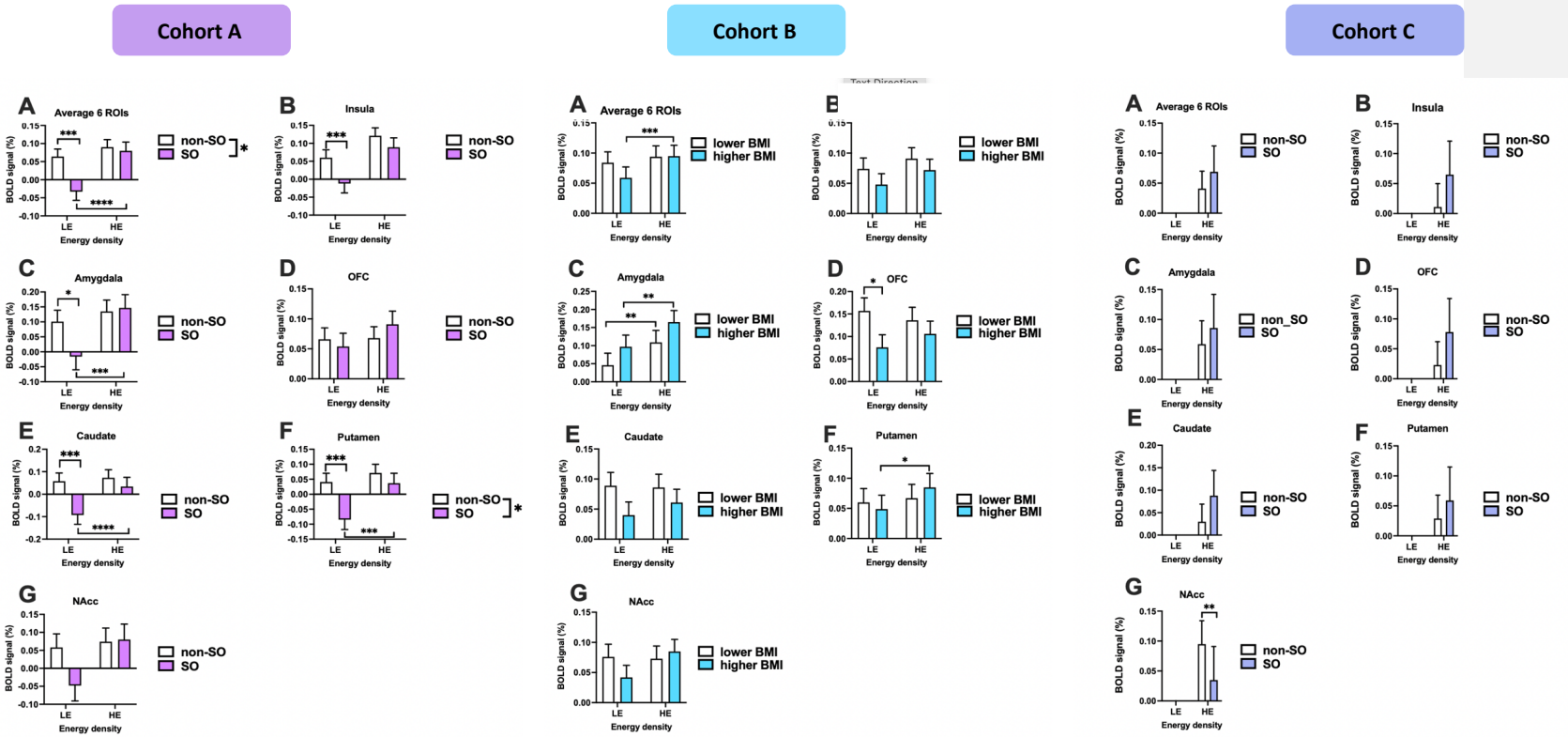


Figure 4.1 BOLD signal in individual fROI analysis

Comparison of BOLD signal from fROI analysis between groups across cohorts, (A) average six fROIS, (B) insula, (C) amygdala, (D) orbitofrontal cortex, (E) caudate, (F) putamen, (G)nucleus accumbens. Data presented as mean ± SEM. Statistics from mixed model repeated measures ANOVA, with fROIs and energy density as within subject factors: post-hoc test *P<0.05, P<0.01,***P<0.005, ****P<0.0001.

Abbreviations: non-SO: non-severe obesity, **SO:** severe obesity, **LE:** low-energy, **HE**: high energy, **NAcc**: nucleus accumbens, **OFC:** orbitofrontal cortex, **BOLD:** blood oxygen level dependent

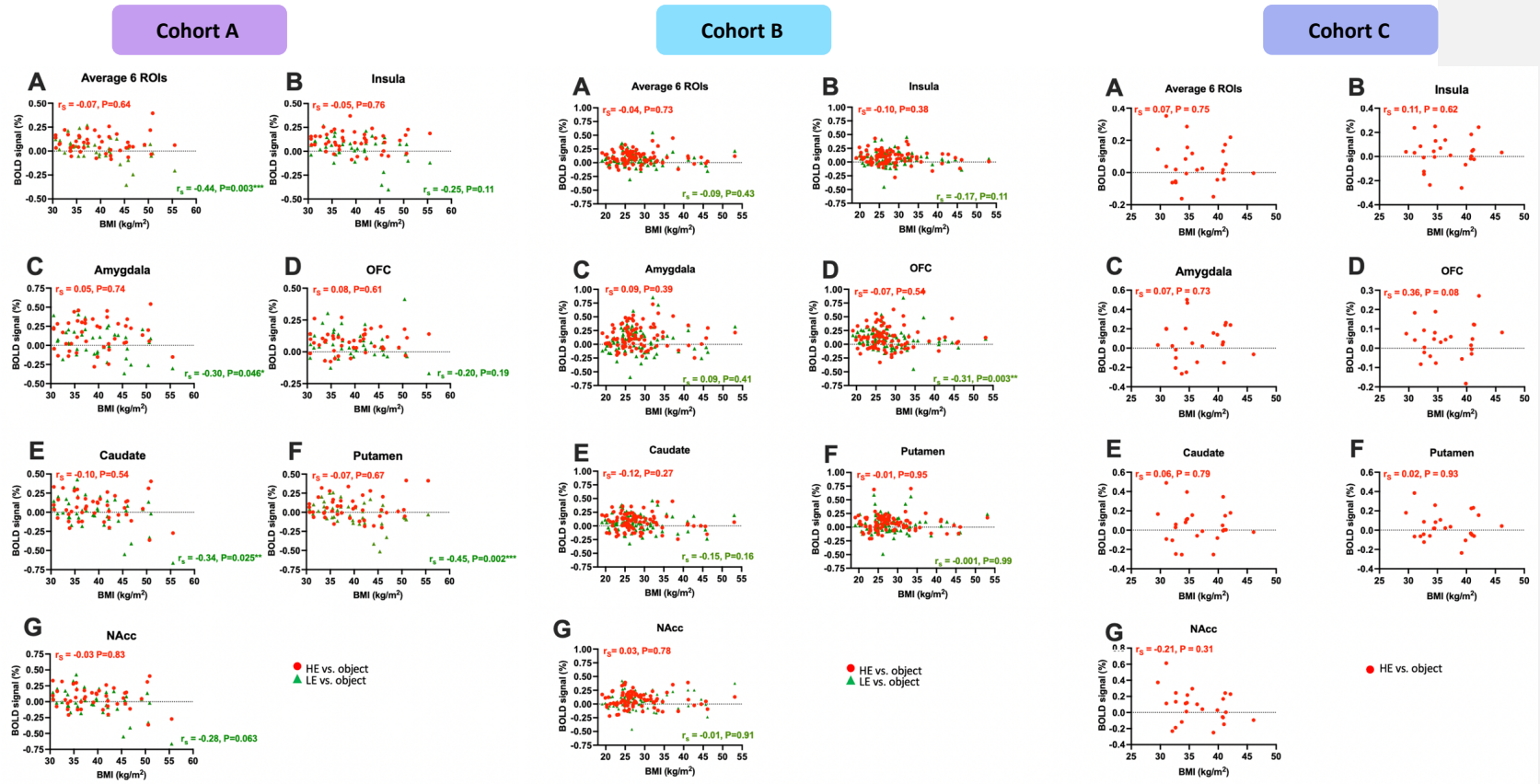


Figure 4.2 Spearman's correlation between BMI and BOLD signal in fROI across cohorts

Spearman's correlations between BMI levels and BOLD signal in A) average six fROIS, (B) insula, (C) amygdala, (D) orbitofrontal cortex, (E) caudate, (F) putamen, (G)nucleus accumbens to HE food vs. objects (red) and LE foods vs objects (green). Data presented as r Spearman correlation coefficient, *P<0.05, **P<0.01,***P<0.001.

Abbreviations: BMI: body mass index, **LE:** low-energy, **HE**: high energy, **NAcc**: nucleus accumbens, **OFC:** orbitofrontal cortex, **BOLD:** blood oxygen level dependent

Cohort A *(pre-RYGB/EB)* Exploratory individual ROI analysis

Insula

Interaction	df	F	P
SO	(1,44)	3.25	0.08
ED	(1,44)	19.25	<0.001****
SO*ED	(1,44)	1.18	0.29

Post-hoc contrast	Mean ± SEM	95% CI		F	df	P
		lower	upper			
LE: SO vs. non-SO	-0.072 ± 0.034	-0.14	-0.004	4.42	(1,74.74)	**0.039***
HE: SO vs. non-SO	-0.032 ± 0.034	-0.1	0.036	0.87	(1,74.74)	0.35
non-SO: HE vs. LE	0.061 ± 0.024	0.012	0.109	6.31	(1,44)	**0.016****
SO: HE vs. LE	0.1 ± 0.028	0.045	0.156	13.18	(1,44)	**0.001*****

Amygdala

Interaction	df	F	P
SO	(1,44)	4.28	0.29
ED	(1,44)	10.01	0.003
SO*ED	(1,44)	4.28	**0.04***

Post-hoc contrast	Mean ± SEM	95% CI		F	df	P
		lower	upper			
LE: SO vs. non-SO	-0.117 ± 0.058	-0.232	-0.001	4.06	(1,74.73)	**0.05***
HE: SO vs. non-SO	0.012 ± 0.058	-0.103	0.128	0.05	(1,74.73)	0.83
non-SO: HE vs. LE	0.034 ± 0.041	-0.048	0.117	0.69	(1,44)	0.41
SO: HE vs. LE	0.163 ± 0.047	0.068	0.258	12.05	(1,44)	**0.001*****

OFC

Interaction	df	F	P
SO	(1,44)	0.05	0.82
ED	(1,44)	1.96	0.17
SO*ED	(1,44)	1.55	0.22

Post-hoc contrast	Mean ± SEM	95% CI		F	df	P
		lower	upper			
LE: SO vs. non-SO	-0.011 ± 0.029	-0.069	0.047	0.15	(1,67.33)	0.70
HE: SO vs. non-SO	0.023 ± 0.029	-0.035	0.08	0.62	(1,67.33)	0.44
non-SO: HE vs. LE	0.002 ± 0.018	-0.034	0.038	0.01	(1,44)	0.91
SO: HE vs. LE	0.036 ± 0.021	-0.005	0.078	3.08	(1,44)	0.09

Caudate

Interaction	df	F	P
SO	(1,44)	3.68	0.06
ED	(1,44)	10.25	0.003**
SO*ED	(1,44)	6.50	**0.014****

Post-hoc contrast	Mean ± SEM	95% CI		F	df	P
		lower	upper			
LE: SO vs. non-SO	-0.151 ± 0.054	-0.26	-0.043	7.79	(1,60.9)	**0.007****
HE: SO vs. non-SO	-0.039 ± 0.054	-0.147	0.07	0.51	(1,60.9)	0.48
non-SO: HE vs. LE	0.014 ± 0.029	-0.044	0.073	0.25	(1,44)	0.62
SO: HE vs. LE	0.127 ± 0.033	0.06	0.195	14.55	(1,44)	**<0.001*****

Putamen						
Interaction		df		F		P
SO		(1,44)		4.48		0.04
ED		(1,44)		10.75		0.002***
SO*ED		(1,44)		3.99		**0.05***
Post-hoc contrast	Mean ± SEM	95% CI		F	df	P
		lower	upper			
LE: SO vs. non-SO	-0.126 ± 0.044	-0.215	-0.038	8.11	(1,72.98)	**0.006****
HE: SO vs. non-SO	-0.034 ± 0.044	-0.122	0.055	0.58	(1,72.98)	0.45
non-SO: HE vs. LE	0.03 ± 0.03	-0.032	0.091	0.95	(1,44)	0.34
SO: HE vs. LE	0.122 ± 0.035	0.052	0.193	12.24	(1,44)	**0.001*****

NAcc						
Interaction		df		F		P
SO		(1,44)		0.93		0.34
ED		(1,44)		8.49		0.006
SO*ED		(1,44)		5.14		0.08
Post-hoc contrast	Mean ± SEM	95% CI		F	df	P
		lower	upper			
LE: SO vs. non-SO	-0.106 ± 0.058	-0.221	0.009	3.40	(1,62.93)	0.07
HE: SO vs. non-SO	0.006 ± 0.058	-0.109	0.121	0.01	(1,62.93)	0.92
non-SO: HE vs. LE	0.016 ± 0.032	-0.049	0.081	0.24	(1,44)	0.63
SO: HE vs. LE	0.128 ± 0.037	0.053	0.203	11.81	(1,44)	0.001***

Table 4.8 Mixed model RMANOVA for exploratory individual fROI analysis and post-hoc pairwise comparison for cohort A (n=44)
Data presented as means ± SEM. **Abbreviations: CI:** confidence intervals, **df:** degrees of freedom, **HE**: high energy, **LE:** low energy, **NAcc:** nucleus accumbens, **non-SO:** non-severe obesity, **SO:** severe obesity, **OFC:** orbitofrontal cortex,.

Cohort B *(nOB/OB)* Exploratory individual ROI analysis

Insula

Interaction	df	F	P
BMI median split	(1,87)	1.05	0.31
ED	(1,87)	2.45	0.12
BMI median split*ED	(1,87)	0.06	0.81

Post-hoc contrast	Mean ± SEM	95% CI		F	df	P
		lower	upper			
LE: higher vs. lower BMI	-0.026 ± 0.026	-0.077	0.025	1.01	(1,141.64)	0.32
HE: higher vs. lower BMI	-0.019 ± 0.026	-0.07	0.031	0.57	(1,141.64)	0.45
Lower BMI : HE vs. LE	0.017 ± 0.019	-0.02	0.055	0.86	(1,87)	0.36
Higher BMI : HE vs. LE	0.024 ± 0.019	-0.013	0.061	1.65	(1,87)	0.20

Amygdala

Interaction	df	F	P
BMI median split	(1,87)	1.60	0.21
ED	(1,87)	13.36	<0.001
BMI median split*ED	(1,87)	0.01	0.91

Post-hoc contrast	Mean ± SEM	95% CI		F	df	P
		lower	upper			
LE: higher vs. lower BMI	0.051 ± 0.046	-0.039	0.142	1.26	(1,117.56)	0.27
HE: higher vs. lower BMI	0.055 ± 0.046	-0.035	0.146	1.46	(1,117.56)	0.23
Lower BMI : HE vs. LE	0.064 ± 0.026	0.013	0.114	6.21	(1,87)	**0.015****
Higher BMI : HE vs. LE	0.068 ± 0.025	0.017	0.118	7.176	(1,87)	**0.009****

OFC

Interaction	df	F	P
BMI median split	(1,87)	2.63	0.11
ED	(1,87)	0.04	0.84
BMI median split*ED	(1,87)	1.53	0.22

Post-hoc contrast	Mean ± SEM	95% CI		F	df	P
		lower	upper			
LE: higher vs. lower BMI	-0.082 ± 0.04	-0.161	-0.002	4.12	(1,143.91)	**0.044***
HE: higher vs. lower BMI	-0.03 ± 0.04	-0.109	0.05	0.55	(1,143.91)	0.46
Lower BMI : HE vs. LE	-0.022 ± 0.03	-0.081	0.037	0.53	(1,87)	0.47
Higher BMI : HE vs. LE	0.03 ± 0.029	-0.028	0.089	1.05	(1,87)	0.31

Caudate

Interaction	df	F	P
BMI median split	(1,87)	1.72	0.19
ED	(1,87)	0.35	0.558
BMI median split*ED	(1,87)	0.68	0.413

Post-hoc contrast	Mean ± SEM	95% CI		F	df	P
		lower	upper			
LE: higher vs. lower BMI	-0.049 ± 0.032	-0.111	0.014	2.38	(1,130.21)	0.13
HE: higher vs. lower BMI	-0.025 ± 0.032	-0.087	0.038	0.62	(1,130.21)	0.43
Lower BMI : HE vs. LE	-0.003 ± 0.021	-0.044	0.038	0.03	(1,87)	0.87
Higher BMI : HE vs. LE	0.02 ± 0.02	-0.02	0.061	1.01	(1,87)	0.32

Putamen						
Interaction		df		F		P
BMI median split		(1,87)		0.01		0.91
ED		(1,87)		2.81		0.10
BMI median split*ED		(1,87)		1.33		0.25
Post-hoc contrast	Mean ± SEM	95% CI		F	df	P
		lower	upper			
LE: higher vs. lower BMI	-0.012 ± 0.033	-0.076	0.053	0.12	(1,117.62)	0.73
HE: higher vs. lower BMI	0.018 ± 0.033	-0.047	0.083	0.31	1,117.62)	0.58
Lower BMI : HE vs. LE	0.007 ± 0.018	-0.03	0.043	0.13	(1,87)	0.72
Higher BMI : HE vs. LE	0.036 ± 0.018	0	0.072	4.05	(1,87)	**0.047***

NACC						
Interaction		df		F		P
BMI median split		(1,87)		0.22		0.64
ED		(1,87)		1.63		0.21
BMI median split*ED		(1,87)		2.12		0.15
Post-hoc contrast	Mean ± SEM	95% CI		F	df	P
		lower	upper			
LE: higher vs. lower BMI	-0.034 ± 0.029	-0.091	0.023	1.39	(1,147.80)	0.24
HE: higher vs. lower BMI	0.011 ± 0.029	-0.046	0.068	0.15	(1,147.80)	0.70
Lower BMI : HE vs. LE	-0.003 ± 0.022	-0.047	0.041	0.02	(1,87)	0.90
Higher BMI : HE vs. LE	0.043 ± 0.022	-0.001	0.086	3.78	(1,87)	0.06

Table 4.9 Mixed model RMANOVA for exploratory individual fROI analysis and post-hoc pairwise comparison for cohort B (n=87)
Abbreviations: CI: confidence intervals, **df:** degrees of freedom, **HE:** high energy, **higher BMI:** BMI higher than median split=26.8, **LE:** low energy, **lower BMI:** BMI lower than median split=26.8, **NAcc:** nucleus accumbens, **OFC:** orbitofrontal cortex,.

Cohort C (OB) Exploratory individual ROI analysis

Insula						
interaction	df		F		P	
SO	(1,25)		1.01		0.33	
Post-hoc contrast	Mean ± SEM	95% CI		F	df	p
		lower	upper			
SO vs. non-SO	0.054 ± 0.07	-0.082	0.19	0.64	(1,66.10)	0.43

Amygdala						
interaction	df		F		P	
SO	(1,25)		0.10		0.75	
Post-hoc contrast	Mean ± SEM	95% CI		F	df	p
		lower	upper			
SO vs. non-SO	0.026 ± 0.068	-0.109	0.162	0.15	(1,66.10)	0.70

OFC						
interaction	df		F		P	
SO	(1,25)		1.99		0.17	
Post-hoc contrast	Mean ± SEM	95% CI		F	df	p
		lower	upper			
SO vs. non-SO	0.055 ± 0.068	-0.081	0.191	0.66	(1,66.10)	0.42

Caudate						
interaction	df		F		P	
SO	(1,25)		0.57		0.46	
Post-hoc contrast	Mean ± SEM	95% CI		F	df	p
		lower	upper			
SO vs. non-SO	0.058 ± 0.068	-0.078	0.194	0.73	(1,66.10)	0.40

Putamen						
interaction	df		F		P	
SO	(1,25)		0.26		0.62	
Post-hoc contrast	Mean ± SEM	95% CI		F	df	p
		lower	upper			
SO vs. non-SO	0.030 ± 0.068	-0.106	0.166	0.19	(1,66.10)	0.66

NAcc						
interaction	df		F		P	
SO	(1,25)		0.51		0.48	
Post-hoc contrast	Mean ± SEM	95% CI		F	df	p
		lower	upper			
SO vs. non-SO	-0.060 ± 0.068	-0.196	0.076	0.78	(1,66.10)	0.38

Table 4.10 Mixed model RMANOVA for exploratory individual fROI analysis and post-hoc pairwise comparison for cohort C (n=24)

Abbreviations: CI: confidence intervals, **df:** degrees of freedom, **HE:** high energy, **NAcc:** nucleus accumbens, **non-SO:** non-severe obesity**, OFC:** orbitofrontal cortex, **SO:** severe obesity

Whole brain analysis

Cohort A (pre-RYGB/EB): (i) LE vs. object: lower BOLD signal in severe obesity group to *low-energy* food pictures in clusters within paracingulate gyrus, nucleus accumbens, caudate, frontal orbital cortex, insular cortex; (ii) HE vs. object: There were no clusters displaying significant differences in BOLD signal between non-severe and severe obesity groups; (iii) HE vs. LE: There were no clusters displaying significant differences in BOLD signal between non-severe and severe obesity groups **Table 4.10, Figure 4.3-A**. Furthermore, BMI was negatively correlated with BOLD signal to (i) LE food pictures in clusters within putamen, hippocampus, insular cortex, precuneus, cingulate gyrus, precentral gyrus, frontal pole; (ii) HE food pictures: in precentral and cingulate gyrus, and to, and (iii) positively correlated with BOLD signal to HE vs. LE food pictures in putamen and pallidum **Table-4.11, Figure 4.3-BA.**

cohort B (nOB/OB): There were no clusters displaying significant differences or correlations in BOLD signal between lower and higher BMI groups

cohort C (OB): There were no clusters displaying significant differences or correlations in BOLD signal between lower and higher BMI groups after adjusting for visit number

When participants with obesity were combined from cohorts, whole brain analysis for: (i) LE vs. object (n=67): lower BOLD signal in severe obesity group to *low-energy* food pictures in clusters within insula, OFC, frontal pole **Figure 4.4.**; (ii) HE vs. object (n=92): There were no clusters displaying significant differences in BOLD signal between non-severe and severe obesity groups; (iii) HE vs. LE food pictures (n=67): There were no clusters displaying significant differences in BOLD signal between non-severe and severe obesity groups **Table 4.12.** Furthermore, BMI was negatively correlated with BOLD signal to (i) LE food pictures in clusters within putamen, hippocampus, insular cortex, precuneus, cingulate gyrus, precentral gyrus, frontal pole **Figure 4.6**; (ii) HE food pictures: in precentral and cingulate gyrus **Figure 4.5**, and (iii) positively correlated with BOLD signal to HE vs. LE food pictures in putamen and pallidum **Table 4.13 Figure 4.7.**

Contrast	Group	Cluster	voxels	Z	R/L	x	y	z	Brain region
HE food > Object	SO > non-SO	none							
	non-SO > SO	none							
LE food > Object	SO > non-SO	none							
	non-SO > SO	1	445	3.79		0	46	10	46% paracingulate gyrus , 41% cingulate gyrus
						8	42	8	25% paracingulate gyrus , 57% cingulate gyrus
						10	40	4	13% paracingulate gyrus , 39% cingulate gyrus
						4	36	10	99% cingulate gyrus
						-18	34	10	
						-4	26	12	8% cingulate gyrus
		2	364	3.9		40	24	-14	81% frontal orbital cortex
					R	12	14	-10	49% accumbens
						22	22	-10	
					R	34	12	-14	79%insular cortex
					R	30	10	-12	10% insular cortex, 7% frontal orbital cortex
					R	16	22	-8	11% caudate, 5% accumbens
HE food > LE food	SO > non-SO	none							
	non-SO > SO	none							

Table 4.11 Whole brain analysis for effect of severe obesity group on HE and LE food evaluation fMRI task for cohort A (n=44)
Spatial coordinates (x,y,z in standard MNI space) for peak voxel of group activation for non-SO: non-severe obesity (n=26) and SO: severe obesity (n=22), for HE vs. object, LE vs. object, and HE vs. LE food picture. Cluster-wise threshold Z>2.6, family wise error P<0.05.

Contrast	Correlation	Cluster	voxels	Z	R/L	x	y	z	Brain region
HE food > Object	BMI pos corr	none							
	BMI neg corr	1	348	3.9		-40	-10	42	26% precentral gyrus
						-22	-20	50	WM
						-28	-12	38	WM
						-16	-16	48	WM
						-12	-16	40	25% cingulate gyrus P, 12% precentral gyrus, 8% cingulate gyrus A
						-38	-24	44	41% postcentral gyrus,
LE food > Object	BMI pos corr	none							
	BMI neg corr	1	1961	4.49		24	-22	-2	WM
					R	18	-24	0	86% thalamus
					R	50	4	-20	32% STG
					R	30	6	-10	8% putamen
					R	40	24	-14	6% hippocampus
					R	38	-14	0	76% insular cortex
		2	671	4.55	R	12	-66	38	46% precuneuos, 6% cuneal
					R	4	-76	38	45% precuneuos, 30% cuneal
					L	-2	-76	40	62% precuneuos, 15% cuneal
					L	-10	-70	44	47% precuneuos, 10% occiptal
					L	-8	-68	32	45% precuneuos, 12% cuneal
		3	618	4.05		-2	-32	48	33% cingulate gyrus, 33% precentral gyrus, 11% precuneuos
						-2	-20	42	75% cingulate gyrus P, 13% cingulate gyrus A, 8% precentral gyrus
						12	-28	46	63% precentral gyrus, 19% cingulate gyrus P,

						0	-40	52	16% precuneous, 7% postcentral gyrus, 6% precentral gyrus
		4	473	4.44		-66	-46	14	46% supramarginal gyrus, 12% angular gyrus, 6% superior temporal gyrus
						-66	-42	12	43% supramarginal gyrus, 29% superior temporal gyrus
						-60	-50	6	49% middle temporal gyrus, 14% angular gyrus
						-56	-48	4	48% middle temporal gyrus, 10% supramarginal gyrus, 8% angular gyrus, 8% middle temporal gyrus P
						-50	-42	-8	6% middle temporal gyrus, 5% middle temporal gyrus P
						-66	-30	6	44% superior temporal gyrus
		5	380	4.08		8	48	40	19% superior frontal gyrus, 19% frontal pole, 35% cluster3 (area9), 29% cluster 10 (area8b)
					R	12	46	44	69% frontal pole, 46% cluster10 (area8b)
						-2	42	28	67% paracingulate gyrus, 10% superior frontal gyrus
						4	42	36	51% superior frontal gyrus, 34% paracingulate gyrus, 29% cluster10 (area 8b), 25% cluster3 (area9)
						-2	38	20	51% cingulate gyrus, 44% paracingulate gyrus
HE food > LE food	BMI pos corr	1	447	4.39		-54	0	-16	55% superior temporal gyrus, 30% ant division MTG
						-46	16	-30	78% Temporaal pole
						-62	-16	-12	54% middle temporal gyrus P, 10% middle temporal gyrus A, 9% superior temporal gyrus P
						-46	4	-10	28% Planum polare, 27% temporal pole
						-62	-16	-6	26% superior temporal gyrus, 24% middle temporal gyrus P, 13% middle temporal gyrus A
						-58	8	-28	
		2	414	4.16	L	-22	-4	4	51% pallidum, 48% putamen
					L	-30	2	-8	21% putamen
					L	-30	-4	-8	36% putamen

					L	-18	14	-10	96% putamen
					L	-16	6	-12	55% putamen
					L	-20	6	-12	50% putamen
	BMI neg corr	none							

Table 4.12 Whole brain analysis for effect of BMI levels on HE and LE food evaluation fMRI task for cohort A (n=44)

Spatial coordinates (x,y,z in standard MNI space) for peak voxel of group activation for non-SO: non-severe obesity (n=26) and SO: severe obesity (n=22), for HE vs. object, LE vs. object, and HE vs. LE food picture. Cluster-wise threshold Z>2.6, family wise error P<0.05.

Abbreviations: A: anterior; **P:** posterior; **STG:** superior temporal gyrus

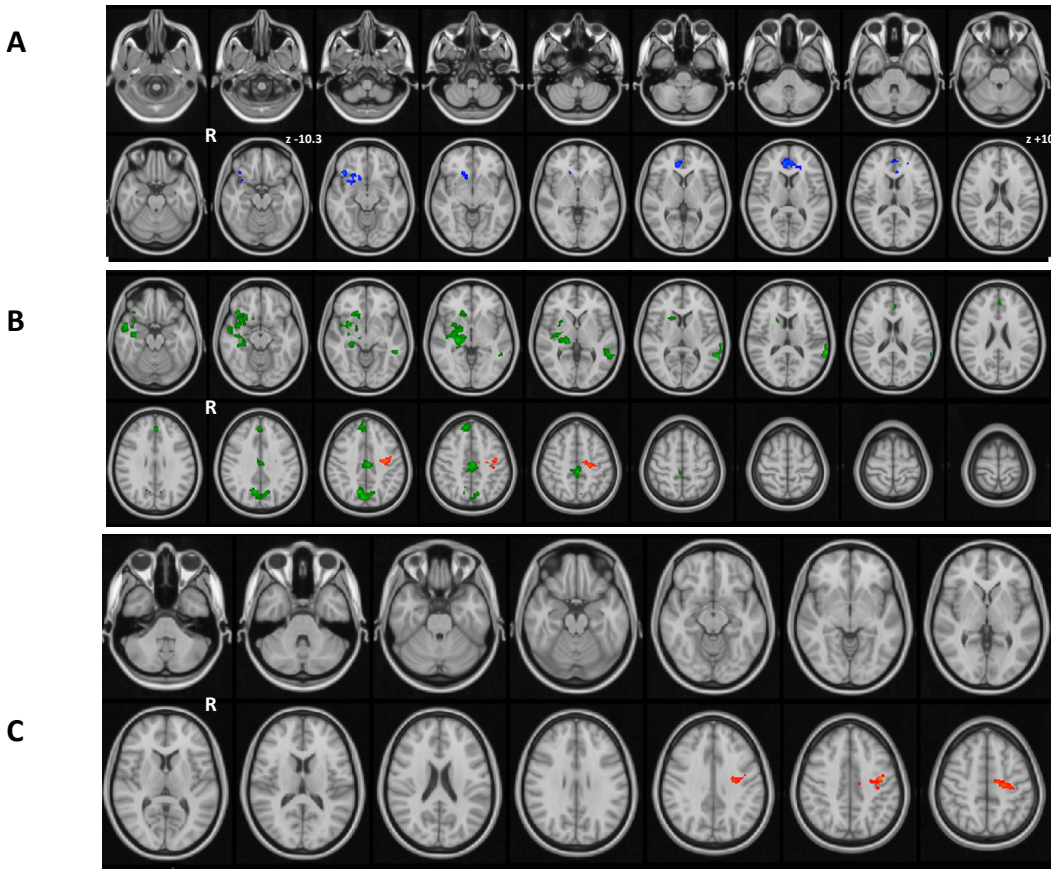


Figure 4.3 Whole brain analysis cohort A (n=44)
Cluster-wise threshold Z>2.6, family-wise Error (FWE) P<0.05. z co-ordinates given in Montreal Neurological Institute (MNI) space. Abbreviations: R, right. **See Table 4.10-4.11 for MNI co-ordinates. (A)** Group level activation for LE food vs. object contrast in participants with non-severe obesity (non-SO) vs. participants with severe obesity; **(B)** BMI negative correlation with HE vs. object contrast in (red) and with LE vs. object contrast in (green), and **(C)** BMI positive correlation with HE vs. LE contrast

Contrast	Group	Cluster	voxels	Z	L/R	x	y	z	Region
HE food > Object	SO > non-SO	none							
Cohorts ABC (n=92)	non-SO > SO	none							
HE food > LE food	SO > non-SO	none							
Cohorts AB (n=67)	non-SO > SO	none							
LE food > Object	SO > non-SO	none							
Cohorts AB (n=67)	non-SO > SO	1	509	4.15	R	8	42	8	57% cingulate gyrus, 25% paracingulate gyrus
					R	10	38	4	19% cingulate gyrus A, 7% paracingulate gyrus
					R	4	44	10	63% cingulate gyrus A, 31% paracingulate gyrus
					L	-14	34	10	
					L	-4	26	16	48% cingulate gyrus A
					L	-4	28	20	70% cingulate gyrus A
		2	1451	4.45	R	18	-24	0	68% thalamus
					R	50	4	-20	32% superior temporal gyrus A, 16% temporal pole, 9% middle temporal gyrus A
					R	40	28	-14	78% frontal orbital cortex, 6% frontal pole
						36	-8	-18	
					R	28	-28	-14	52% hippocampus, 11% parahippocample gyrus P
					R	36	14	-14	78% insular cortex, 8% frontal orbital cortex,

Table 4.13 Whole brain analysis for effect of BMI levels on HE and LE food evaluation fMRI task for all cohorts combined (n=92-67)

Spatial coordinates (x,y,z in standard MNI space) for peak voxel of correlation activation for non-SO; non-severe obesity and SO: severe obesity for HE vs. object, LE vs. object, and HE vs. LE food picture. Cluster-wise threshold Z>2.6, family wise error P<0.05.. Abbreviations: A: anterior; P: posterior; I: interior; R: right; L: left

Contrast	Group	Cluster	voxels	Z	L/R	x	y	z	Region
HE food > Object	BMI pos corr	1	3822	4.42	L	-16	-80	-8	29% occiptal fusiform gyrus, 20% lingual gyrus
Cohorts A,B,C (n=92)	BMI neg corr				R	2	-74	-6	53% lingual gyrus
					L	-16	-88	-4	10% lingual gyrus, 8% occiptal fusiform gyrus, 7% occipital pole
					L	-6	-88	-4	40% lingual gyrus, 21% intracalcarine cortex, 12% occiptal pole
					R	16	-78	-6	26% occiptal fusiform gyrus, 25% lingual gyrus
					L	-26	-80	16	43% lateral occipital cortex S
		1	778	4.45	R	46	-68	26	65% lateral ociiptal cortex
					R	48	-68	16	47% lateral occiptal cortex S, 31% lateral occiptal cortex I
					R	48	-66	22	73% lateral ociiptal cortex S
					R	46	-76	0	56% lateral ociiptal cortex I
					R	50	-70	8	76% lateral occiptal cortex I, 7% lateral occiptal cortex S
					R	48	-50	18	42% angular gyrus, 25% middle temporal gyrus
		2	1088	4.79	L	-62	-58	2	69% middle temporal gyrus, 18% lateral occiptal cortexI
					L	-50	-70	10	71% lateral occiptal cortex I, 15% lateral occiptal cortex S
					L	-56	-48	4	48% middle temporal gyrus, 10% supramarginal gyrus, 8% angular gyrus
					L	-64	-48	16	53% supramarginal gyrus P, 29% angular gyrus
					L	-66	-52	12	17% supramarginal gyrus P, 17% angular gyrus, 11% middle temporal gyrus
					L	-68	-44	6	18% middle temporal gyrus, 14% supramarginal gyrus, 9% middle temporal gyrus P, 9% superior temporal gyrus P
HE food > LE food	BMI pos corr	1	333	3.58	R	64	-44	6	64% middle temporal gyrus, 11% supramarginal gyrus
Cohorts A,B (n=67)					R	54	-66	10	72% lateral occipital cortex I, 7% lateral occipital cortex S
					R	54	-66	6	81% lateral occipital cortex I, 5% lateral occipital cortex S

					R	60	-54	16	57% angular gyrus, 19% middle temporal gyrus, 5% lateral occipital cortex S
					R	54	-58	8	50% middle temporal gyrus, 19% lateral occipital cortex
					R	48	-66	4	65% lateral occipital cortex I
		2	699	4.31	R	52	28	0	54% inferior frontal gyrus, 11% frontal orbital cortex
					R	42	36	-16	60% frontal pole, 23% frontal orbital cortex
					R	54	28	4	73% inferior frontal gyrus
					R	48	32	-4	26% inferior frontal gyrus, 20% frontal orbital cortex, 17% frontal pole
					R	28	32	-18	59% frontal orbital cortex, 33% frontal pole
					R	46	30	-10	44% frontal orbital cortex, 12% inferior frontal gyrus, 12% frontal pole, 5% frontal operculum cortex
		3	891	4.24	L	-44	16	52	55% middle frontal
					L	-22	34	46	49% superior frontal gyrus, 13% frontal pole, 8% middle frontal gyrus
					L	-16	36	44	30% superior frontal gyrus, 18% frontal pole
					L	-20	28	54	70% superior frontal gyrus, 7% middle frontal gyrus
					L	-20	28	48	50% superior frontal gyrus, 5% middle frontal gyrus
					L	-34	26	50	79% middle frontal gyrus
		4	1968	4.97	R	56	2	-20	45% middle temporal gyrus A, 32% superior temporal gyrus A
					R	52	0	-20	46% superior tempral gyrus A, 21% middle temporal gyrus A
					R	14	14	8	96% caudate
					R	18	16	8	62% caudat
					R	3-	6	-4	
					R	54	0	12	29% central opercular cortex, 12% precentral gyrus

		5	2334	5.47	L	-58	-2	-16	56% middle temporal gyrus A, 20% superior temporal gyrus
					L	-28	-26	0	
					L	-58	6	-22	63% temporal pole, 6% middle temporal gyrus A
					L	-50	12	-30	83% temporal pole
					L	-58	8	-28	33% temporal pole
					L	-8	-32	-28	100% brainstem
		6	2499	4.85	R	8	50	4	74% paracingulate gyrus, 6% cingulate gyrus, 5% frontal medical cortex
					L	-22	58	30	62% frontal pole
					L	-2	56	10	33% paracingulate gyrus, 33% frontal pole, 11% superior frontal gyrus
					L	-24	58	24	81% frontal pole
					R	8	68	0	79% frontal pole
					R	0	38	28	80% paracingulate gyrus, 8% cingulate gyrus A
		7	3741	5.1	L	-54	-46	4	40% middle temporal gyrus, 10% supramarginal gyrus P, 7% middle temporal gyrus P
					L	-42	-78	26	75% lateral occipital cortex S
					L	-54	-54	36	48% angular gyrus, 23% supramarginal gyrus P, 7% lateral occipital cortex S
					L	-60	-30	40	69% supramarginal gyrus A, 14% postcentral gyrus
					L	-42	-54	-12	32% inferior temporal gyrus, 30% temporal occipital fusiform cortex
					L	-62	-48	34	57% supramarginal gyrus P, 23% angular gyrus
		8	5938	4.59	L	-8	-64	4	47% lingual gyrus, 24% intracalcarine cortex

					L	-2	-42	42	50% cingulate gyrus P, 43% precuneous cortex
					R	14	-62	16	29% precuneous cortex, 26% supracalcarine cortex, 16% intracalcarine cortex, 11% cuneal cortex
					L	-2	-30	44	73% cingulate gyrus, 10% precuneous cortex, 7% precentral gyrus
					L	-8	-70	20	29% precuneous cortex, 16% supracalcarine cortex, 13% intracalcarine cortex, 17% cuneal cortex
					R	22	-66	20	30% supracalcarine cortex, 29% cuneal cortex, 9% precuneous cortex
	BMI neg corr	1	475	4	L	-8	-96	-6	64% occipital pole, 5% intracalcarine cortex
					L	-16	-92	-12	37% occipital pole, 19% occipital fusiform gyrus, 10% lingual gyrus
					L	-10	-88	-10	33% lingual gyrus, 10% occipital pole, 18% occipital fusiform gyrus
					L	-18	-84	-16	54% occipital fusiform gyrus, 10% lingual gyrus
					L	-18	-96	-2	47% occipital pole
					L	-28	-94	-2	48% occipital pole, 15% lateral occipital cortex I
LE food > Object	BMI pos corr	1	2942	4.84	L	-16	-92	-8	42% occiptal pole, 12% occiptal fusiporm gyrus, 9% lingual gyrus
Cohorts AB (n=67)					L	-12	-94	-12	56% occiptal pole, 7% occiptal fusiform gyrus
					R	10	-90	-6	34% occiptal pole, 9% occiptal fusiporm gyrus, 21% lingual gyrus
					R	14	-78	-6	46% lingual gyrus, 16% occiptal fusiporm gyrus
					L	-12	-94	10	37% occiptal pole
					R	8	-74	-14	16% lingual gyrus, 8% occiptal fusiform gyrus
	BMI neg corr	1	561	5.05	R	50	26	2	24% inferior frontal gyrus, 9% frontal operculum cortex
					R	40	28	-14	78% frontal orbital cortex, 6% frontal pole
					R	46	32	-8	24% frontal orbital cortex, 13% frontal pole, 12% inferior frontal gyrus
					R	54	20	8	48% inferior frontal gyrus

					R	26	22	-14	61% frontal orbital cortex
					R	36	38	-4	8% frontal pole
		2	582	5.11	R	30	-32	-16	60% parahipocampal gyrus P, 13% temporal fusiform cortex P, 6% temporal occiptal fusiform cortex
					R	26	-36	-10	21% parahippocampal gyrus P, 20% lingual gyrus
					R	42	-26	18	70% parietal operculum cortex, 10% planum temporale, % Heschl's gyrus
					R	34	-44	-6	27% ligual gyrus, 17% temporal occiptal fusiform cortex
					R	40	-46	-18	49% temporal occiptal fusiform cortex, 9% inferior temporal gyrus
					R	42	-32	-16	20% temporal fusiform cortex P, 9% inferior temporal gyrus O
		3	687	4.48	R	20	-64	20	37% supracalcarine cortex, 29% cuneal cortex, 21% precuneous cortex
					L	-20	-66	20	27% precuneous cortex, 24% supracalcarine cortex, 15% cuneal cortex
					R	16	-72	32	36% cuneal cortex, 29% precuneous cortex
					L	-4	-70	24	46% precuneous cortex, 21% cuneal cortex, 13% supracalcarine cortex
					L	-8	-64	28	44% precuneous cortex, 6% cuneal cortex
					R	12	-82	28	28% cuneal cortex
		4	1691	5.14	R	48	-64	22	57% lateral occiptal cortex S, 7% angular gyrus, 6% lateral occiptal cortex I
					R	62	-46	6	73% middle temporal gyrus, 5% angular gyrus, 5% supramatginal gyrus P
					R	54	-66	6	81% lateral occiptal cortex I, 5% lateral occiptal cortex

					R	60	-54	16	57% angular gyrus, 19% middle temporal gyrus, 5% lateral occiptal cortex
					R	50	-56	18	46% angular gyrus, 6% middle temporal gyrus, 12% lateral occiptal cortex
		5	1883	5.43	R	54	4	-18	34% superior temporal gyrus A, 17% temporal pole, 17% middle temporal gyrus A
					R	50	12	-22	75% temporal pole
					R	40	-12	0	86% insular cortex
					R	36	-12	-20	32% insular cortex
					R	28	2	-2	100% putamen
					R	40	20	-26	81% temporal pole
		6	4317	6.1	L	-56	-48	2	41% middle temporal gyrus, 11% angular gyrus, 10% middle temporal gyrus P
					L	-60	-54	4	61% middle temporal gyrus, 9% angular gyrus, 5% supramarginal gyrus
					L	-66	-46	14	46% supramarginal gyrus, 12% angular gyrus, 6% superior temporal gyrus P
					L	-60	-66	4	49% lateral occiptal cortex I, 13% middle temporal gyrus
					L	-40	-74	28	58% lateral occiptal cortex
					L	-54	-72	14	40% lateral occiptal cortex S, 35% lateral occiptal cortex I
		7	5634	5.3	L	-56	-2	-16	45% middle temporal gyrus A, 29% superior temporal gyrus A
					L	-34	22	-28	35% temporal pole, 16% frontal orbital cortex
					L	-50	34	-2	48% inferior frontal gyrus, 28% frontal pole, 9% frontal orbital cortex
					L	-16	26	48	27% superior frontal gyrus

					L	-52	6	-18	74% temporal pole, 5 % superior temporal gyrus A
					L	-38	20	-26	65% temporal pole, 14% frontal orbital cortex

Table 4.13 Whole brain analysis for effect of BMI levels on HE and LE food evaluation fMRI task for all cohorts combined (n=92-67)
Spatial coordinates (x,y,z in standard MNI space) for peak voxel of correlation activation for non-SO: non-severe obesity and SO: severe obesity for HE vs. object, LE vs. object, and HE vs. LE food picture. Cluster-wise threshold Z>2.6, family wise error P<0.05. Abbreviations: A: anterior; P: posterior; I: interior; R: right; L: left

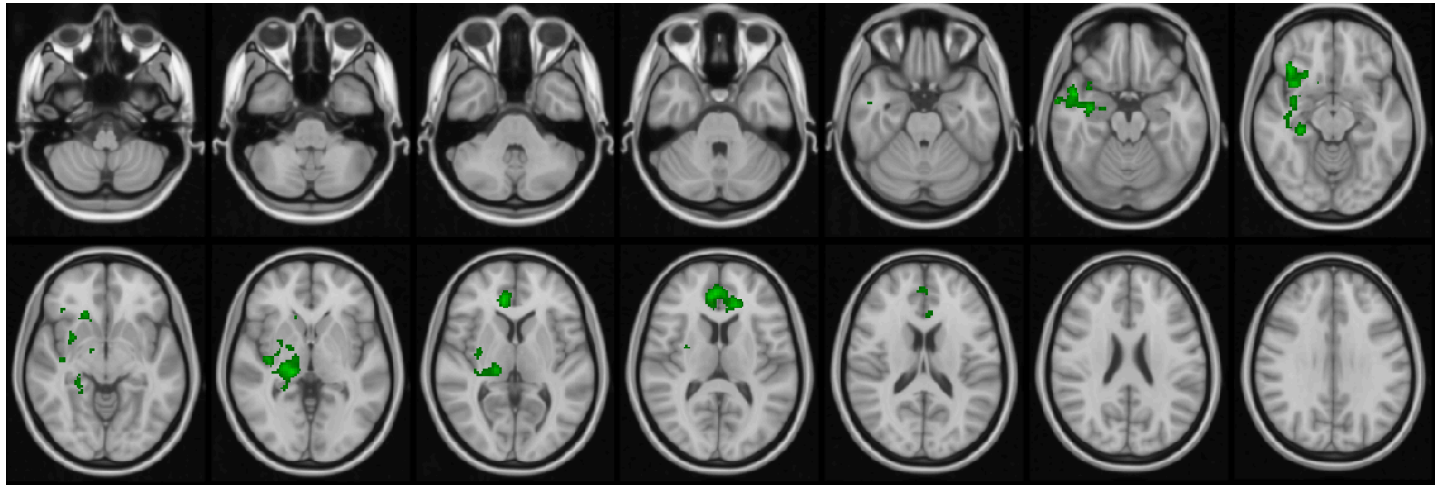


Figure 4.4 Whole brain analysis for LE vs. object contrast in combined cohorts (n=67)
Group level activation for LE food vs. object contrast in participants with non-severe obesity (non-SO) vs. participants with severe obesity
Colour bar indicates Z score. Cluster-wise threshold Z>2.6, family-wise Error (FWE) P<0.05. z co-ordinates given in Montreal Neurological Institute (MNI) space. Abbreviations: R, right. **See Table 4.12 for MNI co-ordinates**.

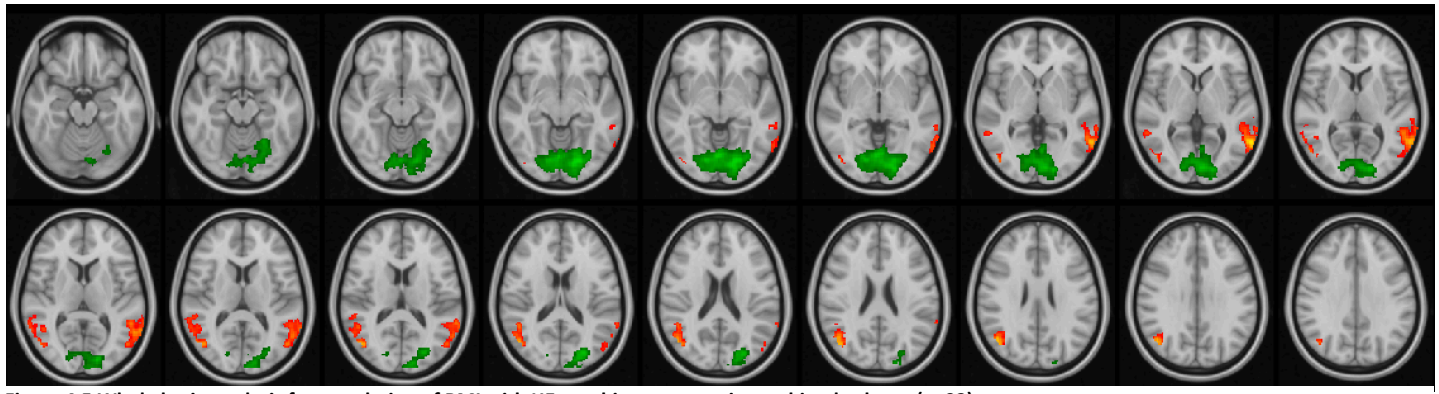


Figure 4.5 Whole brain analysis for correlation of BMI with HE vs. object contrast in combined cohorts (n=92)
BMI positive correlation with HE vs. object contrast in (green) and negative correlation with HE vs. object contrast in (red)
Cluster-wise threshold Z>2.6, family-wise Error (FWE) P<0.05. z co-ordinates given in Montreal Neurological Institute (MNI) space. Abbreviations: R, right. **See Table 4.13 for MNI co-ordinates**.

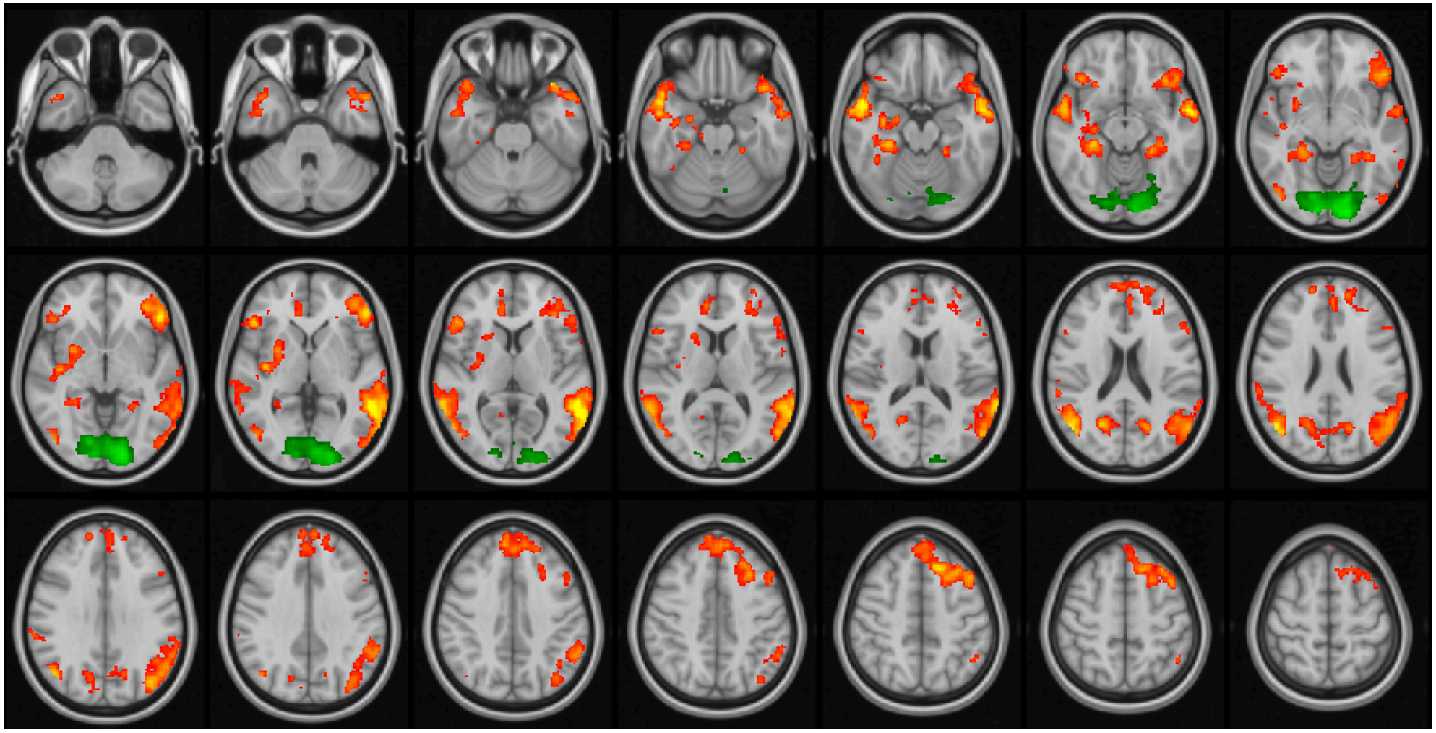


Figure 4.6 Whole brain Whole brain analysis for correlation of BMI with LE vs. object contrast in combined cohorts (n=67)
BMI positive correlation with LE vs. object contrast in (green) and negative correlation with LE vs. object contrast in (red)
Cluster-wise threshold Z>2.6, family-wise Error (FWE) P<0.05. z co-ordinates given in Montreal Neurological Institute (MNI) space. Abbreviations: R, right. **See Table 4.13 for MNI co-ordinates**.

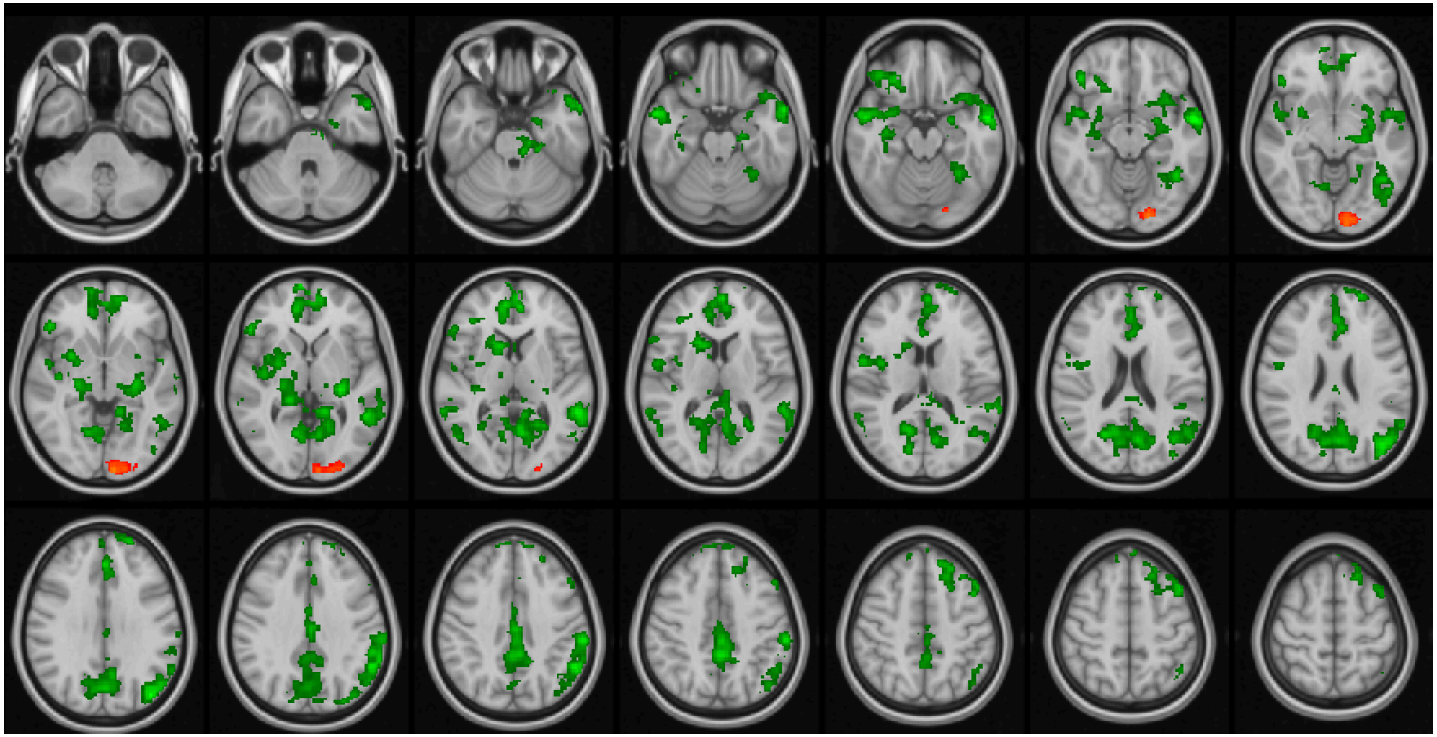


Figure 4.6 Whole brain Whole brain analysis for correlation of BMI with HE vs. LE contrast in combined cohorts (n=67)
BMI levels positive correlation with HE vs. LE contrast in (green) and negative correlation with HE vs. LE contrast in (red)
Cluster-wise threshold Z>2.6, family-wise Error (FWE) P<0.05. z co-ordinates given in Montreal Neurological Institute (MNI) space. Abbreviations: R, right. **See Table 4.13 for MNI co-ordinates**.

Potential confounding factors for scanning visit

The following confounder were examined for differences between groups within each cohort: (i) absolute and relative motion; (ii) menstrual cycle; (iii) visual analogue scales of anxiety, stress, and sleepiness; (iv) fasting duration; (v) hours slept night before; (vi) Positive Affect and Negative Affect Schedule (PANAS). There was no difference between any of the above confounders between groups with higher and lower BMI within each cohort **Table 4.13**

	Cohort A *(pre-RYGB/EB)* n=44				Cohort B *(nOB/OB)* n=87				Cohort C *(OB)* n=24			
	non-SO	SO	t-test	P	Lower BMI	Higher BMI	t-test	P	non-SO	SO	t-test	P
Absolute motion	0.5 ± 0.3	0.7 ± 0.4	-1.9	0.1	0.5 ± 0.3	0.4 ± 0.3	0.9	0.4	-	-	-	-
Relative motion	0.1 ± 0.04	0.2 ± 0.1	-2.2	**0.04**	0.1 ± 0.1	0.1 ± 0.1	-0.1	0.9	-0.9 ± 0.2	-0.9 ± 0.1	0.49	0.6
Menstrual cycle	9.0 ± 8.0	17.0 ± 10.2	-1.2	0.3	-	-	-	-	15.8 ± 16.3	21.5 ± 15.8	-0.6	0.6
VAS												
Anxiety	17.9 ± 18.0	21.3 ± 17.0	-0.6	0.5	1.7 ± 2.0	1.9 ± 2.6	-0.3	0.7	4.8 ± 10.9	0.8 ± 1.4	1.0	0.3
Stress	15.5 ± 16.1	14.2 ± 12.3	0.3	0.8	1.8 ± 2.1	2.0 ± 2.7	-0.4	0.7	5.3 ± 10.1	0.9 ± 1.7	1.2	0.2
Sleepiness	20.3 ± 18.2	18.1 ± 14.8	0.4	0.7	2.8 ± 2.4	3.0 ± 2.3	-0.4	0.7	33.7 ± 26.9	27. 3± 37.2	0.5	0.6
Fasting duration	-	-	-	-	16.2 ± 1.2	16.3 ± 1.2	-0.3	0.8	-	-	-	-
Hours slept night before	6.6 ± 1.2	6.5 ± 1.3	0.3	0.8	7.4 ± 1.0	6.8 ± 1.5	1.8	0.1	-	-	-	-
Positive affect	33.1 ± 6.2	32.0 ± 6.0	0.6	0.6	32.2 ± 6.1	32.6 ± 7.2	-0.3	0.8	34.8 ± 7.0	35.4 ± 4.5	-0.2	0.8
Negative affect	15.5 ± 4.5	17.3 ± 6.1	-1.1	0.3	14.8 ± 4.3	15.1 ± 5.0	-0.3	0.8	13.3 ± 4.7	12.0 ± 3.4	0.8	0.5

Table 4.14 Potential confounding factors of picture evaluation fMRI task

Comparison between groups in each cohort for potential confounders using Mann-Whitney non-parametric test. Data presented as mean rank and test statistic.
VAS: visual analogue scale before scanning

4.4.3 Food appeal ratings

Cohort A (pre-RYGB/EB) **n=48**: for HE and LE (vs. object) food picture appeal rating during scanning, there was no significant interaction effects for: (i) group*ED [F(1,48)=1.87, P=0.18], nor (ii) overall effect of group [F(1,48)= 2.13, P=0.15], but an overall effect of ED [F(1,48)= 6.93, P=0.01]. Furthermore, for HE subcategory (savoury, sweet, chocolate) food picture appeal rating during scanning, there was no significant interaction effects for: (i) group*HE subcategory [F(2,96)=0.70, P=0.5], but a significant overall effect of ii) group [F(1,48)=3.60, P=0.04], and (ii) HE subcategory [F(2,97)= 3.62, P=0.03] in mixed model RMANOVA analysis **Table 4.14 Figure 4.10-A**. Further post-hoc analysis and pairwise comparison summarized in **Table 4.15.** Spearman's correlation between BMI levels and appeal ratings for HE and LE food pictures, and HE categories (chocolate, sweet, savoury) revealed positive correlation between BMI and appeal ratings for HE food picture **Table 4.16**

This was consistent in *cohort B (nOB/OB)* **n=95** where for for HE and LE (vs. object) food picture appeal rating during scanning, there was no significant interaction effects for: i) group*ED [F(1,95)=0.07, P=0.80], nor (ii) overall effect of group [F(1,95)= 2.87, P=0.09], or ED [F(1,95)= 0.51, P=0.48]. Furthermore, for HE subcategory (savoury, sweet, chocolate) food picture appeal rating during scanning, there was no significant interaction effects for: (i) group*HE subcategory [F(2,187.1)=0.001, P=1.00], nor overall effect of (ii) group [F(2,187.1)=0.65, P=0.42], and (ii) HE subcategory [F(2,187.1)= 0.87, P=0.42] in mixed model RMANOVA analysis **Table 4.14 Figure 4.10-B**. Further post-hoc analysis and pairwise comparison summarized in **Table 4.15.** Spearman's correlation between BMI levels and appeal ratings for HE and LE food pictures, and HE categories (chocolate, sweet, savoury) revealed no significant correlation between BMI and appeal ratings for HE and LE food picture **Table 4.16**

nor cohort C (OB) **n=25** where for HE (vs. object) food picture appeal rating during scanning, there was not a significant difference between groups (t-test= -1.71,P=0.63) **Table 4.14, 4.15 and Figure 4.10-B**. Spearman's correlation between BMI levels and appeal ratings for HE food pictures revealed no significant correlation between BMI and appeal ratings for HE food picture **Table 4.16 Figure 4.5-C**

When participants with obesity were combined from cohorts, LE food picture appeal rating during scanning, was lower in participants with non-severe obesity compared to participants with severe obesity [Mean ± SD 0.95 ± 0.71 vs. 1.11 ± 1.04, (t-test= -0.74, P=0.041)] **Table 4.14**

	Cohort A *(pre-RYGB/EB)* **n=48**		**Cohort B** *(nOB/OB)* **n=95**		**Cohort C** [a] *(OB)* **n=25**		**Combined cohorts** *(OB)* **n=67**	
Interaction	**(df) F**	**P**	**(df) F**	**P**	**t-test**	**P**	**t-test**	**P**
group*ED	(1, 48) 1.87	0.18	(1,95) 0.07	0.80	-	-		
group	(1, 48) 2.13	0.15	(1,95) 2.87	0.09	-1.77 [a]	0.63	-0.74 [a]	**0.041***
ED	(1, 48) 6.93	0.011	(1,95) 0.51	0.48	-	-	-0.92 [b]	0.46
group*HE subcategory	(2,96) 0.70	0.50	(2,187.11) 0.001	1.00	-	-	-	-
group	(1, 48) 3.60	**0.04***	(2,187.11) 0.65	0.42	-	-	-	-
HE subcategory	(2,96) 3.62	0.03	(2,187.11) 0.87	0.42	-	-	-	-
BMI*ED	(1,48) 3.03	0.09	0.70 (1,92.98)	0.791	-	-	-	-
BMI	(1,48) 2.07	0.16	3.68 (1,94.12)	**0.058**	(1,24) 4.96	**0.036***	-	-
ED	(1, 48) 1.78	0.19	(1,95) 0.51	0.48	-	-	-	-
BMI*HE subcategory	(2,96) 0.72	0.49	1.69 (2,187.03)	0.19	-	-	-	-
BMI	(1,48) 4.21	**0.046***	1.48 (1,93.93)	0.23	-	-	-	-
HE subcategory	(2,96) 0.54	0.59	(2,187.03) 1.46	0.24	-	-	-	-

Table 4.15 Mixed model RMANOVA for effect of severe obesity group (categorical and continuous variable) on food appeal ratings. Cohort A (n=48), Cohort B (n=95), Cohort C (n=25)
Results from mixed model RMANOVA for appeal ratings for group (non-SO:non-severe vs. SO:severe obesity or lower vs. higher-BMI) as between-subject factor or BMI, and ED energy density (low and high energy food picture) and HE food subcategory (chocolate, sweet, savoury) as within subject factors. [a] comparison between severe and non-severe obesity groups for HE food picture appeal ratings performed by t-test, [b] comparison between severe and non-severe obesity groups for HE food picture appeal ratings performed by t-test Significant results in bold *P<0.05

Cohort A *(pre-RYGB/EB)*			**95% confidence interval**				
	Post-hoc contrast	**Mean ± SEM**	**lower**	**upper**	**df**	**F**	**P**
	LE: SO vs. non-SO	0.17 ± 0.25	-0.33	0.66	(1,71.22)	0.47	0.50
	HE: SO vs. non-SO	0.477 ± 0.25	-0.02	0.97	(1,71.22)	3.69	0.06
	non-SO: HE vs. LE	0.142 ± 0.15	-0.16	0.45	(1,47)	0.87	0.36
	SO: HE vs. LE	0.449 ± 0.17	0.12	0.78	(1,47)	7.38	**0.009****
	Savoury: SO vs. non-SO	0.513 ± 0.27	-0.03	1.05	(1,60.12)	3.63	0.06
	Sweet: SO vs. non-SO	0.554 ± 0.27	0.02	1.09	(1,60.12)	4.23	**0.04***
	Chocolate: SO vs. non-SO	0.38 ± 0.27	-0.16	0.92	(1,60.12)	1.99	0.16
Cohort B *(nOB/OB)*							
	LE: higher vs. lower BMI	-0.25 ± 142.23	-0.62	0.11	(1,142.23)	1.92	0.17
	HE: higher vs. lower BMI	-0.30 ± 142.23	-0.66	0.07	(1,142.23)	2.63	0.11
	Lower BMI: HE vs. LE	0.08 ± 95.00	-0.16	0.32	(1,95)	0.45	0.51
	Higher BMI: HE vs. LE	0.04 ± 95.00	-0.19	0.27	(1,95)	0.11	0.74
	Savoury: higher vs. lower BMI	-0.13 ± 0.17	-0.47	0.21	(1,137.71)	0.55	0.46
	Sweet: higher vs. lower BMI	-0.13 ± 0.17	-0.47	0.21	(1,136.85)	0.54	0.46
	Chocolate: higher vs. lower BMI	-0.12 ± 0.17	-0.46	0.22	(1,136.85)	0.50	0.48
Cohort C *(OB)*							
	non-SO	3.28 ± 0.88	-	-	-	-	0.63
	SO	3.89 ± 0.68	-	-	-	-	

Table 4.16 Post-hoc analysis for effect of severe obesity group appeal ratings. Cohort A (n=48), Cohort B (n=95), Cohort C (n=25)

Results from post-hoc pairwise comparisons for group*ED interaction. Between-subject factor (non-SO: non-severe vs. SO: severe obesity or lower vs. higher-BMI), and within-group factor ED energy density (LE: low energy and HE:high energy food picture). Significant results in bold *P<0.05, **P<0.01.

EB: Endobarrier, **nOB:** non-obesity, OB: obesity**, RYGB:** Roux-En Y gastric bypass, **HE:** high energy, **LE:** low energy, **df:** degree of freedom, **SO:** severe obesity, **non-SO:** non-severe obesity

	Cohort A *(pre-RYGB/EB)* **n=48**		Cohort B *(nOB/OB)* **n=95**		Cohort C *(OB)* **n=25**		Combined cohorts *(OB)* **n=168-143**	
Appeal rating	**r**	**P**	**r**	**P**	**r**	**P**	**r**	**P**
High-energy	0.08	**0.05***	-0.13	0.23	0.32	0.13	0.07	0.36
Low-energy	0.62	0.62	-0.21	0.06	-	-	-0.21	**0.011****
High-energy subcategories								
Chocolate	-0.02	0.91	-0.19	0.08	-	-	-	-
Sweet	0.04	0.80	-0.20	0.06	-	-	-	-
Savoury	0.11	0.48	-0.003	0.98	-	-	-	-

Table 4.17 Spearman's correlation between BMI levels and appeal ratings for HE and LE food picture Cohort A (n=48), Cohort B (n=95), Cohort C (n=25), and combined cohorts (n=143 for HE and LE picture appeal ratings, and n=168 for HE food picture appeal ratings

Spearman's correlations between BMI levels and appeal ratings for HE food vs. objects and LE foods vs objects, and HE subcategory (chocolate, sweet, savoury) food. Data presented as r Spearman's correlation coefficient, *P<0.05.

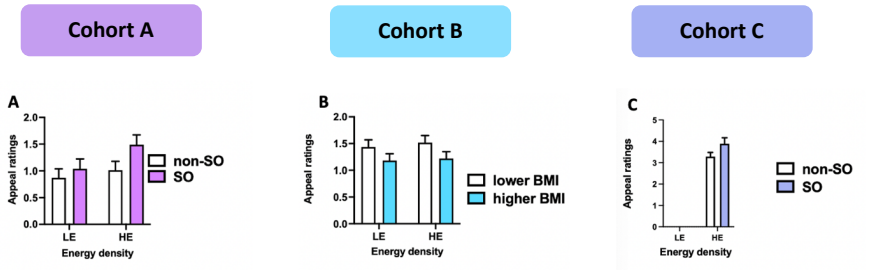


Figure 4.7 Food appeal rating during evaluation fMRI task for HE and LE food picture
Comparison between groups within each cohort for food picture (HE vs. object and LE vs. object) appeal rating during scanning
Abbreviations: non-SO: non-severe obesity, **SO:** severe obesity, **LE:** low-energy, **HE:** high energy

4.4.4 Leeds food preference questionnaire n=47

Explicit liking: For explicit liking of HF, LF, sweet and savoury foods, there was a significant interaction effect for: (i) group*sweet*fat content [F(1,45)=3.98, P=0.05], in RMANOVA analysis **Table 4.17**. Further post-hoc analysis showed a higher explicit liking to HF sweet food in severe obesity group compared to non-severe obesity group (effect size mean ± SEM 15.50 ± 7.40 (95% CI 0.60, 30.40), P=0.42) **Table 4.18 Figure 4.11**

Implicit wanting: For implicit wanting of HF, LF, sweet and savoury foods, there was a significant interaction effect for: (i) group*sweet*fat content [F(1,45)=7.44, P=0.009], in RMANOVA analysis **Table 4.17**. Further post-hoc analysis did not show a significant difference between groups, but rather differences in savoury HF and HF sweet food within groups **Table 4.18 Figure 4.11**

	Explicit liking		**Implicit wanting**	
Interaction	**(df) F**	**P**	**(df) F**	**P**
group*sugar*fat	(1, 45) 3.98	**0.052***	(1, 45) 7.44	**0.009***
group* sugar	(1, 45) 1.76	0.19	(1, 45) 0.72	0.40
group*fat	(1, 45) 0.85	0.36	(1, 45) 0.67	0.42
group	(1, 45) 2.66	0.11	(1, 45) 0.00	0.00

Table 4.18 RMANOVA for effect of severe obesity group on explicit liking and implicit wanting using Leeds food preference questionnaire LFPQ Cohort A (n=47)
Results from RMANOVA for explicit liking and implicit wanting for group (non-SO:non-severe vs. SO: severe obesity) as between-subject factor, and sugar (sweet and savoury) and fat (high fat and low fat) content as within subject factors. Significant results in bold *P<0.05, **P<0.01

Explicit liking			95% confidence interval				
	Post-hoc contrast	**Mean ± SEM**	**lower**	**upper**	**df**	**F**	**P**
	LF: Savoury: SO vs. non-SO	6.70 ± 5.05	-3.46	16.86	(1,45)	1.76	0.19
	LF: Sweet: SO vs. non-SO	6.37 ± 5.29	-4.28	17.01	(1,45)	1.45	0.24
	HF: Savoury: SO vs. non-SO	4.79 ± 5.90	-7.10	16.68	(1,45)	0.66	0.42
	HF: Sweet: SO vs. non-SO	15.50 ± 7.40	0.60	30.40	(1,45)	4.39	**0.04***
	non-SO: Savoury: HF vs LF	8.18 ± 2.82	2.50	13.86	(1,45)	8.42	**0.006****
	non-SO: Sweet: HF vs LF	-0.79 ± 3.56	-7.96	6.38	(1,45)	0.05	0.83
	SO: Savoury: HF vs LF	6.27 ± 3.14	-0.05	12.59	(1,45)	3.99	**0.05***
	SO: Sweet: HF vs LF	8.34 ± 3.96	0.36	16.32	(1,45)	4.43	**0.04***
	non-SO: LF: sweet vs savoury	3.74 ± 2.76	-1.82	9.29	(1,45)	1.84	0.18
	non-SO: HF: sweet vs savoury	-5.24 ± 3.60	-12.48	2.00	(1,45)	2.121	0.15
	SO: LF: sweet vs savoury	3.41 ± 3.07	-2.77	9.58	(1,45)	1.23	0.27
	SO: HF: sweet vs savoury	5.48 ± 4.00	-2.58	13.53	(1,45)	1.87	0.18
Implicit wanting							
	LF: Savoury: SO vs. non-SO	-0.73 ± 7.99	-16.82	15.36	(1,45)	0.01	0.93
	LF: Sweet: SO vs. non-SO	-7.14 ± 5.63	-18.49	4.21	(1,45)	1.61	0.21
	HF: Savoury: SO vs. non-SO	-7.48 ± 6.36	-20.28	5.32	(1,45)	1.38	0.25
	HF: Sweet: SO vs. non-SO	15.35 ± 8.90	-2.57	33.27	(1,45)	2.98	0.09
	non-SO: Savoury: HF vs LF	30.94 ± 7.15	16.55	45.34	(1,45)	18.74	**<0.001****
	non-SO: Sweet: HF vs LF	-6.51 ± 7.56	-21.73	8.71	(1,45)	0.74	0.39
	SO: Savoury: HF vs LF	24.20 ± 7.95	8.18	40.22	(1,45)	9.26	**0.004*****
	SO: Sweet: HF vs LF	15.98 ± 8.41	-0.96	32.91	(1,45)	3.61	0.06
	non-SO: LF: sweet vs savoury	8.50 ± 6.64	-4.88	21.89	(1,45)	1.64	0.21
	non-SO: HF: sweet vs savoury	-28.95 ± 8.10	-45.26	-12.64	(1,45)	12.78	**<0.001****
	SO: LF: sweet vs savoury	2.10 ± 7.39	-12.79	16.99	(1,45)	0.08	0.78
	SO: HF: sweet vs savoury	-6.13 ± 9.01	-24.28	12.02	(1,45)	0.46	0.50

Table 4.19 Post-hoc analysis for effect of severe obesity group on explicit liking and implicit wanting using Leeds food preference questionnaire LFPQ Cohort A (n=47)

Results from post-hoc pairwise comparisons for group*sugar*fat interaction. Between-subject factor (non-SO: non-severe vs. SO: severe obesity), and and sugar (sweet and savoury) and fat (high fat and low fat) content as within subject factors. Significant results in bold *P<0.05, ***P<0.01, ****P<0.001

Abbreviations: LF: low-fat, **HF:** high-fat, **df:** degree of freedom.

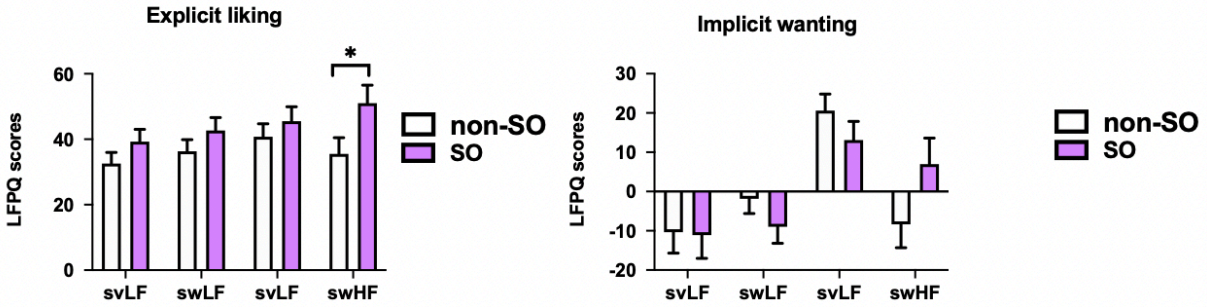


Figure 4.8 Explicit liking and implicit wanting scores from LFPQ in cohort A n=47

Comparison between participants of non-severe and severe obesity in explicit liking ad implicit wanting score for four food categories (savoury low-fat, sweet low-fat, savoury low-fat, sweet low-fat)

Abbr**eviations: LFPQ:** Leeds food preference questionnaire, **non-SO:** non-severe obesity, **SO:** severe obesity, **svLF:** savoury low-fat food, **swLF:** sweet low-fat food, **svLF:** savoury low-fat, **swHF:** sweet high-fat food

4.4.5 Taste ratings

Pleasantness

Cohort A (pre-RYGB/EB) **n=46**: for pleasantness taste ratings, there was a significant interaction effect for group*sweet*fat content [F(2,140.58)=5.38, P=0.006] in mixed model RMANOVA analysis. Further post-hoc analysis did not show a significant difference between groups, but rather a higher rating for sweet HF (ice-cream) compared to sweet LF (yogurt) within groups **Table 4.19 and 4.20 Figure 4.12-A**

cohort B (nOB/OB) **n=76***:* for pleasantness and tastiness ratings, there was not a significant difference between participants with lower BMI and higher BMI in unpaired t-test **Table 4.21**

cohort C (OB) **n=24***: for* pleasantness taste ratings, there was a significant interaction effect for group*sweet*fat content [F(2,96)=4.67, P=0.012] in mixed model RMANOVA analysis. Further post-hoc analysis did not show a significant difference between groups, but rather differences in ratings for sweet HF (ice-cream) compared to sweet LF (yogurt), and HF sweet (ice-cream) compared to HF savoury (chicken of cream soup) within participants with non-severe obesity **Table 4.19 and 4.20 Figure 4.12-B**

Creaminess

Cohort A (pre-RYGB/EB) **n=46**: for creaminess taste ratings, there was a significant interaction effect forgroup*sweet*fat content [F(2,141)=33.79, P<0.001] in mixed model RMANOVA analysis. Further post-hoc analysis did not show a significant difference between groups, but rather higher ratings for savoury HF (chicken of cream soup) compared to savoury LF (chicken broth soup) within groups **Table 4.19 and 4.20 Figure 4.12-A**.

Similarly in *cohort C (OB)* **n=24** for creaminess taste ratings, there was a significant interaction effect for group*sweet*fat content [F(2,72)=11.13, P<0.001] in mixed model RMANOVA analysis. Further post-hoc analysis did not show a significant difference between groups, but rather higher ratings for savoury HF (chicken of cream soup) compared to savoury LF (chicken broth soup), and sweet LF (yogurt) compared to savoury LF (chicken broth soup) within groups **Table 4.19 and 4.20 Figure 4.12-B**.

Ideal creaminess

Cohort A (pre-RYGB/EB) **n=46**: for ideal creaminess taste ratings, there was a significant interaction effect for group*sweet*fat content [F(2,141)=13.93, P<0.001] in mixed model RMANOVA analysis. Further post-hoc analysis showed a lower rating for savoury LF food (chicken broth soup) in participants with severe obesity compared to participants with non-severe obesity group [effect size mean ± SEM -9.37 ± 3.77 (95% CI -16.81, -1.93), P=0.014] **Table 4.19 and 4.20 Figure 4.12-A**.

cohort C (OB) **n=24**: for ideal creaminess taste ratings, there was a significant interaction effect for group*sweet*fat content [F(2,72)=7.29, P=0.001] in mixed model RMANOVA analysis. Further post-hoc analysis showed a higher rating for sweet HF (ice-cream) food in participants with severe obesity compared to participants with non-severe obesity [effect size mean ± SEM 14.88 ± 6.25 (95% CI 2.48, 27.28), P=0.019], whilst a lower rating for savoury HF (chicken broth soup) [effect size mean ± SEM 17.88 ± 6.25 (95% CI 5.48, 30.28), P=0.005] **Table 4.19 and 4.20 Figure 4.12-B**

Sweetness

Cohort A (pre-RYGB/EB) **n=46**: for sweetness taste ratings, there was a significant interaction effect for group*fat content [F(2,47)=82.75, P<0.001] in mixed model RMANOVA analysis. Further post-hoc analysis did not show a significant difference between groups, but rather differences in ratings for sweet HF (ice-cream) compared to sweet LF (yogurt) within groups **Table 4.19 and 4.20 Figure 4.12-A**

cohort C (OB) **n=24**: for sweetness taste ratings, there was a significant interaction effect for group*fat content [F(2,48)=7.70, P<0.001] in mixed model RMANOVA analysis. Further post-hoc analysis did not show a significant difference between groups, but rather differences in ratings for sweet HF (ice-cream) compared to sweet LF (yogurt) within groups **Table 4.19 and 4.20 Figure 4.12-B**

Ideal sweetness

Cohort A (pre-RYGB/EB) **n=46**: for ideal sweetness taste ratings, there was a significant interaction effect for group*sweet content [F(2,47)=39.22, P<0.001] in mixed model RMANOVA analysis. Further post-hoc analysis did not show a significant difference between groups, but rather differences in ratings for sweet HF (ice-cream) compared to sweet LF (yogurt) within groups **Table 4.19 and 4.20 Figure 4.12-A**

cohort C (OB) **n=24**: for ideal sweetness taste ratings, there was a significant interaction effect for group*sweet content [F(2,24)=9.41, P=0.001] in mixed model RMANOVAanalysis. Further post-hoc analysis did not show a significant difference between groups, but rather differences in ratings for sweet HF (ice-cream) compared to sweet LF (yogurt) within groups **Table 4.19 and 4.20 Figure 4.12-B**

Spearman's correlation between BMI levels and taste ratings: creaminess, ideal creaminess, pleasantness, sweetness, and ideal sweetness revealed negative correlation between BMI and savoury LF (chicken broth soup) ideal creaminess in *cohort A* only, but no significant correlation seen in *cohort B and cohort C* **Table 4.22**

		Cohort A *(pre-RYGB/EB)* n=46		Cohort C *(OB)* n=24	
Taste ratings	**Interaction**	**(df) F**	**P**	**(df) F**	**P**
Pleasantness[#]	group*sugar*fat	(2,140.58) 5.38	**0.006**	(2,96) 4.67	**0.012****
	group*sugar	(1,140.55) 1.20	0.28	(1,96) 0.38	0.54
	group*fat	(2,140.58) 8.13	0	(2,96) 2.86	0.06
	group	(1,47.18) 0.08	0.78	(1,96) 0.001	0.97
	BMI*sugar*fat	(1,137.54) 10.30	**0.002**	(1,96) 7.94	**0.006****
	BMI*sugar	(1,137.37) 1.61	0.21	(1,96) 0.02	0.89
	BMI*fat	(2,137.54) 12.52	**0.001*****	(1,96) 2.18	0.14
	BMI	(1,46) 0.69	0.41	(1,96) 0.07	0.80
Creaminess	group*sugar*fat	(2,141) 33.79	**<0.001******	(2,72)11.13	**<0.001******
	group*sugar	(1,141) 1.79	0.18	(1,72)0.10	0.76
	group*fat	(2,141) 58.46	**<0.001******	(2,72) 54.08	**<0.001******
	group	(1,47) 0.66	0.42	(1,24) 0.01	0.939
	BMI*sugar*fat	(1,138) 61.01	**<0.001******	(1,72) 18.57	**<0.001******
	BMI*sugar	(1,138) 0.33	0.57	(1,72) 0.26	0. 61
	BMI*fat	(1,138) 100.25	**<0.001******	(1,72) 102.64	**<0.001******
	BMI	(1,46) 0.33	0.57	(1,24) 0.005	0.94
Ideal creaminess	group*sugar*fat	(2,141) 13.93	**<0.001******	(2,72) 7.29	**0.001*****
	group*sugar	(1,141) 0.14	0.71	(1,72) 0.12	0.74
	group*fat	(2,141) 15.63	**<0.001******	(2,72) 22.62	**<0.001******
	group	(1,47) 2.62	0.11	(1,24) 1.63	0.214
	BMI*sugar*fat	(1,138) 24.45	**<0.001******	(1,72) 11.96	**0.001*****
	BMI*sugar	(1,138) 0.08	0.78	(1,72) 0.14	0.71
	BMI*fat	(1,138) 30.21	**<0.001******	(1,72) 29.41	**<0.001******
	BMI	(1,46) 1.47	0.23	(1,24) 1.13	0.30
Sweetness	group*fat	(2,47) 82.75	**<0.001******	(2,48) 7.70	**0.001*****
	group	(1,47) 0.13	0.73	(1,48) 0.03	0.86

	BMI*fat	(1,46) 166.88	**<0.001******	(1,48) 15.40	**0.001*****
	BMI	(1,46) 0.02	0.88	(1,48) 0.13	0.72
Ideal sweetness	group*fat	(2,47) 39.22	**<0.001******	(2,24) 9.41	**0.001*****
	group	(1,47) 2.06	0.16	(1,24) 2.88	0.10
	BMI*fat	(1,46) 88.53	**<0.001******	(1,24) 17.16	**0.001*****
	BMI	(1,46) 0.76	0.39	(1,24) 2.69	0.11

Table 4.20 Mixed model RMANOVA for effect of severe obesity (categorical and continuous) on taste ratings. Cohort A (n=46), and cohort C (n=24)

Results from mixed model RMANOVA for taste ratings, including: creaminess, ideal creaminess, pleasantness, sweetness, and ideal sweetness for group (non-SO:non-severe vs. SO:severe obesity) as between-subject factor, and and sugar (sweet and savoury) and fat (high fat and low fat) content as within subject factors. $^{\#}$n=45. Significant results in bold **P<0.01, ***P<0.001.

		Cohort A *(pre-RYGB/EB)* **n=46**						**Cohort C** *(OB)* **n=24**					
Taste ratings	**Interaction**	Mean ± SEM	**95% CI**		df	F	P	Mean ± SEM	95% CI		df	F	P
			lower	**upper**					lower	upper			
Pleasantness	Savoury: LF: SO vs. non-SO	-6.79 ± 5.62	**-17.87**	4.29	(1,181.55)	1.46	0.23	2.56 ± 8.20	**-13.72**	18.84	(1,96)	0.10	0.76
	Savoury: HF: SO vs. non-SO	-0.86 ± 5.62	**-11.95**	10.22	(1,181.55)	0.02	0.88	-7.31 ± 8.20	**-23.59**	8.97	(1,96)	0.80	0.38
	Sweet: LF: SO vs. non-SO	-3.90 ± 5.66	**-15.08**	7.28	(1,181.88)	0.47	0.49	12.00 ± 8.20	**-4.28**	28.28	(1,96)	2.14	0.15
	Sweet: HF: SO vs. non-SO	7.95 ± 5.62	**-3.14**	19.03	(1,181.55)	2.00	0.16	-6.69 ± 8.20	**-22.97**	9.59	(1,96)	0.67	0.42
	non-SO: Savoury: HF vs. LF	-1.50 ± 5.03	**-11.45**	8.45	(1,140.30)	0.09	0.77	-2.00 ± 6.70	**-15.29**	11.29	(1,96)	0.09	0.77
	non-SO: Sweet: HF vs. LF	13.01 ± 5.09	**2.95**	23.07	(1,141.41)	6.54	**0.012****	24.19 ± 6.70	**10.90**	37.48	(1,96)	13.05	**<0.001****
	SO: Savoury: HF vs. LF	4.43 ± 5.60	**-6.65**	15.50	(1,140.30)	0.63	0.43	-11.88 ± 9.47	**-30.67**	6.92	(1,96)	1.57	0.21
	SO: Sweet: HF vs. LF	24.86 ± 5.60	**13.78**	35.93	(1,140.30)	19.69	**<0.001****	5.50 ± 9.47	**-13.30**	24.30	(1,96)	0.34	0.56
	non-SO: LF: sweet vs. savoury	-10.51 ± 5.09	**-20.57**	-0.45	(1,141.41)	4.27	**0.041***	-10.56 ± 6.70	**-23.86**	2.73	(1,96)	2.49	0.12
	non-SO: HF: sweet vs. savoury	4.00 ± 5.03	**-5.95**	13.95	(1,140.30)	0.63	0.43	15.63 ± 6.70	**2.33**	28.92	(1,96)	5.44	**0.022****
	SO: LF: sweet vs. savoury	-7.62 ± 5.60	**-18.69**	3.46	(1,140.30)	1.85	0.18	-1.13 ± 9.47	**-19.92**	17.67	(1,96)	0.01	0.91
	SO: HF: sweet vs. savoury	12.81 ± 5.60	**1.74**	23.88	(1,140.30)	5.23	**0.024***	16.25 ± 9.47	**-2.55**	35.05	(1,96)	2.94	0.09
Creaminess	Savoury: LF: SO vs. non-SO	-1.81 ± 5.08	-11.84	8.22	(1,155.17)	0.1	0.72	-3.38 ± 7.72	-18.72	11.97	(1,92.33)	0.19	0.66
	Savoury: HF: SO vs. non-SO	-9.52 ± 5.08	-19.54	0.51	(1,155.17)	3.5	0.06	0.44 ± 7.72	-14.90	15.78	(1,92.33)	0.00	0.96
	Sweet: LF: SO vs. non-SO	0.75 ± 5.08	-9.27	10.78	(1,155.17)	0.0	0.88	-8.81 ± 7.72	-24.15	6.53	(1,92.33)	1.30	0.26

	Sweet: HF: SO vs. non-SO	-0.46 ± 5.08	-10.48	9.57	(1,155.17)	0.0	0.93	10.38 ± 7.72	-4.97	25.72	(1,92.33)	1.80	0.18
	non-SO: Savoury: HF vs. LF	44.42 ± 4.11	36.30	52.55	(1,141)	116.7	**<0.001******	49.69 ± 5.93	37.86	61.52	(1,72)	70.14	**<0.001******
	non-SO: Sweet: HF vs. LF	6.12 ± 4.11	-2.01	14.24	(1,141)	2.2	0.14	13.06 ± 5.93	1.24	24.89	(1,72)	4.85	0.031
	SO: Savoury: HF vs. LF	36.71 ± 4.58	27.7	45.8	(1,141)	64.4	**<0.001******	53.50 ± 8.39	36.77	70.23	(1,72)	40.66	**<0.001******
	SO: Sweet: HF vs. LF	4.91 ± 4.58	-4.1	13.9	(1,141)	1.1	0.29	32.25 ± 8.39	15.52	48.98	(1,72)	14.77	**<0.001******
	non-SO: LF: sweet vs. savoury	33.96 ± 4.11	25.83	42.09	(1,141)	68.23	**<0.001******	32.69 ± 5.93	20.86	44.52	(1,72)	30.35	**<0.001******
	non-SO: HF: sweet vs. savoury	-4.35 ± 4.11	-12.48	3.78	(1,141)	1.12	0.29	-3.94 ± 5.93	-15.77	7.89	(1,72)	0.44	0.51
	SO: LF: sweet vs. savoury	36.52 ± 4.58	27.48	45.57	(1,141)	63.73	**<0.001******	27.25 ± 8.39	10.52	43.98	(1,72)	10.55	**0.002*****
	SO: HF: sweet vs. savoury	4.71 ± 4.58	-4.33	13.76	(1,141)	1.06	0.31	6.00 ± 8.39	-10.73	22.73	(1,72)	0.51	0.48
Ideal creaminess	Savoury: LF: SO vs. non-SO	-9.37 ± 3.77	-16.81	-1.93	(1,174.92)	6.17	**0.014****	-11.38 ± 6.25	-23.78	1.03	(1, 95.26)	3.32	0.07
	Savoury: HF: SO vs. non-SO	0.67 ± 3.77	-6.78	8.11	(1,174.92)	0.03	0.86	17.88 ± 6.25	5.48	30.28	(1, 95.26)	8.19	**0.005****
	Sweet: LF: SO vs. non-SO	-0.66 ± 3.77	-8.10	6.79	(1,174.92)	0.03	0.86	-4.25 ± 6.25	-16.65	8.15	(1, 95.26)	0.46	0.50
	Sweet: HF: SO vs. non-SO	-5.47 ± 3.77	-12.91	1.97	(1,174.92)	2.11	0.15	14.88 ± 6.25	2.48	27.28	(1, 95.26)	5.67	**0.019****
	non-SO: Savoury: HF vs. LF	13.35 ± 3.91	6.88	19.81	(1,141)	16.64	**0.001*****	16.50 ± 4.97	6.60	26.40	(1,72)	11.03	**0.001*****
	non-SO: Sweet: HF vs. LF	3.39 ± 2.70	-3.08	9.85	(1,141)	1.07	0.21	-1.50 ± 4.97	-11.40	8.40	(1,72)	0.09	0.76
	SO: Savoury: HF vs. LF	23.38 ± 4.35	16.19	30.58	(1,141)	41.26	**<0.001******	45.75 ± 7.03	31.74	59.76	(1,72)	42.40	**<0.001******
	SO: Sweet: HF vs. LF	-1.43 ± 3.00	-8.63	5.77	(1,141)	0.15	0.64	17.63 ± 7.03	3.62	31.63	(1,72)	6.29	**0.014****
	non-SO: LF: sweet vs. savoury	9.39 ± 3.64	2.92	15.85	(1,141)	8.23	**0.013****	17.13 ± 4.97	7.22	27.03	(1,72)	11.88	**0.001*****
	non-SO: HF: sweet vs. savoury	-0.58 ± 2.63	-7.04	5.89	(1,141)	0.03	0.83	-0.88 ± 4.97	-10.78	9.03	(1,72)	0.03	0.86

	SO: LF: sweet vs. savoury	18.10 ± 4.05	10.90	25.29	(1,141)	24.71	**<0.001******	24.25 ± 7.03	10.24	38.26	(1,72)	11.91	**0.001*****
	SO: HF: sweet vs. savoury	-6.71 ± 2.93	-13.91	0.48	(1,141)	3.40	**0.027****	-3.88 ± 7.03	-17.88	10.13	(1,72)	0.30	0.58
Sweetness	LF: SO vs. non-SO	0.91 ± 4.23	-7.49	9.30	(1,93.68)	0.05	0.83	-5.19 ± 9.29	-23.86	13.49	(1,48)	0.31	0.58
	HF: SO vs. non-SO	-3.08 ± 4.23	-11.48	5.31	(1,93.68)	0.53	0.47	2.88 ± 9.29	-15.80	21.55	(1,48)	0.10	0.76
	non-SO: HF vs. LF	38.85 ± 3.88	31.04	46.65	(1,93.68)	0.05	**<0.001******	21.31 ± 7.58	6.07	36.56	(1,48)	7.90	**0.007****
	SO: HF vs. LF	34.86 ± 4.316	26.17	43.54	(1,93.68)	0.53	**<0.001******	29.38 ± 10.72	7.81	50.94	(1,48)	7.50	**0.009****
Ideal sweetness	LF: SO vs. non-SO	-5.23 ± 4.25	-13.67	3.22	(1,88.41)	1.51	0.22	1.94 ± 5.53	-9.19	13.06	(1, 47.31)	0.12	0.73
	HF: SO vs. non-SO	-4.43 ± 4.25	-12.88	4.01	(1,88.42)	1.09	0.30	12.13 ± 5.53	1.00	23.25	(1, 47.31)	4.81	**0.03***
	non-SO: HF vs. LF	22.54 ± 3.48	15.55	29.53	(1,47)	42.04	**<0.001******	10.81 ± 4.23	2.08	19.55	(1,24)	6.52	**0.017****
	SO: HF vs. LF	23.33 ± 3.87	15.55	31.11	(1,47)	36.39	**<0.001******	21.00 ± 5.99	8.64	33.36	(1,24)	12.30	**0.002****

Table 4.21 Post-hoc analysis for effect of severe obesity group on taste ratings. Cohort A (n=46), and cohort C (n=24)

Results from mixed model RMANOVA for taste ratings, including: creaminess, ideal creaminess, pleasantness, sweetness, and ideal sweetness for group (non-SO:non-severe vs. SO:severe obesity) as between-subject factor, and and sugar (sweet and savoury) and fat (high fat and low fat) content as within subject factors. Significant results in bold **P<0.01, ***P<0.001

Abbreviations: SO: severe obesity group; **non-SO:** non-severe obesity group; **LF:** low fat; **HF:** high fat, **df:** degrees of freedom, **CI:** confidence intervals

		Cohort B *(nOB/OB)* n=76	
		Mean ± SD	**P**
Tastiness	lower BMI	5.68 ± 2.09	0.96
	higher BMI	5.66 ± 2.46	
Pleasantness	Lower BMI	5.83 ± 2.28	0.59
	Higher BMI	5.54 ± 2.41	

Table 4.22 Unpaired t-test for effect of lower and higher BMI groups on taste ratings in cohort B (n=76)
Results from unpaired t-tests for taste ratings, including: tastiness and pleasantness for groups in cohort B (lower vs. higher BMI median split = 26.8 kg/m^2).

		Cohort A *(pre-RYGB/EB)* **n=46**		***Cohort B*** *(nOB/OB)* **n=95**		***Cohort C*** *(OB)* **n=24**	
Taste category	**Food category**	**r**	**P**	**r**	**P**	**r**	**P**
Creaminess	chicken broth soup *Savoury low-fat*	-0.21	0.16	-	-	-0.19	0.38
	chicken cream soup *Savoury high-fat*	-0.16	0.27	-	-	-0.19	0.37
	yogurt *Sweet low-fat*	0.01	0.93	-	-	-0.24	0.26
	ice-cream *Sweet high-fat*	0.01	0.95	-	-	0.18	0.40
Ideal creaminess	chicken broth soup *Savoury low-fat*	-0.32	**0.029***	-	-	-0.24	0.26
	chicken cream soup *Savoury high-fat*	0.07	0.65	-	-	0.31	0.14
	yogurt *Sweet low-fat*	-0.12	0.43	-	-	-0.21	0.33
	ice-cream *Sweet high-fat*	-0.25	0.10	-	-	0.38	0.07
Pleasantness	chicken broth soup *Savoury low-fat*	-0.12	0.42	-0.07	0.57	0.06	0.78
	chicken cream soup *Savoury high-fat*	-0.12	0.43	-	-	-0.05	0.81
	yogurt *Sweet low-fat*	-0.11	0.49	-	-	0.14	0.50
	ice-cream *Sweet high-fat*	0.20	0.19	-	-	0.08	0.73
Sweetness	*yogurt* *Sweet low-fat*	0.06	0.67	-	-	-0.13	0.55
	ice-cream *Sweet high-fat*	-0.02	0.89	-	-	0.09	0.67
Ideal sweetness	*yogurt* *Sweet low-fat*	-0.08	0.62	-	-	0.09	0.67
	ice-cream *Sweet high-fat*	-0.19	0.20	-	-	0.15	0.48
Tasty[a]		-	-	0.02	0.89	-	-

Table 4.23 Spearman's correlation between BMI levels and taste ratings in all cohorts

Spearman's correlations between BMI levels and taste ratings including creaminess, ideal creaminess, pleasantness, sweetness, ideal sweetness. Data presented as r Spearman correlation coefficient, *P<0.05, **P<0.01,***P<0.001. [a] taste rating in cohort B included pleasantness and tastiness for one savoury dish for *ad libitum meal*

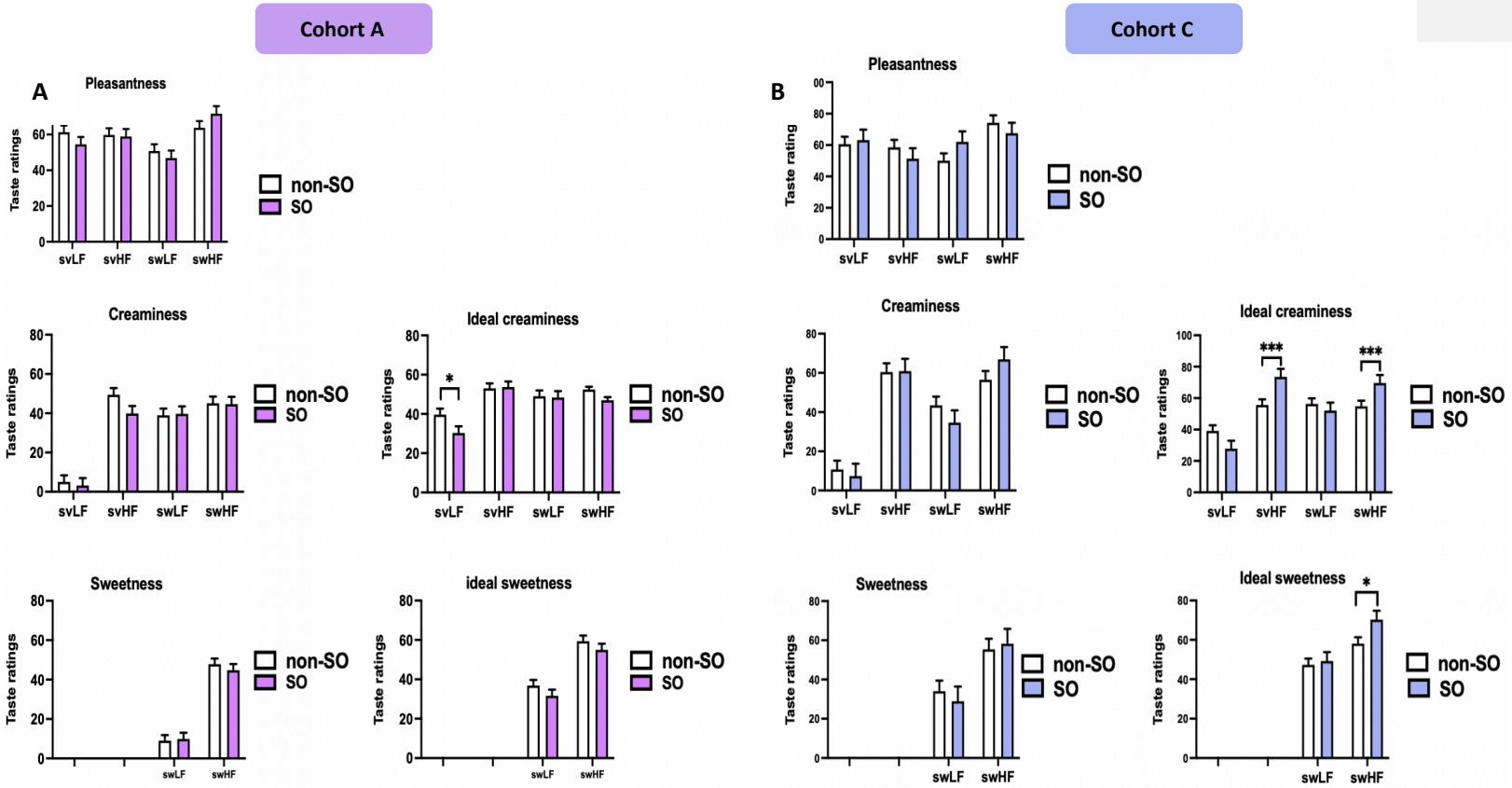


Figure 4.9 Taste rating scores in cohort A (n=46) and cohort C (n=24)

Comparison between severe and non-severe obesity groups in taste ratings, including: pleasantness, creaminess, ideal creaminess, sweetness, and ideal sweetness) for four dishes (svLF: chicken broth soup, svHF: chicken cream soup, swLF: yogurt, swHF: ice-cream). Data presented as mean ± SEM. Statistics from mixed model repeated measures ANOVA, with sweet and fat content as within subject factors: post-hoc test *P<0.05, P<0.01,***P<0.005, ****P<0.0001.

Abbreviations: nonSO: non-severe obesity, **SO:** severe obesity, **svLF:** savoury low-fat, **svHF:** savoury high-fat, **swLF:** sweet low-fat, **swHF:** sweet high-fat

4.4.6 ad libitum lunch and energy intake

Total energy in take (kcal):

Cohort A (pre-RYGB/EB) **n=47**: for total energy intake (kcal) from *ad libitum* meal, there was not a significant interaction effect for group*sweet*fat content [F(2,188)=2.93, P=0.06] in mixed model RMANOVA analysis, allowing for analysis separately by sweet and fat categories. There was a significant interaction effect for group*fat content (independent of sweet category) [F(2,188)=28.52, P<0.001]. This was driven by a higher energy intake from HF (ice-cream and chicken of cream soup) compared to LF (yogurt and chicken broth soup) (independent of sweet content) in participants with non-severe obesity (effect size mean ± SEM 143.34 ± 33.24 (95% CI 77.76, 208.91), P<0.001), and severe obesity (effect size mean ± SEM 229.32 ± 36.99 (95% CI 156.36, 302.28), P<0.001) **Table 4.23 and 4.24 Figure 4.13-A**

cohort B (nOB/OB) **n=76***:* for total energy intake and % of REE kcal from *ad libitum* meal, there was not a significant difference between participants with lower and higher BMI in Mann-whitney test **Table 4.25**

cohort C (OB) **n=24**, for total energy intake (kcal) from *ad libitum* meal, there was not a significant interaction effect for group*sweet*fat content [F(2,72)=0.53, P=0.59] in mixed model RMANOVA analysis, allowing for analysis separately by sweet and fat categories. There was a significant interaction effect for group*fat content (independent of sweet category) [F(2,72)=26.39, P<0.001]. This was driven by a higher energy intake from HF in participants with non-severe obesity compared to participants with severe obesity (independent of sweet content) [effect size mean ± SEM -149.97 ± 47.90 (95% CI -245.56, -54.38), P=0.003] **Table 4.23 and 4.24 Figure 4.13-A**

Percentage of REE

Cohort A (pre-RYGB/EB) **n=47**: for % of REE from *ad libitum* meal, there was a significant interaction effect for group*sweet*fat content [F(2,188)=3.45, P=0.035] in mixed model RMANOVA analysis. Further post-hoc analysis showed a higher intake of sweet HF (ice-cream) in participants with severe-obesity compared to participants with non-severe obesity [effect size mean ± SEM 12.51 ± 3.74 (95% CI 5.13, 19.90), P=0.001]. Also, differences in sweet HF (ice-cream) compared to sweet LF (yogurt) within groups **Table 4.23 and 4.24 Figure 4.13-B**

cohort C (OB) **n=24**, for % of REE from *ad libitum* meal, there was not a significant interaction effect for group*sweet*fat content [F(2,72)=0.50, P=0.61] in mixed model RMANOVA analysis, allowing for analysis separately by sweet and fat categories. There was a significant interaction effect for group*fat content (independent of sweet category) [F(2,72)=27.57, P<0.001]. This was driven by a higher energy intake from HF (ice-cream and chicken cream soup) (independent of sweet content) in participants with non-severe obesity (effect size mean ± SEM -8.35 ± 2.57 (95% CI -13.48, -3.22), P=0.002) compared to participants with severe obesity **Table 4.23 and 4.24 Figure 4.13-B**

% of total kcal

Cohort A (pre-RYGB/EB) **n=47**: for percentage of total energy intake (kcal) from *ad libitum* meal, there was a significant interaction effect for group*sweet*fat content [F(2,188)=5.06, P=0.007] in mixed model RMANOVA analysis. Further post-hoc analysis did not show a significant difference between groups, but rather differences in sweet HF (ice-cream) compared to sweet LF (yogurt) within groups **Table 4.23 and 4.24 Figure 4.13-C**

cohort C (OB) **n=24** for percentage of total energy intake (kcal) from *ad libitum* meal, there was not a significant interaction effect for group*sweet*fat content [F(2,72)=0.02, P=0.98] in mixed model RMANOVA analysis, allowing for analysis separately by sweet and fat categories. There was a significant interaction effect for group*fat content (independent of sweet category) [F(2,72)=29.04, P<0.001]. This was driven by a higher energy intake from HF (ice-cream and chicken cream soup) (independent of sweet content) in participants with non-severe-obesity [effect size mean ± SEM -12.60 ± 2.04 (95% CI -22.57, -2.64), P=0.014] compared to participants with severe obesity **Table 4.23 and 4.24 Figure 4.13-C**

Spearman's correlation between BMI levels and taste ratings: creaminess, ideal creaminess, pleasantness, sweetness, and ideal sweetness revealed negative correlation between BMI and savoury LF (chicken broth soup) ideal creaminess in *cohort A* only, but no significant correlation seen in *cohort B and cohort C* **Table 4.25**

		Cohort A *(pre-RYGB/EB)* n=47		Cohort C *(OB)* n=24	
Energy intake	**Interaction**	**(df) F**	**P**	**(df) F**	**P**
Total kcal	group*sugar*fat	(2,188) 2.93	0.06	(2,72) 0.53	0.59
	group*sugar	(1,188) 0.21	0.64	(1,72) 0.13	0.72
	group*fat	(2,188) 28.52	**<0.001******	(2,72) 26.39	**<0.001******
	group	(1,188)0.51	0.48	(1,24) 2.19	0.15
	BMI*sugar*fat	(1,188) 6.18	**0.014****	(1,96) 0.24	0.623
	BMI*sugar	(1,188) 1.28	0.30	(1,96) 0.31	0.58
	BMI*fat	(1,188) 58.47	**<0.001******	(1,96) 33.42	**<0.001******
	BMI	(1,188) 0.95	0.33	(1,96) 3.89	**0.052***
% REE	group*sugar*fat	(2,138) 3.45	**0.035***	(2,72) 0.50	0.61
	group*sugar	(1,138) 0.65	0.42	(1,72) 0.13	0.72
	group*fat	(2,138) 27.03	**<0.001******	(2,72) 27.57	**<0.001******
	group	(1,46) 4.33	**0.043***	(1,24) 2.60	0.12
	BMI*sugar*fat	(1,138)6.80	**0.01****	(1,96) 0.23	0.64
	BMI*sugar	(1,138) 2.37	0.126	(1,96) 0.28	0.60
	BMI*fat	(1,138) 53.96	**<0.001******	(1,96) 35.15	**<0.001******
	BMI	(1,46) 8.46	**0.006****	(1,96) 4.70	**0.03***
% kcal	group*sugar*fat	(2,188) 5.06	**0.007****	(2,72) 0.02	0.98
	group*sugar	(1,188) 1.07	0.30	(1,72) 0.79	0.38
	group*fat	(2,188) 30.43	**<0.001******	(2,72) 29.04	**<0.001******
	group	0.00	1.00	0.00	1.00
	BMI*sugar*fat	(1,188) 10.72	**0.001*****	(1,96) 0.04	0.85
	BMI*sugar	(1,188) 3.04	0.08	(1,96) 1.12	0.29
	BMI*fat	(1,188) 62.07	**<0.001******	(1,96) 34.53	**<0.001******
	BMI	(1,188) 0	1.00	(1,96) 0.00	1.00

Table 4.24 Mixed model RMANOVA for effect of severe obesity group (categorical and continuous) on energy intake from *ad libitum* meal. Cohort A (n=47), and cohort C (n=24)

Results from mixed model RMANOVA for energy intake, including: total kcal, %REE, %kcal for group (non-SO:non-severe vs. SO:severe obesity) as between-subject factor, and sugar (sweet and savoury) and fat

(high fat and low fat) content as within subject factors. Significant results in bold *P<0.05,**P<0.01, ***P<0.001

		Cohort A *(pre-RYGB/EB)* n=47						Cohort C *(OB)* n=24					
Energy intake	**Post-hoc contrast**	Mean ± SEM	**95% CI**		df	F	P	Mean ± SEM	**95% CI**		df	F	P
			lower	**upper**					lower	upper			
Total kcal	Savoury: SO vs. non-SO	6.23 ± 35.16	-63.13	75.60	(1,188)	0.03	0.86	-39.57 ± 47.90	-135.16	56.017	(1,67.83)	0.68	0.41
	Sweet: SO vs. non-SO	29.25 ± 35.16	-40.11	98.62	(1,188)	0.69	0.41	-63.47 ± 47.90	-159.06	32.125	(1,67.83)	1.76	0.19
	LF: SO vs. non-SO	-25.25 ± 35.16	-94.61	44.12	(1,188)	0.52	0.47	46.93 ± 47.90	-48.66	142.52	(1,67.83)	0.96	0.33
	HF: SO vs. non-SO	60.73 ± 35.16	-8.63	130.10	(1,188)	2.98	0.09	-149.97 ± 47.90	-245.56	-54.38	(1,67.83)	9.80	**0.003****
	non-SO: sweet vs. savoury	43.14 ± 33.24	-22.44	108.71	(1,188)	1.68	0.20	20.05 ± 37.96	-55.62	95.712	(1,72)	0.28	0.60
	SO: sweet vs. savoury	66.16 ± 36.99	-6.81	139.12	(1,188)	3.20	0.08	-3.85 ± 53.68	-110.86	103.16	(1,72)	0.01	0.94
	non-SO: HF vs. LF	143.34 ± 33.24	77.76	208.91	(1,188)	18.60	**<0.001****	270.78 ± 37.96	195.11	346.45	(1,72)	50.89	**<0.001****
	SO: HF vs. LF	229.32 ± 36.99	156.36	302.28	(1,188)	38.44	**<0.001****	73.88 ± 53.68	-33.13	180.89	(1,72)	1.89	0.17
% kcal of REE	Savoury: LF: SO vs. non-SO	-0.03 ± 3.74	-7.42	7.35	(1,182)	0	0.99	2.33 ± 2.57[a]	-2.801	7.457	(1,67.87)	0.82	0.37
	Savoury: HF: SO vs. non-SO	5.57 ± 3.74	-1.82	12.95	(1,182)	2.21	0.14	-8.35 ± 2.57 [a]	-13.478	-3.22	(1,67.87)	10.55	**0.002*****
	Sweet: LF: SO vs. non-SO	-1.14 ± 3.74	-8.53	6.24	(1,182)	0.09	0.76	x	x	x	x	x	x
	Sweet: HF: SO vs. non-SO	12.51 ± 3.74	5.13	19.90	(1,182)	11.18	**0.001*****	x	x	x	x	x	x
	non-SO: Savoury: HF vs. LF	5.54 ± 3.47	-1.32	12.40	(1,138)	2.55	0.112	14.84 ± 2.04[a]	10.78	18.9	(1,72)	53.05	**<0.001****
	non-SO: Sweet: HF vs. LF	10.46 ± 3.47	3.61	17.32	(1,138)	9.10	**0.003*****	x	x	x	x	x	x
	SO: Savoury: HF vs. LF	11.14 ± 3.78	3.66	18.62	(1,138)	8.67	**0.004*****	4.16 ± 2.88[a]	-1.58	9.906	(1,72)	2.09	0.15

	SO: Sweet: HF vs. LF	24.12 ± 3.78	16.64	31.60	(1,138)	40.64	**<0.001******	x	x	x	x	x	x
	non-SO: LF: sweet vs. savoury	0.25 ± 3.47	-6.61	7.10	(1,138)	0.01	0.94	x	x	x	x	x	x
	non-SO: HF: sweet vs. savoury	5.17 ± 3.47	-1.69	12.03	(1,138)	2.22	0.14	x	x	x	x	x	x
% kcal	Savoury: LF: SO vs. non-SO	-6.72 ± 5.75	-18.06	4.61	(1,188)	1.37	0.24	12.60 ± 5.02 [a]	2.64	22.57	(1,72)	6.30	**0.014****
	Savoury: HF: SO vs. non-SO	0.79 ± 5.75	-10.54	12.12	(1,188)	0.02	0.89	-12.60 ± 5.02 [a]	-22.57	-2.64	(1,72)	6.30	**0.014****
	Sweet: LF: SO vs. non-SO	-3.28 ± 5.75	-14.61	8.06	(1,188)	0.33	0.57	x	x	x	x	x	x
	Sweet: HF: SO vs. non-SO	9.22 ± 5.75	-2.12	20.55	(1,188)	2.57	0.11	x	x	x	x	x	x
	non-SO: Savoury: HF vs. LF	9.36 ± 5.43	-1.36	20.07	(1,188)	2.97	0.087	30.98 ± 4.10 [a]	22.84	39.12	(1,72)	57.09	**<0.001******
	non-SO: Sweet: HF vs. LF	25.14 ± 5.43	14.43	35.86	(1,188)	21.43	**<0.001******	x	x	x	x	x	x
	SO: Savoury: HF vs. LF	16.88 ± 6.04	4.95	28.79	(1,188)	7.80	**0.006****	5.77 ± 5.80 [a]	-5.74	17.28	(1,72)	0.99	0.32
	SO: Sweet: HF vs. LF	37.63 ± 6.04	25.71	49.55	(1,188)	38.79	**<0.001******	x	x	x	x	x	x
	non-SO: LF: sweet vs. savoury	-5.22 ± 5.43	-15.93	5.50	(1,188)	0.92	0.34	x	x	x	x	x	x
	non-SO: HF: sweet vs. savoury	10.57 ± 5.43	-0.15	21.28	(1,188)	3.79	**0.053***	x	x	x	x	x	x
	SO: LF: sweet vs. savoury	-1.77 ± 6.04	-13.69	10.15	(1,188)	0.09	0.77	x	x	x	x	x	x
	SO: HF: sweet vs. savoury	18.99 ± 6.04	7.07	30.91	(1,188)	9.88	**0.002*****	x	x	x	x	x	x

Table 4.25 Post-hoc analysis for effect of severe obesity group on energy intake from *ad libitum* meal. Cohort A (n=47), and cohort C (n=24)

Results from mixed model RMANOVA for energy intake, including: absolute energy intake (kcal), percentage of estimated 24-hour resting energy expenditure (%kcal of REE), percentage of total meal energy intake (%kcal) for group (non-SO:non-severe vs. SO:severe obesity) as between-subject factor, and and sugar (sweet and savoury) and fat (high fat and low fat) content as within subject factors. [a] in cohort C: group*sugar*fat interaction did not reach significance, hence post-hoc contrasts were reported for group*fat interaction independent of sweet, post-hoc contrasts are: LF: SO vs. non-SO and HF: SO vs. non-SO, non-SO: HF vs. LF, SO: HF vs. LF, respectively, Significant results in bold **P<0.01, ***P<0.001. **Abbreviations: df**: degrees of freedom**, CI:** confidence intervals. **LF:** low-fat, **HF:** high-fat

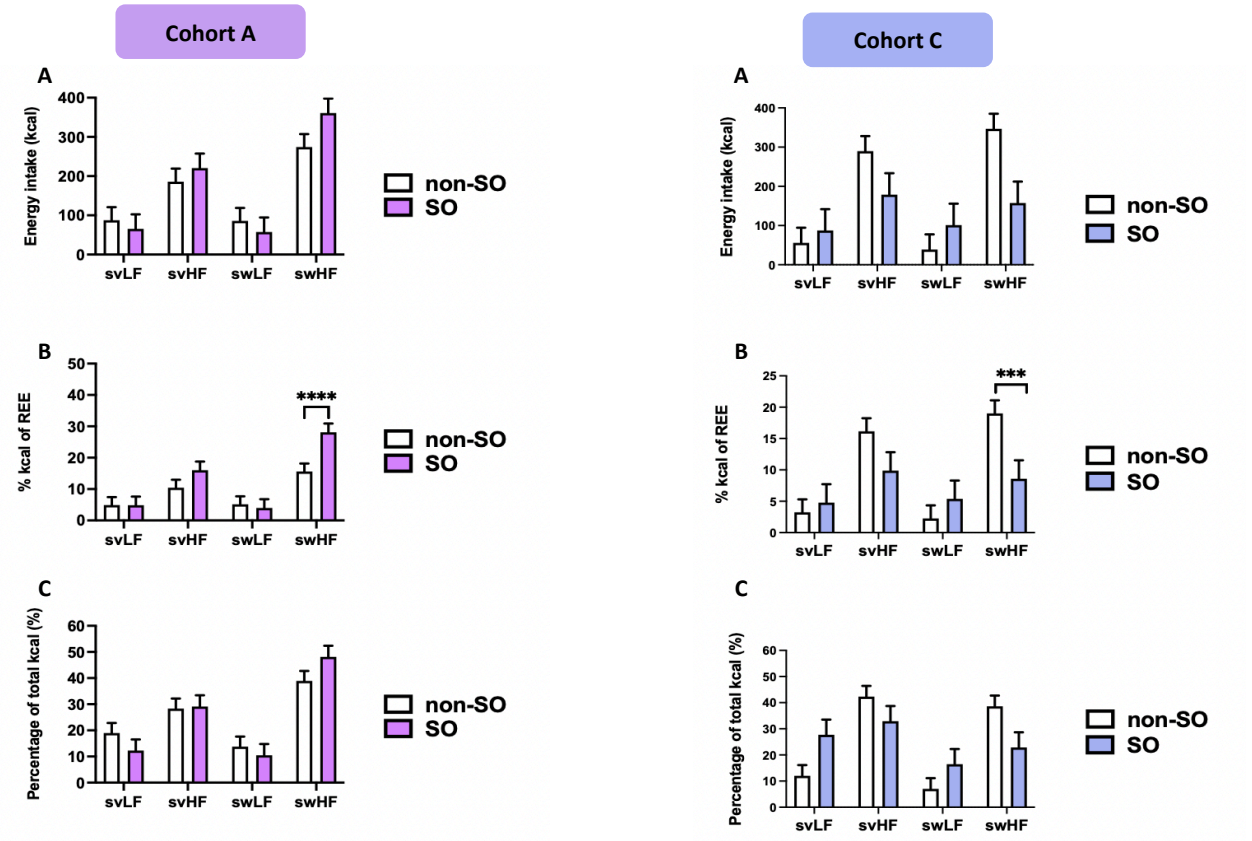


Figure 4.10 Energy intake in cohort A (n=47) and cohort C (n=24)

Comparison between severe and non-severe obesity groups in energy intake, including: (A) absolute energy intake (kcal), (B) percentage of estimated 24-hour resting energy expenditure (REE), (C) percentage of total meal energy intake for four dishes (svLF: chicken broth soup, svHF: chicken cream soup, swLF: yogurt, swHF: ice-cream). Data presented as mean ± SEM. Statistics from mixed model repeated measures ANOVA, with sweet and fat content as within subject factors: post-hoc test *P<0.05, P<0.01,***P<0.005, ****P<0.0001.

Abbreviations: non-SO: non-severe obesity, **SO:** severe obesity, **svLF:** savoury low-fat, **svHF:** savoury high-fat, **swLF:** sweet low-fat, **swHF:** sweet high-fat

		Cohort B *(nOB/OB)* n=76		
		Mean rank	**Test statistic**	**P**
Total kcal	lower BMI	37.5	757.0	0.68
	higher BMI	39.6		
% REE kcal	Lower BMI	39.9	659.5	0.55
	Higher BMI	36.8		

Table 4.26 Mann-Whitney test for effect of BMI group on energy intake in cohort B (n=76)
Results from Mann-Whitney for food intake including absolute energy intake (kcal), percentage of estimated 24-hour resting energy expenditure (%kcal of REE) for groups (lower vs. higher BMI median split = 26.8).

		Cohort A *(pre-RYGB/EB)* **n=47**		Cohort B *(OB)* **n=76**		Cohort C *(OB)* **n=24**	
Taste category	**Food category**	**r**	**P**	**r**	**P**	**r**	**P**
Absolute energy intake	chicken broth soup *Savoury low-fat*	-0.29	**0.045***	0.03^{a}	0.81	0.21	0.33
	chicken cream soup Savoury high-fat	-0.06	0.69	-	-	-0.23	0.27
	yogurt Sweet low-fat	-0.11	0.46	-	-	-0.09	0.69
	ice-cream *Sweet high-fat*	0.22	0.15	-	-	-0.40	**0.05***
% REE kcal	chicken broth soup *Savoury low-fat*	-0.14	0.37	-0.096^{a}	0.40	0.16	0.46
	chicken cream soup Savoury high-fat	0.07	0.65	-	-	-0.26	0.22
	yogurt Sweet low-fat	-0.02	0.91	-	-	-0.09	0.69
	ice-cream *Sweet high-fat*	0.32	**0.03****	-	-	-0.46	**0.025***
% kcal	chicken broth soup *Savoury low-fat*	-0.25	0.09	-	-	-	-
	chicken cream soup Savoury high-fat	-0.05	0.72	-	-	-	-
	yogurt Sweet low-fat	-0.12	0.41	-	-	-	-
	ice-cream *Sweet high-fat*	0.24	0.11	-	-	-	-

Table 4.27 Spearman's correlation between BMI levels and energy intake from *ad libitum* meal in all cohorts

Spearman's correlations between BMI levels and energy intake, including: absolute energy intake (kcal), percentage of estimated 24-hour resting energy expenditure (%kcal of REE), percentage of total meal energy intake (%kcal). Data presented as r Spearman correlation coefficient, *P<0.05, **P<0.01,***P<0.001. [a] cohort B was offered one savoury dish

4.4.7 Progressive ratio task and appetite ratings

For total number of completed clicks and breakpoint (last completed click to earn an M&M), there were no difference between participants with non-severe and severe obesity in *cohort A and cohort C* **Table 4.28**

Moreover, there was no difference in appetite ratings (hunger and fullness), measured by visual analogue scales, between participants with non-severe and severe obesity in *cohort A. cohort B, and cohort C* **Table 4.29**

	Cohort A *(pre-RYGB/EB)* **n=47**				**Cohort C** *(OB)* **n=24**			
	non-SO	**SO**	**Test statistic**	**P**	**non-SO**	**SO**	**test statistic**	**P**
Breakpoint	23.8	24.2	279.5	0.10	13.4	9.4	39.0	0.15
Total clicks	23.6	24.5	285.5	0.23	13.1	10.0	44.0	0.29

Table 4.28 Mann-Whitney test for effect of BMI group on progressive ratio task in cohort A (n=47) and cohort C (n=24)

	Cohort A *(pre-RYGB/EB)* **n=48**				**Cohort B** *(nOB/OB)* **n=93**				**Cohort C** *(OB)*			
Appetite ratings	**non-SO**	**SO**	**Test statistic**	**P**	**Lower BMI**	**Higher BMI**	**Test statistic**	**P**	**non-SO**	**SO**	**Test statistic**	**P**
Hunger	23.5	25.7	313.0	0.58	49.2	46.0	1025.0	0.57	13.0	11.0	56.0	0.65
Fullness	26.4	22.30	237.5	0.31	45.8	49.0	1176.0	0.56	12.9	11.8	58.0	0.74

Table 4.29 Mann-Whitney test for effect of BMI group on appetite ratings
Results from Mann-Whitney for progressive ratio task PRT including breakpoint and total clicks for groups (non-SO: non-severe obesity vs. SO: severe obesity). Data presented as mean rank and test statistic

4.4.8 Eating behaviour questionnaires

Participants with higher BMI compared to participants with lower BMI in *cohort B*, showed higher scores of restraint eating measured by DEBQ, TFEQ, and EDEQ **Table 4.30.** However, no differences in restraint eating scores between participants with severe and non-severe obesity in *cohort A and cohort C.*

Participants from three cohorts were combined to examine the correlation between BMI levels and eating behaviours. Higher BMI levels correlated positively with higher restraint, disinhibition, and emotional eating scores **Table 4.31.**

	Cohort A *(pre-RYGB/EB)* **n=48**				**Cohort B** *(nOB/OB)* **n=93**				**Cohort C** *(OB)* ***n-24***			
Food restraint	**non-SO**	**SO**	**Test statistic**	**P**	**Lower BMI**	**Higher BMI**	**Test statistic**	**P**	**non-SO**	**SO**	**Test statistic**	**P**
DEBQ	23.1	26.2	322.5	0.45	36.2	59.8	1714.5	**<0.001******	12.2	15.9	98.5	0.24
TFEQ	22.7	26.6	332.0	0.34	36.4	54.6	1446.5	**0.001*****	13.3	12.4	66.5	0.76
EDE	23.0	26.3	324.0	0.42	36.3	59.8	1712.5	**<0.001******	-	-	-	-

Table 4.30 Comparison of restraint eating scores between groups in all cohorts

	Cohort A *(pre-RYGB/EB)* **Cohort B** *(nOB/OB)* **Cohort C** *(OB)*	
Eating behaviour questionnaire	**r**	**P**
DEBQ		
Restraint	0.56	**<0.001******
Emotional	0.43	**<0.001******
External	0.10	0.20
TFEQ		
Restraint	0.24	**0.002*****
Disinhibition	0.46	**<0.001******
Hunger	0.18	**0.02****
EDEQ		
Restraint	0.48	**<0.001******
Weight	0.67	**<0.001******
Eating	0.50	**<0.001******
BDI-II	0.53	**<0.001******
BIS	0.12	**0.15**
BES	0.14	**0.24**

Table 4.31 Spearman's correlation between BMI levels and eating behaviour questionnaires in all cohorts combined

Correlations between BMI levels and eating behaviour questionnaire. Data presented as r Spearman correlation coefficient, [a] n=170, [b]n=165, [c] n=144 , **P<0.01,***P<0.001.

4.5 Discussion

This chapter aims to investigate the effect of BMI in obesity on food cue reactivity and other aspects of eating behavior by comparing the findings from three cohorts including participants with obesity. Findings across cohorts for each outcome measure are summarized in **Table 4.31**.

	Cohort A n=48		Cohort B n=96		Cohort C n=26		Combined cohorts n=67 [f] /92 [e]	
Measure	**SO > non-SO**	***corr. w/ BMI***	**higher > lower BMI**	***corr. w/ BMI***	**SO > non-SO**	***corr. w/ BMI***	**SO > non-SO**	***corr. w/ BMI***
Food cue reactivity	**Legend:** ↑ higher in participants with severe obesity, ↓ lower in participants with severe obesity, → no difference between groups, **"o"** no significant correlation between BMI and outcomes, **()**exploratory analysis interaction group*ED not significant**)**							
fROI								
HE	→	o	→	o	→	o	→ [e]	o [e]
LE	↓ av 6 ROIs, amygdala, caudate, putamen	-ve av. 6 ROIs, amygdala, caudate, putamen	(↓) OFC	-ve OFC	n/a	n/a	(↓) insula and caudate [f]	-ve insula, caudate, putamen [f]
HE vs. LE	↑ HE>LE av 6 ROIs, amygdala, caudate, putamen		(↑) HE>LE av 6 ROIs, amygdala, putamen		n/a	n/a	↑ HE>LE av 6 ROIs [f]	
Whole brain								
HE	→	-ve precentral gyrus	→	o	→	o	→ [e]	-ve and +ve in regions irrelative to fROIs
LE	↓OFC, NAcc, insula, caudate	-ve putamen, hippocampus, insula	→	o	n/a	n/a	↓ insula, hippocampus, frontal orbital cortex	-ve putamen, insula, precuneus
HE vs. LE	→	+ve[a]	→	o	n/a	n/a	→ [f]	+ve caudate, brainstem, frontal pole
Food appeal ratings	→ HE, LE, (↑) HE>LE	+ve HE o LE	→ HE, LE, HE>LE	o HE o LE	→ HE	o HE	→ HE [g], LE [h], HE>LE [f]	o HE [g] -ve LE [h]
Food intake								
Energy intake (kcal)	→ [c]	o	→ [b]	o [b]	↓ HF [cd]	-ve HF	n/a	n/a
Energy intake (kcal % REE)	↑ sweet HF [c]	+ve sweet HF	→ [b]	o [b]	↓HF [cd]	-ve HF	n/a	n/a
Dishes (% total kcal)	→ [c]	o	n/a	n/a	n/a	n/a	n/a	n/a
Taste ratings								
Pleasantness	→	o	→	o	→	o	n/a	n/a
Creaminess	→	o	n/a	n/a	→	o	n/a	n/a
Ideal creaminess	↓ savoury LF	-ve savoury LF	n/a	n/a	↑ savoury HF ↑ sweet HF	o	n/a	n/a
Sweetness	→	o	n/a	n/a	→	o	n/a	n/a
Ideal sweetness	→	o	n/a	n/a	→	o	n/a	n/a
LFPQ								
Explicit Liking	↑ sweet HF	+ve sweet HF	n/a	n/a	n/a	n/a	n/a	n/a
Implicit wanting	→	o	n/a	n/a	n/a	n/a	n/a	n/a
PRT	→	o			→	o		
Breakpoint	→		n/a	n/a	→		n/a	n/a
Total clicks	→		n/a	n/a	→		n/a	n/a
Appetite ratings								
Hunger	→		→		→		n/a	n/a
Fullness	→		→		→		n/a	n/a

Table 4.32 Summary of all outcome measures across cohorts based on BMI

[a] other regions showed significant clusters, [b] energy intake from *ad libitum* meal of one dish, [c] energy intake from four dishes (savoury HF/LF and sweet HF/LF), [d]effect of group*fat independent of sweetness, [e] combined cohorts A, B, C for HE food cue reactivity n=92, [f] combined cohorts A, B for LE and HE vs. LE food cue reactivity n=67, [g] combined cohorts A, B, C for HE vs. object appeal ratings n=156, [h] combined cohorts A, B for LE vs.

object appeal ratings n=14.
Abbreviations: av 6 ROIs: average BOLD signal in six functional regions of interest (amygdala, insula, OFC, putamen, NAcc, caudate), **SO:** severe obesity; **non-SO:** non-severe obesity, **HE:** high energy, **LE:** low energy**, corr.:** correlation, **BMI:** body mass index; **HF:** high fat, **LF:** low fat**, -ve:** negative correlation with BMI; **+ve:** positive correlation with BMI; **LFPQ:** Leeds Food Preference Questionnaire; **fROI:** functional regions of interest; **NAcc:** nucleus accumbens; **OFC:** orbitofrontal cortex; **PRT:** progressive ratio task; **n/a:** data/analysis for outcome measure is not available

4.5.1 Food cue reactivity to LE food pictures

In this section, differences in BOLD signal between groups will be discussed for all cohorts by fMRI contrast analysis (LE vs. object, HE vs. object, and HE vs. LE)

Hypothesis: Higher BMI is associated with lower BOLD signalto LE foods

Result: Higher BMI was associated with lower cue BOLD signal to LE food

Summary of results

Participants with severe obesity compared to participants with non-severe obesity, showed lower BOLD signal to LE food picture in average 6 ROIs, amygdala, caudate and putamen using fROI analysis; similar reduction is seen in whole brain analysis in paracingulate gyrus, nucleus accumbens, insula, and caudate in *cohort A*. In addition, BMI levels negatively correlated with BOLD signal to LE food picture in similar regions (av 6 ROIs, amygdala, caudate, putamen) in fROI and whole brain analysis (putamen, hippocampus, insula)

These findings were not seen in *cohort B* where participants with higher BMI compared to participants with lower BMI, did not show any differences in BOLD signal to LE food pictures in average 6 ROIs; however, exploratory individual ROI analysis showed lower BOLD signal to LE food picture in OFC in participants with higher BMI compared to participants with lower BMI, in addition to a negative correlation between BMI and OFC. Moreover, whole brain analysis did not show any difference between groups of lower and higher BMI nor a correlation between BMI and BOLD signal to LE food picture in this cohort.

When participants with obesity from *cohort A and cohort B* were combined, there was a trend for overall effect of group (p=0.056) on BOLD signal to LE food picture. Further exploratory individual fROI analysis showed lower BOLD signal to LE food picture in insula and caudate in participant with severe obesity compared to participants with non-severe obesity, and a negative correlation between BMI and BOLD signal to LE food picture in similar regions (insula, caudate and putamen)

The number of participants with obesity is smaller in *cohort B* compared to *cohort A* (n=23 vs. 48). *Cohort B* included lean participants (n=30) and participants with overweight (n=34); hence the effect of obesity may not be clear in this cohort. This might explain why findings of lower BOLD signal to LE food picture was not replicated in this cohort; however, when two cohorts were combined (including only participants with obesity), there was a lower BOLD signal to LE food picture in participants with severe obesity compared to participants with non-severe obesity.

Most neuroimaging studies in the field of eating behaviour have focused on the hypothesis of higher reactivity to HE food rather than lower reactivity to LE food in obesity. The scarcity in studies examining the effect of LE food picture on food cue reactivity was also seen in my fMRI review chapter, where fMRI paradigms generally included, HE food only or combined HE and LE foods in one contrast. On a PubMed search using the terms [human obesity fMRI food AND ("low-energy" OR "low-calorie" OR "low energy" OR low-calorie)], few studies included LE contrast in the analysis, while most of studies either combine HE and LE food picture in the final analysis or buried LE findings in supplementary tables.

In contrast to my findings, a cross-sectional study concluded that participants with obesity (n=22, mean BMI = 31.6 kg/m^2) compared to participants with normal weight (n=16, mean BMI = 22.7 kg/m^2), showed *higher* BOLD signal to LE food picture in prefrontal cortex and superior frontal gyrus in pre-meal condition, and in dlPFC and caudate in post-meal condition using corrected statistics for whole brain analysis (247). In the same study, similar results to HE food picture in post-meal in participants with obesity compared to participants with normal weight, suggesting a continued hyperresponsivity to food cues (HE and LE) in participants with obesity even after a meal. These differences were not accompanied by differences in food preference for LE or HE food pictures, or hunger ratings. The same research group conducted another study using the same protocol with a focus on the relationship between food cue reactivity and food-related problems (preoccupation with food and difficulty with satiety) using food related problem questionnaire FRPQ (250). This study included participants with obesity and overweight (n=35, mean BMI = 30.6 kg/m^2) and

participants with normal weight (n=14, mean BMI = 21.8 kg/m^2), and used corrected fROI analysis (OFC, dlPFC, insula, cingulate, hypothalamus, thalamus, striatum, amygdala, hippocampus) and whole brain analysis. Their findings showed a negative correlation between FRPQ-satiety scores and BOLD signal to LE food picture in dlPFC in pre-meal condition, and a positive correlation with BOLD signal to LE food picture in putamen and amygdala in post-meal condition, these correlations were only seen in participants with overweight and obesity and not in participants with normal weight (250). Findings of the latter study suggested that food cue reactivity is mediated by satiety-related problems depending on energy density, nutritional state, and BMI. It also implied a dysfunctional satiety in participants with obesity manifested by altered food cue reactivity to LE food picture in dlPFC, putamen and amygdala.

In a 12-week weight-loss program study and after 8-hour fasting, there was no difference between participants with obesity (n=25, mean BMI = 32.9 kg/m^2) and participant with normal weight (n=13, mean BMI = 22.6 kg/m^2) in BOLD signal to LE picture (in ACC, amygdala, caudate, putamen, hippocampus, insula, mPFC, NAcc, VTA) before weight-loss program and at 9 months after weight loss using corrected statistics in fROI and whole brain analysis (222).

Taken together, there might be a disagreement between my findings and findings from previous studies in the literature. Here are some factors that might explain the disagreement between findings.

In one study, participants were scanned 3-8 hours after light breakfast (not standardized; but calorie intake and time since last meal did not differ between groups) (247), or in another study, participants were scanned twice on the same day before and after a meal of 650 kcal (222). Participants from both cohorts in my analysis were fasted before scanning session, and this might explain why the direction of BOLD signal was not the same in my analysis and Dimitropoulos *et al* study (247)

The severity of obesity was also different between the studies. The BMI mean is 31.6 kg/m^2 in (247) and 30.6 kg/m^2 in (250), these values are lower than mean BMI of both groups in *cohort A* (35.17 and 45.32 kg/m^2), and higher BMI group in *cohort B* (33.10 kg/m^2).

While most fMRI studies usually have a sample size of ~20-25, my analysis allowed for combining two cohorts with a total of 67 participants with obesity. This number gives more power for my analysis, and findings from the combined cohort analysis demonstrated lower BOLD signal to LE food picture in participants with severe obesity.

Lastly, differences in methodological approaches result in variable findings, for example: passive viewing of food picture inside the scanner in (247, 250) vs. engaged appeal rating in my analysis; in addition, food preference was assessed indirectly by rating photograph flash cards of LE food pictures (247, 250); while in my analysis in *cohort A,* food preference was assessed by LFFPQ and *ad libitum* meal that included LE dish (chicken broth soup). In my analysis and other studies, lower or higher BOLD signals to LE food picture were not accompanied by differences in liking, wanting, or energy intake of LE food.

Hypothesis: Higher BMI is associated with higher BOLD signal to HE food

Result: Higher BMI is not associated with higher BOLD signal to HE food

Summary of results

Participant with severe obesity compared to participants non-severe obesity, did not show higher BOLD signal to HE food picture in average ROIs, neither in exploratory individual ROI analysis in all cohorts. Furthermore, BMI levels did not correlate with BOLD signal to HE food picture in fROI analysis. However, a negative correlation between BMI and BOLD signal to HE food picture in precentral gyrus was seen whole brain analysis in *cohort A* only

Findings were similar when participants with obesity were combined from three cohorts (n=92), where no difference between participants with severe obesity and participants with non-severe obesity in BOLD signal to HE food picture in average 6ROIs or exploratory individual ROI in fROI analysis. In whole brain analysis, higher BMI levels positively correlated with BOLD signal to HE food picture in fusiform gyrus, and negative correlations were seen in other clusters not related to my regions of interest.

Findings for BOLD signal to HE food picture were consistent in all cohorts, despite of differences between cohorts in participants characteristics and fMRI protocol; for example: participants in *cohort A and cohort B* were fasted and participants in *cohort C* had a small snack before scanning session and were actively dieting; moreover, *Cohort A* included more participants with T2DM than *cohort B and cohort C*

My findings contrast with previous studies from the literature, whereby food cue reactivity was differential in fasting and fed states. For example: in a randomized cross-over design, participants with normal weight (n=20, BMI 22.1 kg/m^2) were scanned twice in fasted (12-hour overnight fast) and fed (after filling breakfast) conditions (214). Higher BOLD signal to HE vs. LE food picture was selectively higher in fasting condition compared to fed condition in the ventral striatum, amygdala, insula, and OFC using fROI analysis (214).

In another study, participants were scanned shortly (2 hours) after consuming a meal. Participants with obesity (n=25, mean of BMI = 32.6 kg/m^2) compared with participants with

normal weight (n=25, mean of BMI = 22.9 kg/m^2) showed higher BOLD signal to favorite food cue in putamen, insula, and inferior frontal gyrus using corrected statistics whole brain analysis, suggesting heightened activity in reward and cognitive control circuits in participants with obesity (71). Another study examined differential food cue reactivity in two nutritional states revealed more pronounced activation in *pre-meal state* (after 4 hours of fasting) compared to *post-meal state* (500 kcal meal) in participants with obesity (n=10) compared to participants with normal weight (n=10) (246). Higher BOLD signal to HE food picture in participants with obesity compared to participants with normal weight in anterior cingulate cortex, mPFC, amygdala, and inferior frontal gyrus (but not hippocampus, OFC, and insula) in *pre-meal state*, and in mPFC and caudate and hippocampus (but not anterior cingulate cortex, amygdala, insula, OFC) in *post-meal state* using fROI analysis (246). Findings of the latter study are in agreement with another study that showed higher BOLD signal to HE food picture in participants with obesity compared to participants with normal weight in pre-meal and post-meal states (247)

While findings from the literature suggest a differential response to food cue in fasting compared to sated state; it may not be the case in obesity where heightened food cue reactivity override satiety signals and consequently result in overeating

Hypothesis: Higher BMI is associated with higher BOLD signal to HE vs. LE food

Result: Higher BMI is associated with higher BOLD signal to HE vs LE food, this heightened reactivity is mainly driven by lower BOLD to LE

summary of results

Participants with severe obesity compared to participants with non-severe obesity, showed higher BOLD signal to HE vs. LE food picture in average 6 ROIs, amygdala, caudate, putamen using fROI analysis, this was mainly driven by reduced BOLD signal to LE in participants with severe obesity. Similar findings were not seen in whole brain analysis in *cohort A* when comparing between the two groups; however, a positive correlation was seen between BMI and BOLD signal to HE vs. LE in putamen

In combined cohorts whole brain analysis, no differences in BOLD signal to HE vs. LE between participants with severe and non-severe obesity. However, BMI levels positively correlated with clusters within frontal pole, precuneus and caudate.

Findings from my analysis are different from many studies in the literature that suggested a heightened reactivity in brain regions associated with reward processing to HE food picture in obesity (19, 243, 251). For example, women with obesity showed higher BOLD signal to HE food picture in dorsal striatum, insula, and OFC compared to women with normal weight (19, 251). In another cross-sectional study, participants with obesity also showed higher BOLD signal to appetizing food pictures in amygdala, hippocampus, posterior cingulate gyrus compared to participants with normal weight (252). Higher BOLD signal in these regions may suggest a higher reward responsivity in obesity, that are further translated into higher consumption of HE food and consequently weight gain.

Previous fMRI studies had small sample sizes and variable methodological approaches; hence, I sought to evaluate the evidence from the literature by looking at findings from systematic reviews and meta-analyses. A systematic review examined food cue reactivity across different weight status, it included 17 studies that compared participants with obesity and participants with normal weight (143). Across included studies, participants with obesity had higher BOLD signal to HE vs. LE food picture in insula, OFC, amygdala, putamen, caudate, hippocampus, PFC compared to participants with normal weight in fasted and fed state (143). In this systematic review, meta-analysis was only performed for studies that included weight loss data.

A metanalysis of fMRI studies included activation likelihood estimation ALE analyzed data from 22 studies using whole brain analysis. In participants with obesity (n=227, mean BMI 35.6 kg/m^2) compared to participants with normal weight (n=329, BMI mean 22.4 kg/m^2), higher BOLD signal to HE/LE food cues in caudate, NAcc and ventral striatum in fed state (253). However, this meta-analysis did not mention whether the contrast for BOLD signal in the included studies was to HE or HE and LE food and did not include correlations with BMI.

The most recent meta-analysis included 14 fMRI studies with mixed nutritional state (fasted and fed) and included participants with a BMI range of 20.3 – 43.87 kg/m^2. In nine studies, participants with obesity compared to participants with normal weight, showed higher BOLD signal to HE/LE food in superior frontal gyrus and caudate (254). When HE vs. LE contrast was examined in seven studies, participants with obesity compared to participants with normal weight, showed higher BOLD signal in amygdala, OFC, and caudate (254).

Prefrontal and corticolimbic regions including amygdala, insula, OFC and caudate were consistently showing differences in BOLD signal in fMRI studies, and they are often predefined as fROIs. These regions largely contribute to emotional regulation, memory formation, reward evaluation and finally decision making (21, 255-258). Amygdala is one of the key regions in emotional and reward processing, and it is one of the regions that consistently shows differential activation related to fMRI food task; indeed, hyperresponsivity of amygdala to highly palatable food is more pronounced in obesity (12). Ventral striatum (including caudate and putamen) is associated with reward conditioning, motivation, and associative learning (243, 259). Finally, the OFC is one of the key areas in the prefrontal cortex that is involved in cognitive control and reward appraisal (243). In the disease of obesity, dysfunctional food reward processing (hyperresponsivity to food cue) may contribute to pathological eating behaviour (excessive food intake) and weight gain. Findings also suggest that obesity impose higher reward value of food or lower cognitive and restraint to HE food.

My findings showed a higher BOLD signal to HE vs. LE that it is mainly driven by lower BOLD signal to LE food in participants with sever obesity compared to participants non-severe obesity, and no differences in BOLD signal to HE food picture between the two groups in individual cohort and combined cohorts' analysis. There are several possible explanations for differences between my findings and other findings, but most importantly, previous studies and meta-analyses in the literature predominantly compare participants with obesity to participants with normal weight, whilst my analysis is a comparison between the severity of obesity (except for *cohort B*). In the current analysis, participants were divided based on their BMI levels to severe and non-severe obesity with the hypothesis that participants with severe obesity will show higher BOLD signal to HE compared to participants with non-severe obesity.

As discussed earlier, the heterogeneity in methodological approaches contribute to the variability in the findings. In fMRI studies that that included two scanning sessions (fasting and fed conditions) (71, 214, 246), differences in food cue reactivity to HE food were seen in both conditions in participants with obesity, except for one study where fasting selectively modulated food cue reactivity in participants with normal weight (214); however, in my analysis participants from all cohorts did not show higher activation to HE food picture in fasting (cohort A and cohort B) and after a meal (cohort C)

The nature of cross-sectional design may not allow to capture differences or control for potential confounders; whilst longitudinal studies generally give stronger weight of evidence because of long-term effect or intervention manipulation. For example, a weight loss intervention (dietary or surgical intervention) can manipulate responses to food cue reactivity before and after the intervention. As previously shown in my fMRI review chapter, an increase in BOLD signal to LE food picture in accumbens and caudate, at 14 weeks after RYGB surgery (162), and a decrease in BOLD signal to HE food picture in striatal and limbic regions at 1 month after RYGB surgery (20, 25).

Lastly, it is well known, food reactivity measured by fMRI have an inherent analytical variability, and responses to food cues inside the scanner do not necessarily reflect response to food cues in real life; thus, when findings from fMRI are accompanied by other eating behaviour measures such as food intake and appetite ratings, they are more meaningful.

4.5.2 Appeal rating to LE and HE food picture during scanning

Summary of results

Participants from all cohorts were actively engaged in food picture appeal rating during scanning sessions. Differences in BOLD signal to LE food pictures in *cohort A* were not accompanied by differences in LE food picture appeal ratings between groups; however, there was a trend for higher appeal rating for HE food picture in participants with severe obesity compared to participants with non-severe obesity (P=0.056). Similarly, BMI levels correlated positively with HE food appeal in *cohort A* only.

In *cohort B and cohort C*, no differences in appeal rating for HE and LE (in *cohort B*) between higher and lower BMI groups, neither were BMI levels correlated with HE and LE food appeal picture.

When participants with obesity were combined from three cohorts, no differences between participants with non-severe and severe obesity in appeal ratings for HE or LE food pictures.

It is unclear why differences between groups in HE food appeal ratings were only seen in *cohort A,* and there is no indication that participants in this cohort were engaging in the task differently; however, as discussed above differences between cohorts might explain the variability between cohorts, for example: participants in *cohort A* were fasted and this might explain the higher appeal ratings for HE food pictures, whilst participants in *cohort C* had a small snack prior to scanning and it may have inhibited the appeal of HE food pictures. In addition, sample size in *cohort A* (n=48) is larger than *cohort C* sample size (n=26).

4.5.3 Ratings of explicit liking and implicit wanting (LFPQ) and motivation progressive ratio task (PRT)

Summary of results

Food preferences measured by explicit liking and implicit wanting ratings, were further assessed by Leeds Food Preference Questionnaire in *cohort A.* Liking scores of HF sweet food (ice-cream) was higher in participants with severe obesity compared to participants with non-severe obesity, this is seen when BMI was analyzed as categorical and continuous variable. In addition, both groups with severe and non-severe obesity showed higher liking scores to savoury HF food compared to savoury LF.

No difference between groups of severe and non-severe obesity in implicit wanting scores (in *cohort A*), and in food reward motivation measured by progressive ratio task PRT in *cohort A* and *cohort C.*

As expected, higher BMI was associated with higher liking of sweet HF food, this finding is in agreement with other behavioral studies in the literature (260), and with fMRI studies included in my fMRI review chapter, where baseline liking ratings for HE food in participants with obesity were higher before obesity surgery compared to ratings at 1 month after obesity surgery (25, 33, 44)

While my analysis did not show differences in implicit wanting ratings between groups with severe and non-severe obesity; a possible explanation is that implicit wanting might be more apparent when a comparison is made between participants with obesity and participants with normal weight, or perhaps participants with obesity and binge eating trait and non-binge eating trait. For example: in a cross-sectional study, participants with obesity and binge eating compared to participants with obesity and without binge eating trait, showed higher explicit liking ratings for HF sweet foods (261) and for all foods (262) These findings were also similar for implicit wanting (262). Unfortunately, I don't have data for explicit liking and implicit wanting in *cohort C* which would allow a comparison between cohorts.

LFPQ is a validated tool for measuring food preference as used in several studies to measure

explicit liking and implicit wanting. However, given the fact that these tasks are usually performed in a controlled lab setting may not replicate real world responses. For example, high fat food picture may not be enough to elicit real response to food cue as it lacks other aspects of reward such as odour, texture, environmental and social factors.

Differences in reward motivation measured by PRT were reported in a longitudinal study after RYGB surgery, suggesting less reward motivation for sweet HF food after obesity surgery (174). Differences in reward motivation tasks such as LFPQ and PRT might be mediated by weight loss and hence, cross-sectional examination may not reveal differences between groups with obesity.

To the best of my knowledge, there was not a behavioral study that compared between severe and non-severe obesity groups, but rather, differences were examined between participants with obesity and participants with normal weight or other eating behaviour trait, or engaging in dietary lifestyle intervention.

4.5.4 Taste ratings

Hypothesis: Higher BMI is associated with higher pleasantness ratings for HF sweet food

Result: Difference in taste ratings between participants with higher BMI compared to participants with lower BMI was only significant for ideal creaminess creaminess and sweetness

Summary of results

It was unexpected to see no difference between participants with severe and non-severe obesity in pleasantness ratings for high fat sweet food (ice cream) in *cohort A and cohort C.* Moreover, no differences between groups in other taste ratings (creaminess and sweetness) in *cohort A and cohort C.*

Participants with severe obesity compared to participants with non-severe obesity, had higher ratings for ideal creaminess for HF food (chicken cream soup and ice-cream) *cohort A and cohort C*, suggesting participants with higher BMI find high fat food too creamy but not necessarily pleasant.

In *cohort C:* Participants with severe obesity compared to participants with non-severe obesity had higher ratings of ideal creaminess for sweet and savoury HF food (ice cream and chicken of cream soup); this might explain why they consumed less compared to participants with non-severe obesity.

No difference in pleasantness or tastiness ratings between higher and lower BMI participants in *cohort B*; however, participants in this cohort were only offered one savoury dish.

Collectively, in all cohorts, pleasantness ratings for high fat or sweet foods did not differ between participants with higher BMI and lower BMI. This finding is in contrast with findings from LFPQ, where participants with severe obesity compared to participants with non-severe obesity, scored higher liking ratings for sweet HF food. However, when actual food intake was measured in *ad libitum* meal, participants with severe obesity compared to participants with non-severe obesity, consumed more sweet HF (ice-cream) in *cohort A* but not in *cohort C.*

The evidence is not yet conclusive regarding the effect of obesity on taste perception, and consequently food choices. Several reviews discussed alterations in taste in obesity, these reviews included studies using different methods to investigate taste perception, including detection, recognition threshold, acuity, and intensity. A recent systematic review concluded that taste ratings, including taste perception and detection, are not different between participants with obesity and participants with normal weight (263).

In another review paper, authors examined the effect of obesity-induced taste dysfunction on food intake (264). This review explored the hypothesis that in obesity, higher inflammation markers are associated with impaired taste sense leading to increased HF food intake. Participants with obesity have either increased or no difference in taste sensitivity when compared with participants with normal weight (264). While keeping in mind the variety of methods used in taste studies, low sweet taste intensity and high liking ratings of sweet food in participants with obesity may contribute to higher intake of sweet foods.

As discussed above, my analysis focused on BMI levels in obesity (i.e. severe >40 kg/m^2 and non-severe obesity <40 kg/m^2), thus, the effect on BMI on taste ratings in these two groups may not be as apparent as in comparison with participants with normal weight, or with participants after weight loss intervention.

Commented [AS5]: In studies comparing taste perception between individuals with obesity and control subjects, using direct measures of taste, one of the most explored outcomes was detection and/or recognition thresholds. Distinct methods have been used, and overall, the results do not consistently support that individuals with obesity have altered taste sensitivity or require different concentrations of a specific tastant (e.g., sucrose) to detect taste (Table 1). Detailed inspection of the available data shows that 3 studies, using the constant stimuli method (see Supplementary Table 1 for details on this and other methods), did not find differences between individuals with obesity and normal weight control subjects in detection thresholds for sweet taste [18,19,26]. Another study, using the 3-stimulus drop method, found no differences relating to the presence of obesity for both detection and recognition thresholds for sweet, salt, bitter and sour tastants[24].

4.5.5 Food intake from ad libitum lunch meal

Hypothesis: Higher BMI is associated with higher food intake, especially high fat and sweet

Result: Difference in food intake between participants with higher BMI compared to participants with lower BMI was in opposite direction in two cohorts

Summary of results

Food intake was measured by *ad libitum* meal, participants were asked to eat until comfortably full of four dishes: chicken broth, chicken cream soup, yogurt, and ice-cream . Energy intake was then assessed by calculating absolute energy intake (kcal), percentage of estimated 24 hour resting energy expenditure, and percentage of total meal energy intake

Higher intake of sweet HF (ice-cream) in participants with *severe obesity* compared to participants with *non-severe obesity* when energy intake was corrected as percentage of REE in *cohort A.* In contrast, intake of high fat food (chicken cream soup and ice-cream) independent of sweetness content was higher in participants with *non-severe obesity* compared to participants with *severe obesity* in *cohort C,* despite no differences in pleasantness ratings between the two groups in this cohort. There was no difference between groups in energy intake from one savoury dish (total kcal and percentage of estimated REE) in *cohort B*

As expected higher intake of high fat food (chicken cream soup and ice-cream) was seen in all participants compared to low fat food (chicken broth soup and yogurt) in *cohort A and cohort C.* Unexpectedly, while participants with severe obesity had higher intake sweet HF (ice cream) compared to participants with non-severe obesity in *cohort A*, findings were in the opposite direction in *cohort C,* where participants with *non-severe obesity* had higher intake of sweet high fat (ice-cream) compared to participants with severe-obesity

This unexpected discrepancy might be explained by several factors: In *cohort A,* the number of participants with T2DM in the non-severe obesity group (n=23/26) was more than the number in the severe obesity group (n=14/22), and perhaps they were more aware (watching

what they eat) and restraining intake from ice-cream, in a manner that participants with severe obesity appeared to be consuming more ice-cream.

Restrain eating is a potential factor that might explain differences in sweet HF intake. Higher restraint eating scores were positively correlated with BMI levels in all cohorts; however, restraint scores were not different between groups assessed by DEBQ and TFEQ, and there is no other unhealthy eating behaviour differed between groups (disinhibition and emotional eating).

Effect of habituation, in which a decreased response to a stimulus due to repeated presentation, in *cohort C*. Participants in this cohort had multiple visits as part of GHADD trial protocol, this means that some of them may have been offered these dishes one or two times before. It is suggested from previous research that *higher* energy intake of food is seen from high variety compared to low variety diets in laboratory settings (265). Hence, it might be the case that participants with higher BMI ate less because they habituated to food "more" than participants with lower BMI.

In *cohort A*, participants with severe obesity compared to participants with non-severe obesity, had higher explicit liking ratings for sweet HF food, which was translated into higher intake of sweet HF (ice-cream); however, it is not the same in *cohort C*, where no difference was seen in pleasantness ratings for HF food between participants with severe and non-severe obesity that can explain the "reduced" HF intake in the severe obesity group

As for *cohort B*, there was no difference between groups in taste ratings, and it could be attributed to the inclusion of participants with overweight which diluted the effect of BMI on energy intake and this cohort was only offered a one savoury dish.

Previous studies from the literature suggested higher intake of high fat food in participants with obesity. For example, total energy intake was higher in participants with obesity and overweight (n=25, BMI = 30.7 kg/m^2) compared to participants with normal weight (n=25, BMI = 22.1 kg/m^2) when tested by *ad libitum* meal; however, there was no difference between the two groups in food choices (sweet and non-sweet food). In this study *ad libitum* meal

included six different bowls of highly palatable foods that were either sweet or non-sweet (262).

In another cross-sectional study, participants with severe obesity (n= 43 mean of BMI >44.5 kg/m^2) were recruited to assess energy intake from a buffet meal based on food preference questionnaire (266). Participants were divided into two groups based on BMI median split of 42.5 kg/m^2. Participants with higher BMI had higher energy intake from *ad libitum* buffet meal compared to participants with lower BMI, also BMI correlated positively with energy intake (266). These findings are consistent with my findings from *cohort A* and the BMI in the two studies are comparable.

Evidence from systematic reviews and meta-analyses support these findings (267-270). In a recent meta-analysis, overweight and obesity were associated with higher intake of ultra-processed food (268). Ultra-processed foods are usually high in fat and sugar content. This meta-analysis was also consistent with another meta-analysis concluding greater fast-food consumption, especially high fat foods in individuals with greater obesity risk (269).

It is important to highlight methodological issues in my analysis and behavioural studies. Usually, the dishes offered to participants are chosen based on their sweet savoury/sweet and fat content HF/ LF, and not on participants preferences. This means that an ice-cream for example, may not be perceived as the favorite sweet HF food. Also, lab-setting food intake measurements do not reflect real-life consumption, where social and environmental factors play a crucial role in food intake.

In the disease of obesity, disrupted appetite control is attributed in part to dysfunctional inhibitory (anorexigenic) mechanism from adipose tissues. Meaning, adipocyte-induced inflammation affects appetite control within the hypothalamus (271), afferent vagal signaling (272), gut hormones release (98), and insulin resistance (273). This disruption affects appetite and food intake, particularly the reward system, on multi-levels predisposing individuals with obesity to pathological overeating and obesity.

4.5.6 Eating behaviour questionnaire

Summary of results

As expected, higher BMI levels positively correlated with higher eating behaviours scores including dietary restraint, emotional, and disinhibition eating assessed by eating behaviour questionnaires (DEBQ, TFEQ, EDE). Restrain eating is referred to the conscious control over food intake, and emotional eating refers to eating in response to a negative feeling, where as disinhibition reflects tendency towards overeating in an obesogenic environment. These associations suggest a higher susceptibility of overeating with increased BMI

There was no different in restraint scores assessed by (DEBQ, TFEQ, EDE) questionnaires between participants with severe and non-severe obesity in *cohort A* and *cohort C*, and in three cohorts combined analysis. However, in *cohort B,* participants with higher BMI compared to participants with lower BMI, had higher restraint eating scores. Differences in restraint eating score might be more pronounced after dietary intervention, or weight loss, or when compared between participants with obesity and participants with normal weight, as in *cohort B* where a wide range of BMI was included (this is the only cohort that included participants with normal weight, overweight and obesity). Moreover, *cohort B* is the largest cohort with a sample size of 96, compared to 48 and 26 in *cohort A* and *cohort C,* respectively.

Evidence from studying unhealthy eating behaviours in obesity suggests that as BMI increases, disinhibition and hunger eating increase (274, 275); whilst restraint eating either increases (276, 277) or decreases, perhaps depending on whether an individual is actively dieting or not. My findings are in line with other studies that found an association between obesity and unhealthy eating behaviours.

In a prospective weight reduction study, women with obesity (n= 42, mean of BMI = 34.47 kg/m^2) were divided according to binge eating severity (absence of binge eating n=23, moderate binge eating n=11, severe binge eating n=8)(278). Using TFEQ questionnaire, restraint, disinhibition, and hunger eating scores were significantly higher in the severe binge eating group compared to absence and moderate binge eating groups (278). While impulsivity scores assessed by BIS did not correlate with BMI levels in my analysis, higher scores of

impulsivity were shown to be correlated with higher BMI levels in several systematic reviews (91, 279). Indeed, impulsivity is associated with overeating, especially in individuals with Binge Eating Disorder (85).

Emotional and disinhibition eating, and impulsivity are commonly associated with obesity and may influence food choices. In a cross-sectional study included 473 participants and using DEBQ, restraint and emotional eating scores were compared between participants with overweight (n= 181, mean BMI = 30.2 kg/m^2) and participants with normal weight (n= 292, mean BMI = 21.8 kg/m^2)(83). Participants with overweight compared to participants with normal weight, had higher scores in restraint and emotional eating (83).

In food cue reactivity analysis, frontal regions; that are involved in cognitive control and decision making; were not included as fROIs which might have given an insight on whether dietary restraint modulated food cue reactivity. Although in whole brain analysis for combined cohorts, a positive correlation between BMI and BOLD signal to HE vs. LE in frontal pole, the frontal pole is one of the largest lobes in the brain including multiple regions that are associated with cognitive control, decision making and executive functions. Findings from my fMRI review chapter summarized changes in unhealthy eating behaviours after obesity surgery. In seven studies after obesity surgeries (RYGB and VSG), restraint eating either increased (45, 149, 158, 163) or decreased (16), or did not change (159).

However, BMI levels did not correlate with psychological trait questionnaires scores including Barrat Impulsivity Scale (BIS) and Binge Eating Scale (BES). It is important to examine the association between BMI levels and these confounding traits as they contribute to altered food cue reactivity and food intake. Previous search demonstrated an association between obesity and psychological traits such as impulsivity and addiction

The main limitation of eating behaviours questionnaires is that they are self-reported, and they assess eating behaviour in isolation from the individual's eating episode experience that is usually accompanied by social, environmental, emotional state. Nevertheless,

incorporating these assessments with other eating behaviour measures expands our understanding of mechanisms related to eating behaviour in obesity.

4.6 Strengths and limitations

The present analysis improves upon other cross-sectional studies by including three cohorts underwent same fMRI protocol paradigm. It also allowed combining participants with obesity from three cohorts with a total of 92 participants to examine food cue reactivity. Larger sample size of participants with obesity allows for a better representation of obesity phenotype heterogeneity. More importantly, it showed that heightened reactivity to HE food is not necessarily seen in all individuals with obesity

Additionally, this analysis aimed to examine differences between severe and non-severe obesity, and to my knowledge there are not many studies that examined eating behaviour measures across obesity severity. However, one of the limitations in this analysis is that participants in cohorts were recruited from different sources to take part in clinical trials that were designed to meet different objectives, hence different inclusion and exclusion criteria and participants characteristics resulted in wide heterogeneity between cohorts.

Here is a summary of differences between participants characteristics and study paradigms, within each cohort, which may have attributed to the variability in findings:

In Cohort A: patients were either on the waiting list for an obesity surgery or patients who are taking part in the Endobarrier randomized clinical trial, included more participants with T2DM in lower BMI group than higher BMI group. Participants underwent scanning session fasted and fMRI paradigm included HE and LE food pictures. Food preferences using LFPQ was only assessed in this group, alongside with PRT, taste ratings and *ad libitum* lunch

Cohort B: While it is the largest cohort (n=96), participants with obesity counted for only 24%. Participants were recruited for multiple observational and interventional studies, and very few of them with T2DM. Participants underwent scanning session fasted and fMRI paradigm included HE and LE food pictures. Food preferences using PRT and LFPQ were not assessed in this cohort, and ad libitum lunch included one savoury dish.

Cohort C: has the smallest sample size including patients who were actively on a weight

reduction diet and taking part in GHADD trial, and participants with T2DM were excluded. Participants underwent scanning session after a small snack and fMRI paradigm only included, HE food pictures.

4.7 Conclusion

Findings from this analysis suggest that obesity severity defined by BMI ≥ 40 kg/m^2, have an effect of food cue reactivity, specifically lower BOLD signal in average six fROIs (amygdala, insula, OFC, putamen, NAcc, caudate) to LE food picture but not higher BOLD signal to HE food picture. The regions of brain included in this analysis represent regions frequently identified in reward processing. These findings may suggest that participants with severe obesity are less likely to consume healthy low energy foods because these foods are not perceived rewarding, and consequently higher consumption of less healthy high energy food.

Findings from other measures also suggest an effect of obesity severity on eating behaviour, such as higher food intake for HF sweet foods that is accompanied by higher liking and pleasantness ratings. In addition, obesity is associated with eating behaviours and psychological traits (ex. Restraint and emotional eating and impulsivity) that also contribute to overeating and weight gain. These effects can be further translated into higher susceptibility to pathological eating behavior and weight gain.

While these findings were not replicable in all cohorts as discussed above, this analysis highlights an important characteristic of obesity, that it is a heterogeneous phenotype and there is a need to differentiate between individuals with obesity to optimize treatment options. Thus, individualized treatments for patients with obesity may include assessment of neural, physiological, and psychological risks.

Chapter 5 Food cue reactivity and eating behaviour and insulin resistance in obesity

5.1 Introduction

Insulin is a pancreatic derived hormone with a well-established role in homeostatic network controlling food intake. Insulin receptors have been also identified in several regions of the brain including nucleus accumbens, caudate, putamen and amygdala suggesting its role in hedonic appetite and food intake (64). Insulin resistance is associated with obesity and may have an impact on food cue reactivity in reward processing regions.

Previous fMRI studies including insulin infusion, demonstrated the lowering effect of insulin on food cue reactivity in normal insulin sensitive individuals (66, 67, 280). For example: when comparing the effect of intranasal insulin condition to baseline condition in participants with normal weight, reduced BOLD signal to food pictures in fusiform gyrus and hippocampus, in intranasal compared to baseline condition (66). Furthermore, in another interventional study intranasal insulin, lower intrinsic brain activity by fractional amplitude of low-frequency fluctuations (fALFF) in hypothalamus and OFC in participants with normal weight (67). However, in the case of insulin resistance, the inhibitory effect of insulin is disrupted in individuals with insulin resistance (70). These findings indeed suggest a role of central insulin in the regulation of the reward response to food cues.

The further characterisation of patients with obesity based on their peripheral and even central insulin resistance, and not just BMI, is an important step forward in the understanding of eating behaviour in obesity. Hence, this chapter aims to re-analyse data from previous chapter based on insulin resistance defined by HOMA-IR>2.5 and examine its association with food cue reactivity and eating behaviour measures.

5.2 Objectives

The main aim of this chapter is to examine the following objectives in three cohorts and examine whether findings are replicated in all cohorts

1. Examine the relationship between HOMA-IR and neural activation in response to food cues via region of interest (ROI) and whole brain analysis including brain regions implicated in reward processing.
2. Examine the relationship between HOMA-IR and food intake using *ad libitum* lunch and taste ratings
3. Examine the relationship between HOMA-IR and measures of eating behaviour using questionnaires (DEBQ, TFEQ, YFAS, BES, PFS)

4.3 Hypothesis

1. Higher HOMA-IR is associated with higher cue reactivity in brain reward systems to HE food and/or lower reactivity to LE foods, as well as similar differences in food appeal
2. Higher HOMA-IR is associated with increased food intake, especially high fat and sweet/ or lower low fat and savoury food
3. Higher HOMA-IR is associated with increased appetite and unhealthier eating behaviour

5.4 Results

5.4.1 Participants characteristics

Participants characteristics for three cohorts according to their HOMA-IR levels are summarized in **Table 5.1**. There were no significant differences between groups (HOMA-IR below or above 2.5) in age and white ancestry distribution in all cohorts. There was no significant difference between groups in BMI *cohort A and cohort C*, but significant in cohort B. Number of participants with type 2 diabetes was significantly higher in cohort A only.

	Cohort A (pre-RYGB/EB)				Cohort B (nOB/OB)				Cohort C (OB)			
Variable	**All**	**HOMA-IR < 2.5**	**HOMA-IR > 2.5**	**P#**	**All**	**HOMA-IR < 2.5**	**HOMA-IR > 2.5**	**P#**	**All**	**HOMA-IR < 2.5**	**HOMA-IR > 2.5**	**P#**
n	47	9	38		93	82	11		25	17	8	
Female n (%)	29 (61.7%)	8 (88.9%)	21 (55.3%)	0.12[d]	57 (61.3%)	49 (59.8%)	8 (72.7%)	0.52[d]	18 (72.0%)	12 (70.6%)	6 (75.0%)	1.00[d]
Age (years) (range)	50.0 ± 8.4 (31-64)	50.44 ± 9.3 (31-62)	49.9 ± 8.4 (31-63)	0.29[e]	33.4 ± 10.3 (19-55)	33.2 ± 10.0 (19-55)	35.0 ± 12.5 (20-54)	0.59[e]	42.2 ± 11.4 (24-60)	43.4 ± 12.0 (24-57)	40.6 ± 10.5 (28-60)	0.58[e]
Caucasian n (%)	27 (57.4%)	5 (55.6%)	22 (57.9%)	1.00[d]	58 (62.4%)	52 (63.4%)	6 (54.5%)	0.74[d]	16 (64.0%)	11 (64.7%)	5 (62.5%)	1.00[d]
BMI kg/m^2 (range)	39.9 ± 6.2 (30.6-55.5)	42.5 ± 5.5 (34.3-50.4)	39.3 ± 6.3 (30.6-55.5)	0.58[e]	28.8 ± 6.7 (19.1-53.1)	27.6 ± 5.4 (19.1-44.5)	38.2 ± 7.8 (29.0-53.1)	0.001[e]****	37.1 ± 4.0 (29.6-46.3)	36.2 ± 4.8 (29.6-46.3)	39.1 ± 4.3 (32.6-46.1)	0.16[e]
Type 2 diabetes millitus n (%)	36 (76.6%)	4 (44.4%)	32 (84.2%)	0.02[d]**	3 (3.2%)	1 (1.2%)	2 (18.2%)		0	0	0	
HOMA-IR [quartiles], (range)	3.91 [2.68,6.21], (1.35-11.95)[a]	1.72 [1.46,2.03], (1.35-2.57)	4.35 [3.43-6.87], (2.57-11.95)	<0.001[f]****	1.10 [0.71,1.74], (0.33-9.02)[b]	1.04 [0.68,1.51], (0.33-2.46)	3.70 [2.57,4.37], (1.60-9.02)	<0.001[f]***	1.7 [0.97,2.88], (0.28-9.13)	1.32 [0.72,1.75], (0.28-2.14)	3.35 [2.85,4.53], (2.78-9.13)	<0.001[f]****
Severe obesity n (%) BMI > 40 kg/m^2	22/47 (46.8%)	6 (66.7%)	16 (42.1%)		50/93 (53.8%)[g]	39 (78.0%)	11 (22.0%)		9/25 (36.0%)	6 (66.67%)	3 (33.33%)	

Table 5.1 Participants characteristics in cohorts

Data presented as mean SD, median [interquartile range] (minimum-maximum), or n (%). ****P<0.001

[a] n=47, [b] n=93, [c] median=26.85, # P value for the difference between participants with HOMA-IR>2.5 and participants with HOMA-IR<2.5, [d] P value for fisher's exact test, [e] P value for unpaired t-test, [f] P value for Mann-whitney test, [g] Groups based on BMI median split =26.85 kg/m^2

Abbreviations: EB: Endobarrier, **HOMA-IR**: homeostasis model of assessment-insulin resistance, **RYGB:** Roux-En Y gastric bypass, **T2DM:** type 2 diabetes mellitus, **BMI:** body mass index

5.4.2 Food-pictures cue reactivity

Functional regions of interest analysis

Cohort A (pre-RYGB/EB) **n=43**: for BOLD signal during evaluation of HE and LE food pictures (vs. objects), there was no significant interaction effects for: (i) group*ED*ROI [F(10,473)= 0.84, P=0.59 Greenhouse-Geisser correction]. However, there was a significant interaction effect for (ii) group*ROI (independent of energy density) [F(10,473)= 2.36, P=0.01], (iii) group*ED (across average 6 ROIs) [F(1,473)= 4.69, P=0.031]. Moreover, no (iv) overall effect of group [F(1,43)= 0.02, P=0.89], in mixed model RMANOVAanalysis **Table 5.2 and 5.3.** Spearman's correlation between HOMA-IR levels and BOLD signal in 6 fROIs to HE and LE food pictures revealed negative correlation between HOMA-IR and BOLD signal to HE food picture in average 6 ROIS, anterior insula, and caudate **Table 5.4 Figure 5.2**

This was consistent in *cohort B (nOB/OB)* **n=86**, where for BOLD signal during evaluation of HE and LE food pictures (vs. objects), there was no significant interaction effects for: (i) group*ED*ROI [F(10,946)= 0.83, P=0.60 Greenhouse-Geisser correction]. However, there was a significant interaction effect for (ii) group*ROI (independent of energy density) [F(10,946)= 2.84, P=0.002], (iii) group*ED (across average 6 ROIs) [F(1,946)= 6.10, P=0.014]. Moreover, no (iv) overall effect of group [F(1,86)= 0.83, P=0.36], in mixed model RMANOVA analysis **Table 5.2 and 5.3.** Spearman's correlation between HOMA-IR levels and BOLD signal in 6 fROIs to HE and LE food pictures revealed no correlation between HOMA-IR and BOLD signal to HE and LE food pictures in any fROI **Table 5.4 Figure 5.2**

Similarly *cohort C* **n=23**, where for BOLD signal during evaluation of HE food pictures (vs. objects), there was no significant interaction effects for: (i) group*ROI [F(5,24)= 1.91, P=18] Greenhouse-Geisser correction, nor (ii) overall effect of group [F(1,120)= 1.60, P=0.17], in mixed model RMANOVA analysis **Table 5.2 and 5.3**. Spearman's correlation between HOMA-IR levels and BOLD signal in 6 fROIs to HE food picture revealed no correlation between HOMA-IR and BOLD signal to HE food picture in any fROI **Table 5.4 Figure 5.2**

	Cohort A *(pre-RYGB/EB)* ***n=43***		Cohort B *(nOB/OB)* ***n=86***		Cohort C [a] *(OB)* ***n=23***	
Interaction	**(df) F**	**P**	**(df) F**	**P**	**(df) F**	**P**
group*ED*ROI	(10,473) 0.84	0.59	(10,946) 0.83	0.60	-	-
group*ROI	(10,473) 2.36	**0.01****	(10,946) 2.84	**0.002*****	(1,24) 1.91	0.18
group*ED	(10,473) 4.69	**0.031****	(1,946) 6.10	**0.014****	-	-
group	(1,43) 0.02	0.89	(1,86) 0.83	0.36	(5,120) 1.60	0.17
HOMA-IR*ED*ROI	(5,473) 0.22	0.95	-	-	-	-
HOMA-IR *ROI	(5,473) 3.77	**0.02****	-	-	0.02 (5,125)	0.90
HOMA-IR *ED	(1,473) 5.44	**0.002*****	-	-	-	-
HOMA-IR	(1,43) 2.267	0.14	-	-	0.55(5,120)	0.74

Table 5.2 Mixed model RMANOVA for effect of HOMA-IR (categorical and continuous variable) on food cue reactivity

Results from mixed model RMANOVA for BOLD signal for group (HOMA-IR<2.5 vs. HOMA-IR>2.5) as between-subject factor, and ED energy density (low and high energy food picture) and average six fROI region of interest (insula, amygdala, OFC, NAcc, putamen and caudate) as within subject factors. [a] no energy density within subject factor because fMRI paradigm in this cohort only included HE picture. Significant results in bold *P<0.05, **P<0.03, ***P< 0.005, ****P<0.001.

Abbreviations: EB: Endobarrier, **nOB:** non-obesity, OB: obesity, **RYGB:** Roux-En Y gastric bypass, **ED:** energy density, **ROI:** region of interest, **HOMA-IR:** homeostasis model of assessment-insulin resistance

Cohort A *(pre-RYGB/EB)*			**95% confidence interval**				
	Post-hoc contrast	**Mean ± SEM**	**lower**	**upper**	**df**	**F**	**P**
	LE: HOMA-IR>2.5 vs. HOMA-IR<2.5	0.028 ± 0.037	-0.047	0.102	(1,61.08)	0.549	0.46
	HE: HOMA-IR>2.5 vs. HOMA-IR<2.5	-0.037 ± 0.037	-0.112	0.037	(1,61.08)	1.008	0.32
	HOMA-IR<2.5: HE vs. LE	0.116 ± 0.027	0.063	0.168	(1,473)	18.809	**<0.001******
	HOMA-IR>2.5: HE vs. LE	0.051 ± 0.014	0.024	0.078	(1,473)	13.663	**<0.001******
Cohort B *(nOB/OB)*							
	LE: HOMA-IR>2.5 vs. HOMA-IR<2.5	-0.066 ± 0.039	-0.143	0.011	(1,110.79)	2.92	0.09
	HE: HOMA-IR>2.5 vs. HOMA-IR<2.5	3.810 ± 0.039	-0.077	0.077	(1,110.79)	0	1.00
	HOMA-IR<2.5: HE vs. LE	0.018 ± 0.009	0.001	0.035	(1,946)	4.138	**0.042***
	HOMA-IR>2.5: HE vs. LE	0.084 ± 0.025	0.034	0.134	(1,946)	10.929	**0.001*****
Cohort C[a] *(OB)*							
	HOMA-IR<2.5	0.076 ± 0.030	0.014	0.138	24	-	-
	HOMA-IR>2.5	0.005 ± 0.042	-0.083	0.092	24	-	-

Table 5.3 Post-hoc analysis for effect of HOMA-IR group on food cue reactivity

Results from post-hoc pairwise comparisons for group*ED interaction. Between-subject factor (HOMA-IR>2.5 vs. HOMA-IR<2.5), and within-group factor ED energy density (LE: low energy and HE:high energy food picture). [a] estimates for BOLD signal to HE vs. object in HOMA-IR<>2.5 groups Significant results in bold *P<0.05, *P<0.001.

EB: Endobarrier, nOB: non-obesity, OB: obesity, RYGB: Roux-En Y gastric bypass, HOMA-IR: homeostasis model of assessment-insulin resistance

		Cohort A *(pre-RYGB/EB)* ***n=43***		Cohort B *(nOB/OB)* ***n=87***		Cohort C *(OB)* ***n=23***	
Energy density	**fROI**	**r**	**P**	**r**	**P**	**r**	**P**
High-energy pictures	av 6 ROIs	-0.38	**0.012****	0.08	0.49	0.08	0.73
	ant. insula	-0.32	**0.035***	0.05	0.67	0.05	0.82
	amygdala	-0.22	0.2	0.15	0.16	0.02	0.93
	OFC	0.02	0.91	-0.02	0.85	0.30	0.16
	caudate	-0.40	**0.007*****	-0.04	0.75	0.09	0.68
	putamen	-0.29	0.06	0.12	0.29	0.24	0.27
	NAcc	-0.18	0.25	-0.02	0.83	-0.13	0.55
Low-energy pictures	av 6 ROIs	-0.04	0.79	-0.04	0.68	-	-
	ant insula	0.08	0.60	-0.15	0.17	-	-
	amygdala	-0.004	0.98	0.08	0.49	-	-
	OFC	-0.03	0.84	-0.13	0.24	-	-
	caudate	-0.17	0.26	-0.07	0.50	-	-
	putamen	-0.02	0.90	-0.01	0.90	-	-
	NAcc	-0.04	0.79	-0.06	0.61	-	-

Table 5.4 Spearman's correlation between HOMA-IR levels and BOLD signal to HE and LE food picture in all cohorts

Spearman's correlations between HOMA-IR levels and BOLD signal in averaged across all 6 fROIS, anterior insula, amydala, OFC, caudate, putamen, nucleus accumbens to HE food vs. objects and LE foods vs objects. Data presented as r Spearman correlation coefficient, *P<0.05, **P<0.01,P***<0.005, ***P<0.001.

Abbreviations: av 6 ROIs: average of six functional regions of interest; **ant:** anterior; **OFC:** orbitofrontal cortex; **NAcc:** nucleus accumbens, **HOMA-IR**: homeostasis model of assessment-insulin resistance

Exploratory analysis for individual fROIs

Difference in BOLD signal amygdala, anterior insula, orbitofrontal cortex, NAcc, putamen, caudate was examined between groups within each cohort for HE food vs. objects and LE food vs objects

Cohort A (pre-RYGB/EB): for BOLD signal during evaluation of HE and LE food pictures (vs. objects), there was a significant interaction effects for group*ED in nucleus accumbens [F(1,43)= 5.14, P=0.03]. Pairwise comparison between groups and within groups for HE and LE food pictures are summarized in **Table 5.5 Figure 5.1-A.**

Cohort B (nOB/OB): for BOLD signal during evaluation of HE and LE food pictures (vs. objects), there was a significant interaction effects for group*ED in amygdala [F(1,86)= 7.11, P=0.009]. Pairwise comparison between groups and within groups for HE and LE food pictures are summarized in **Table 5.6 Figure 5.1-B**.

cohort C (OB): BOLD signal to HE vs. object food pictures was not different between groups in any individual ROI. Pairwise comparison between groups for HE food pictures are summarized in **Table 5.7 Figure 5.1-C**.

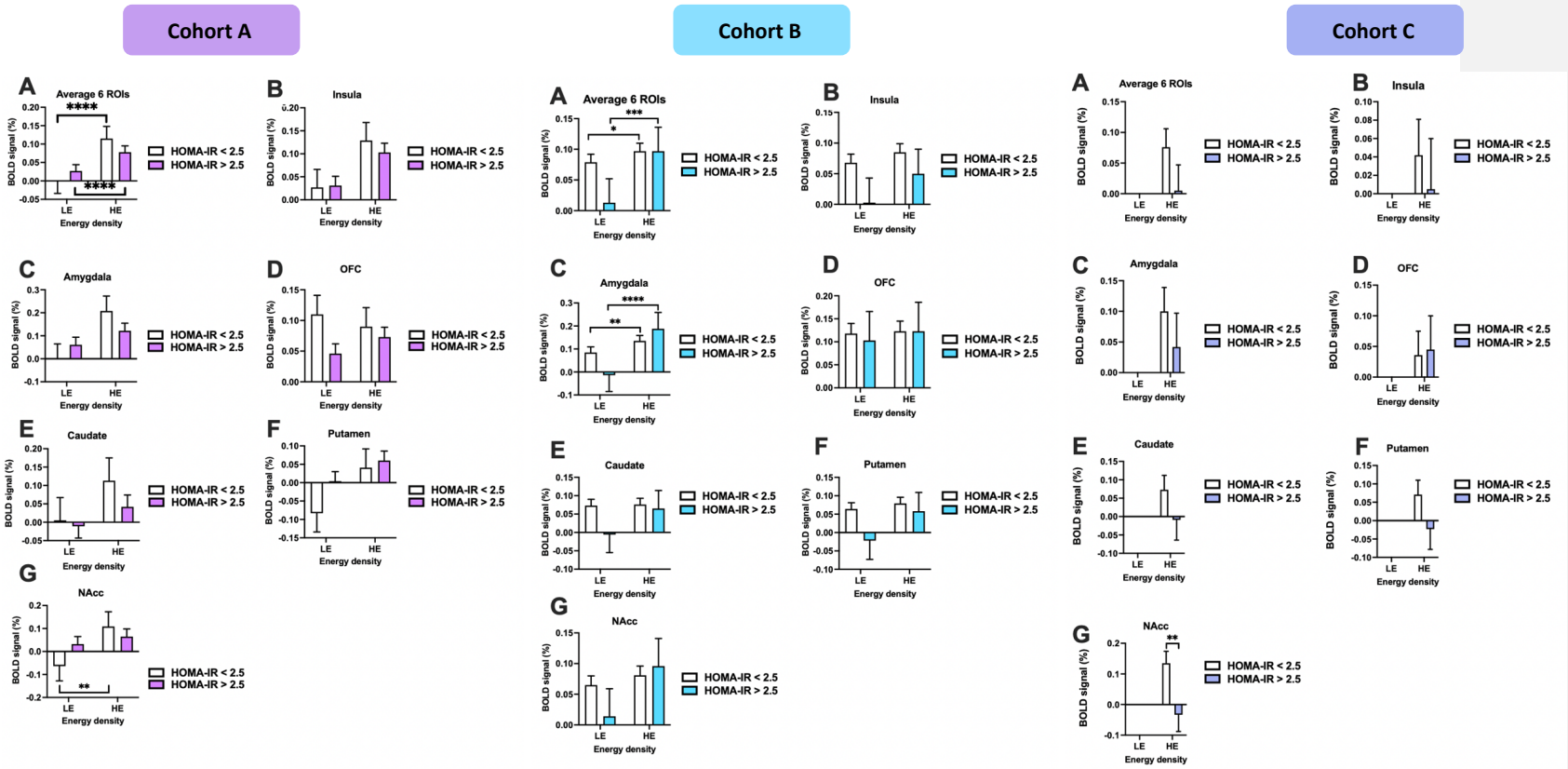


Figure 5.1 BOLD signal in individual fROI analysis

Comparison of BOLD signal from fROI analysis between groups (HOMA-IR>2.5 vs. HOMA-IR<2.5) across cohorts, (A) average six fROIS, (B) insula, (C) amygdala, (D) orbitofrontal cortex, (E) caudate, (F) putamen, (G)nucleus accumbens. Data presented as mean ± SEM. Statistics from mixed model repeated measures ANOVA, with fROIs and energy density as within subject factors: post-hoc test *P<0.05, P<0.01,***P<0.005, ****P<0.0001.

Abbreviations: HOMA-IR: homeostasis model of assessment - insulin resistance, **LE:** low-energy**, HE:** high energy, **NAcc:** nucleus accumbens, **OFC:** orbitofrontal cortex, **BOLD:** blood oxygen level dependent

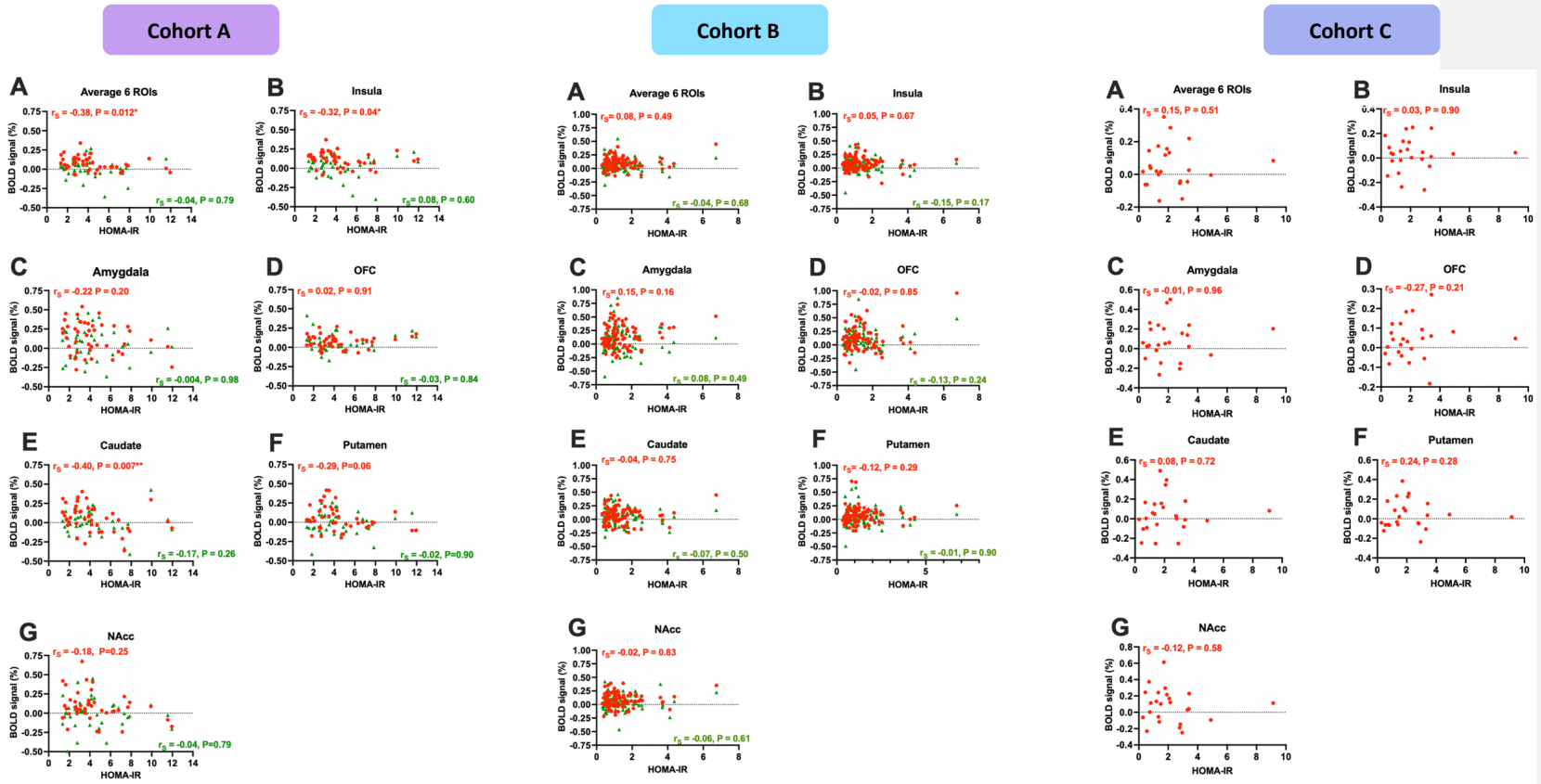


Figure 5.2 Spearman's correlation between HOMA-IR and BOLD signal in fROI across cohorts

Spearman's correlations between BMI levels and BOLD signal in A) average six fROIS, (B) insula, (C) amygdala, (D) orbitofrontal cortex, (E) caudate, (F) putamen, (G)nucleus accumbens to HE food vs. objects (red) and LE foods vs objects (green). Data presented as r Spearman correlation coefficient, *P<0.05, **P<0.01,***P<0.001.

Abbreviations: HOMA-IR: homeostasis model of assessment - insulin resistance, **LE:** low-energy, **HE:** high energy, **NAcc:** nucleus accumbens, **OFC:** orbitofrontal cortex, **BOLD:** blood oxygen level dependent

Cohort A *(pre-RYGB/EB)* Exploratory individual ROI analysis

Insula

Interaction	F	df	P
HOMA-IR > 2.5	0.09	(1,43)	0.77
ED	14.61	(1,43)	<0.001****
HOMA-IR > 2.5*ED	0.43	(1,43)	0.52

Post-hoc contrast	Mean ± SEM	95% CI		F	df	P
		lower	upper			
LE: HOMA-IR>2.5 vs. HOMA-IR<2.5	0.004 ± 0.043	-0.082	0.091	0.01	(1,72.00	0.92
HE: HOMA-IR>2.5 vs. HOMA-IR<2.5	-0.026 ± 0.043	-0.113	0.061	0.36	(1,72.00	0.55
HOMA-IR<2.5: HE vs. LE	0.103 ± 0.041	0.021	0.185	6.34	(1,43)	0.016**
HOMA-IR>2.5: HE vs. LE	0.073 ± 0.021	0.030	0.115	11.97	(1,43)	0.001***

Amygdala

Interaction	F	df	P
HOMA-IR > 2.5	0.042	(1,43)	0.84
ED	11.70	(1,43)	0.001***
HOMA-IR > 2.5*ED	3.51	(1,43)	0.07

Post-hoc contrast	Mean ± SEM	95% CI		F	df	P
		lower	upper			
LE: HOMA-IR>2.5 vs. HOMA-IR<2.5	0.061 ± 0.073	-0.085	0.206	0.69	(1,72.86)	0.41
HE: HOMA-IR>2.5 vs. HOMA-IR<2.5	-0.086 ± 0.073	-0.231	0.059	1.39	(1,72.86)	0.24
HOMA-IR<2.5: HE vs. LE	0.207 ± 0.07	0.067	0.348	8.86	(1,43)	0.005**
HOMA-IR>2.5: HE vs. LE	0.061 ± 0.036	-0.012	0.133	2.86	(1,43)	0.10

OFC

Interaction	F	df	P
HOMA-IR > 2.5	1.73	(1,43)	0.20
ED	0.05	(1,43)	0.82
HOMA-IR > 2.5*ED	2.00	(1,43)	0.16

Post-hoc contrast	Mean ± SEM	95% CI		F	df	P
		lower	upper			
LE: HOMA-IR>2.5 vs. HOMA-IR<2.5	-0.065 ± 0.035	-0.135	0.006	3.36	(1,66.46)	0.07
HE: HOMA-IR>2.5 vs. HOMA-IR<2.5	-0.017 ± 0.035	-0.087	0.054	0.23	(1,66.46)	0.63
HOMA-IR<2.5: HE vs. LE	-0.02 ± 0.03	-0.081	0.041	0.45	(1,43)	0.51
HOMA-IR>2.5: HE vs. LE	0.028 ± 0.015	-0.003	0.059	3.23	(1,43)	0.08

Caudate

Interaction	F	df	P
HOMA-IR > 2.5	0.46	(1,43)	0.50
ED	7.76	(1,43)	0.008
HOMA-IR > 2.5*ED	0.88	(1,43)	0.35

Post-hoc contrast	Mean ± SEM	95% CI		F	df	P
		lower	upper			
LE: HOMA-IR>2.5 vs. HOMA-IR<2.5	-0.016 ± 0.07	-0.157	0.124	0.05	(1,60.14)	0.82
HE: HOMA-IR>2.5 vs. HOMA-IR<2.5	-0.071 ± 0.07	-0.211	0.07	1.01	(1,60.14)	0.32
HOMA-IR<2.5: HE vs. LE	0.108* ± 0.052	0.004	0.213	4.38	(1,43)	0.042*
HOMA-IR>2.5: HE vs. LE	0.054 ± 0.027	9.085	0.108	4.08	(1,43)	0.05*

Putamen						
Interaction		F		df		P
HOMA-IR > 2.5		1.18		(1,43)		0.28
ED		9.12		(1,43)		0.004
HOMA-IR > 2.5*ED		1.28		(1,43)		0.26
Post-hoc contrast	Mean ± SEM	95% CI		F	df	P
		lower	upper			
LE: HOMA-IR>2.5 vs. HOMA-IR<2.5	0.087 ± 0.057	-0.027	0.200	2.30	(1,71.08)	0.13
HE: HOMA-IR>2.5 vs. HOMA-IR<2.5	0.019 ± 0.057	-0.095	0.133	0.11	(1,71.08)	0.74
HOMA-IR<2.5: HE vs. LE	0.123 ± 0.053	0.017	0.230	5.45	(1,43)	0.024**
HOMA-IR>2.5: HE vs. LE	0.056 ± 0.027	0.001	0.111	4.24	(1,43)	0.045*

NAcc						
Interaction		F		df		P
HOMA-IR > 2.5		0.15		(1,43)		0.70
ED		11.33		(1,43)		**0.002****
HOMA-IR > 2.5*ED		5.14		(1,43)		**0.03***
Post-hoc contrast	Mean ± SEM	95% CI		F	df	P
		lower	upper			
LE: HOMA-IR>2.5 vs. HOMA-IR<2.5	0.095 ± 0.072	-0.049	0.239	1.74	(1,61.16)	0.19
HE: HOMA-IR>2.5 vs. HOMA-IR<2.5	-0.044 ± 0.072	-0.188	0.100	0.37	(1,61.16)	0.54
HOMA-IR<2.5: HE vs. LE	0.173 ± 0.055	0.063	0.283	10.03	(1,43)	**0.003****
HOMA-IR>2.5: HE vs. LE	0.034 ± 0.028	-0.023	0.090	1.44	(1,43)	0.24

Table 5.5 Mixed model RMANOVA for exploratory individual ROI analysis and post-hoc pairwise comparison for cohort A (n=43)

Data presented as mean ± SEM. Abbreviations: CI: confidence intervals, df: degrees of freedom, HE: high energy, LE: low energy, NAcc: nucleus accumbens, OFC: orbitofrontal cortex

Cohort B *(nOB/OB)* Exploratory individual ROI analysis

Insula

Interaction		F		df		P
HOMA-IR above 2.5		1.91		(1,86)		0.17
ED		2.26		(1,86)		0.14
HOMA-IR above 2.5*ED		0.50		(1,86)		0.48
Post-hoc contrast	Mean ± SEM	95% CI		F	df	P
		lower	upper			
LE: HOMA-IR>2.5 vs. HOMA-IR<2.5	-0.066 ± 0.042	-0.149	0.018	2.40	(1,140.32)	0.12
HE: HOMA-IR>2.5 vs. HOMA-IR<2.5	-0.035 ± 0.042	-0.119	0.049	0.68	(1,140.32)	0.41
HOMA-IR<2.5: HE vs. LE	0.017 ± 0.014	-0.011	0.045	1.53	(1,86)	0.22
HOMA-IR>2.5: HE vs. LE	0.048 ± 0.041	-0.034	0.129	1.36	(1,86)	0.25

Amygdala

Interaction		F		df		P
HOMA-IR above 2.5		0.11		(1,86)		0.74
ED		19.59		(1,86)		<0.001****
HOMA-IR above 2.5*ED		7.11		(1,86)		**0.009****
Post-hoc contrast	Mean ± SEM	95% CI		F	df	P
		lower	upper			
LE: HOMA-IR>2.5 vs. HOMA-IR<2.5	-0.099 ± 0.075	-0.248	0.049	1.75	(1,114.09)	0.19
HE: HOMA-IR>2.5 vs. HOMA-IR<2.5	0.052 ± 0.075	-0.096	0.201	0.49	(1,114.09)	0.49
HOMA-IR<2.5: HE vs. LE	.050 ± 0.018	0.013	0.087	7.39	(1,86)	**0.008****
HOMA-IR>2.5: HE vs. LE	0.202 ± 0.054	0.095	0.309	14.04	(1,86)	**<0.001****

OFC

Interaction		F		df		P
HOMA-IR above 2.5		0.02		(1,86)		0.90
ED		0.12		(1,86)		0.73
HOMA-IR above 2.5*ED		0.05		(1,86)		0.83
Post-hoc contrast	Mean ± SEM	95% CI		F	df	P
		lower	upper			
LE: HOMA-IR>2.5 vs. HOMA-IR<2.5	-0.015 ± 0.067	-0.147	0.118	0.05	(1,141.79)	0.83
HE: HOMA-IR>2.5 vs. HOMA-IR<2.5	0 ± 0.067	-0.133	0.132	0	(1,141.79)	1.00
HOMA-IR<2.5: HE vs. LE	0.005 ± 0.023	-0.04	0.049	0.04	(1,86)	0.84
HOMA-IR>2.5: HE vs. LE	0.019 ± 0.066	-0.112	0.15	0.09	(1,86)	0.77

Caudate

Interaction		F		df		P
HOMA-IR above 2.5		0.96		(1,86)		0.33
ED		2.47		(1,86)		0.12
HOMA-IR above 2.5*ED		2.03		(1,86)		0.16
Post-hoc contrast	Mean ± SEM	95% CI		F	df	P
		lower	upper			
LE: HOMA-IR>2.5 vs. HOMA-IR<2.5	-0.079 ± 0.052	-0.182	0.024	2.30	(1,127.54)	0.13
HE: HOMA-IR>2.5 vs. HOMA-IR<2.5	-0.012 ± 0.052	-0.115	0.091	0.05	(1,127.54)	0.82
HOMA-IR<2.5: HE vs. LE	0.003 ± 0.015	-0.027	0.034	0.05	(1,86)	0.82
HOMA-IR>2.5: HE vs. LE	0.071 ± 0.045	-0.018	0.159	2.50	(1,86)	0.12

Putamen						
Interaction		F		df		P
HOMA-IR above 2.5		1.18		(1,86)		0.28
ED		5.09		(1,86)		0.03
HOMA-IR above 2.5*ED		2.42		(1,86)		0.12
Post-hoc contrast	Mean ± SEM	95% CI		F	df	P
		lower	upper			
LE: HOMA-IR>2.5 vs. HOMA-IR<2.5	-0.087 ± 0.054	-0.193	0.02	2.60	(1,116.36)	0.11
HE: HOMA-IR>2.5 vs. HOMA-IR<2.5	-0.021 ± 0.054	-0.127	0.085	0.15	(1,116.36)	0.70
HOMA-IR<2.5: HE vs. LE	0.015 ± 0.014	-0.012	0.042	1.17	(1,86)	0.28
HOMA-IR>2.5: HE vs. LE	0.080 ± 0.04	0.001	0.16	4.05	(1,86)	0.047

NAcc						
Interaction		F		df		P
HOMA-IR above 2.5		0.20		(1,86)		0.66
ED		3.71		(1,86)		0.06
HOMA-IR above 2.5*ED		1.73		(1,86)		0.19
Post-hoc contrast	Mean ± SEM	95% CI		F	df	P
		lower	upper			
LE: HOMA-IR>2.5 vs. HOMA-IR<2.5	-0.051 ± 0.047	-0.145	0.042	1.18	(1,146.47)	0.28
HE: HOMA-IR>2.5 vs. HOMA-IR<2.5	0.016 ± 0.047	-0.077	0.109	0.11	(1,146.47)	0.74
HOMA-IR<2.5: HE vs. LE	0.015 ± 0.016	-0.017	0.048	0.88	(1,86)	0.35
HOMA-IR>2.5: HE vs. LE	0.083 ± 0.048	-0.013	0.178	2.94	(1,86)	0.09

Table 5.6 Mixed model RMANOVA for exploratory individual fROI analysis and post-hoc pairwise comparison for cohort B (n=86)

Data presented as mean ± SEM. Abbreviations: CI: confidence intervals, df: degrees of freedom, HE: high energy, LE: low energy, NAcc: nucleus accumbens, OFC: orbitofrontal cortex

Cohort C (OB) Exploratory individual ROI analysis

Insula

interaction	F		df	P		
HOMA-IR > 2.5	0.43		(1,24)	0.52		
Post-hoc contrast	Mean ± SEM	95% CI		F	df	p
		lower	upper			
HOMA-IR>2.5 vs. HOMA-IR<2.5	-0.037 ± 0.07	-0.172	0.098	0.30	(1,62.75)	0.59

Amygdala

interaction	F		df	P		
HOMA-IR > 2.5	0.52		(1,24)	0.48		
Post-hoc contrast	Mean ± SEM	95% CI		F	df	p
		lower	upper			
HOMA-IR>2.5 vs. HOMA-IR<2.5	-0.058 ± 0.067	-0.193	0.076	0.75	(1,62.75)	0.39

OFC

interaction	F		df	P		
HOMA-IR > 2.5	0.05		(1,24)	0.82		
Post-hoc contrast	Mean ± SEM	95% CI		F	df	p
		lower	upper			
HOMA-IR>2.5 vs. HOMA-IR<2.5	0.009 ± 0.067	-0.125	0.144	0.02	(1,62.75)	0.89

Caudate

interaction	F		df	P		
HOMA-IR > 2.5	1.11		(1,24)	0.30		
Post-hoc contrast	Mean ± SEM	95% CI		F	df	p
		lower	upper			
HOMA-IR>2.5 vs. HOMA-IR<2.5	-0.082 ± 0.067	-0.217	0.052	1.49	(1,62.75)	0.23

Putamen

interaction	F		df	P		
HOMA-IR > 2.5	2.63		(1,24)	0.12		
Post-hoc contrast	Mean ± SEM	95% CI		F	df	p
		lower	upper			
HOMA-IR>2.5 vs. HOMA-IR<2.5	-0.094 ± 0.067	-0.228	0.041	1.93	(1,62.75)	0.17

NAcc

interaction	F		df	P		
HOMA-IR > 2.5	4.41		(1,24)	**0.05***		
Post-hoc contrast	Mean ± SEM	95% CI		F	df	p
		lower	upper			
HOMA-IR>2.5 vs. HOMA-IR<2.5	-0.168 ± 0.067	-0.303	-0.034	6.23	(1,62.75)	**0.015****

Table 5.7 Mixed model RMANOVA for exploratory individual fROI analysis and post-hoc pairwise comparison for cohort C (n=23)

Data presented as mean ± SEM. Abbreviations: CI: confidence intervals, df: degrees of freedom, HE: high energy, LE: low energy, NAcc: nucleus accumbens, OFC: orbitofrontal cortex

Whole brain analysis

Cohort A (pre-RYGB/EB): There were no clusters displaying significant differences or correlations in BOLD signal between groups

Cohort B (nOB/OB): There were no clusters displaying significant differences or correlations in BOLD signal between groups

Cohort C (OB): There were no clusters displaying significant differences or correlations in BOLD signal between groups

Potential confounding factors for scanning visit

The following potential confounders were examined for differences between groups within each cohort: (i) absolute and relative motion; (ii) menstrual cycle; (iii) visual analogue scales of anxiety, stress, and sleepiness; (iv) fasting duration; (v) hours slept night before; (vi) Positive Affect and Negative Affect Schedule (PANAS). There was no difference between any of the above confounders between groups with HOMA-IR above and below 2.5 within each cohort **Table 5.8**

	Cohort A *(pre-RYGB/EB)* ***n=43***				Cohort B *(nOB/OB)* ***n=87***				Cohort C *(OB)* ***n=23***			
	HOMA-IR<2.5	**HOMA-IR>2.5**	**Test statistic**	**P**	**HOMA-IR<2.5**	**HOMA-IR>2.5**	**Test statistic**	**P**	**HOMA-IR<2.5**	**HOMA-IR>2.5**	**Test statistic**	**P**
Absolute motion	17.6	23.9	219.0	0.2	47.1	46.6	446.5	1.0	n/a	n/a	n/a	n/a
Relative motion	15.7	24.5	238.0	0.1	45.2	60.5	599.0	0.1	12.4	12.7	65.5	0.9
Menstrual cycle	-	-	-	-	-	-	-	-	7.8	4.0	6.0	0.1
VAS												
Anxiety	21.6	22.8	179.0	0.8	44.8	58.9	581.5	0.1	12.3	13.0	67.5	0.8
Stress	21.9	22.7	176.0	0.9	44.6	60.8	602.5	0.1	11.7	14.1	76.5	0.5
Sleepiness	22.4	22.5	171.5	1.0	46.3	48.0	462.0	0.8	11.8	14.0	76.0	0.5
Fasting duration	-	-	227.0	0.36	47.0	47.5	456.0	1.0	-	-	-	-
Hours slept night before	24.4	22.0	151.5	0.6	47.5	31.5	280.0	0.1	-	-	-	-
Positive affect	23.0	22.4	165.5	0.9	46.7	49.1	474.5	0.8	12.0	15.1	85.0	0.3
Negative affect	22.9	22.4	166.5	0.9	46.0	54.7	536.5	0.3	14.4	9.9	43.5	0.2

Table 5.8 Potential confounding factors of picture evaluation fMRI task

Comparison between groups in each cohort for potential confounders using Mann-Whitney non-parametric test. Data presented as mean rank and test statistic.
VAS: visual analogue scale before scanning

5.4.3 Food appeal ratings

Cohort A (pre-RYGB/EB) **n=47**:for HE and LE (vs. object) food picture appeal rating during scanning, there was no significant interaction effects for: (i) group*ED [F(1,47)=0.58, P=0.45], nor (ii) overall effect of group [F(1,47)= 3.36, P=0.07], but an overall effect of ED [F(1,47)= 5.12, P=0.03]. Furthermore, for HE subcategory (savoury, sweet, chocolate) food picture appeal rating during scanning, there was no significant interaction effects for: (i) group*HE subcategory [F(2,94)=0.60, P=0.55], nor an overall effect of ii) group [F(1,47)=3.53, P=0.07], and (ii) HE subcategory [F(2,94)= 1.50, P=0.23] in mixed model RMANOVA analysis **Table 5.8 Figure 5.3-A**. Further post-hoc analysis and pairwise comparison summarized in **Table 5.9.** Spearman's correlation between HOMA-IR levels and appeal ratings for HE and LE food pictures, and HE categories (chocolate, sweet, savoury) revealed no significant correlation between HOMA-IR and appeal ratings for HE food and LE food picturs **Table 5.10**

This was consistent in *cohort B (nOB/OB)* **n=93**, where for for HE and LE (vs. object) food picture appeal rating during scanning, there was no significant interaction effects for: (i) group*ED [F(1,92.17)=0.03, P=0.88], nor (ii) overall effect of group [F(1,92.79)= 0.37, P=0.55], or ED [F(1,92.17)= 0.26, P=0.61]. Furthermore, for HE subcategory (savoury, sweet, chocolate) food picture appeal rating during scanning, there was no significant interaction effects for: (i) group*HE subcategory [F(2,183.06)=0.082, P=0.92], nor overall effect of (ii) group [F(1,91.95)=0.47, P=0.50], and (ii) HE subcategory [F(2,183.06)= 0.40, P=0.67] in mixed model RMANOVA analysis **Table 5.8 Figure 5.3-B**. Further post-hoc analysis and pairwise comparison summarized in **Table 4.9.** Spearman's correlation between HOMA-IR levels and appeal ratings for HE and LE food pictures, and HE categories (chocolate, sweet, savoury) revealed no significant correlation between HOMA-IR and appeal ratings for HE food and LE food picturs **Table 5.10**

nor cohort C (OB) **n=24***:*where for HE (vs. object) food picture appeal rating during scanning, there was no different between groups of higher and lower HOMA-IR [F(1,24)=0.09, P=0.77] **Table 5.8, 5.9 Figure 5.3-C.** Spearman's correlation between HOMA-IR levels and appeal ratings for HE food pictures revealed no significant correlation between HOMA-IR and appeal ratings for HE food picturs **Table 5.10**

	Cohort A *(pre-RYGB/EB)* n=47		Cohort B *(nOB/OB)* n=93		Cohort C *(OB)* n=24	
Interaction	**(df) F**	**P**	**(df) F**	**P**	**(df) F**	**P**
group*ED	(1,47) 0.58	0.45	(1,92.17) 0.03	0.88	-	-
group	(1,47) 3.36	0.07	(1,92.79) 0.37	0.55	(1,24) 0.09 [a]	0.77
ED	(1,47) 5.12	0.03	(1,92.17) 0.26	0.61	-	-
group*HE subcategory	(2,94) 0.60	0.55	(2,183.06) 0.08	0.92	-	-
group	(1, 47) 3.53	0.07	(1,91.95) 0.47	0.50	-	-
HE subcategory	(2,94) 1.50	0.23	(2,183.06) 0.40	0.67	-	-
HOMA-IR*ED	(1,47) 0.37	0.55	-	-	-	-
HOMA-IR	(1,47) 2.60	0.11	(1,92) 1.92	0.17	(1,24) 0.02	0.89

Table 5.8 Mixed model RMANOVA for effect of HOMA-IR (categorical and continuous variable) on food appeal ratings. Cohort A (n=47), Cohort B (n=95), Cohort C (n=25)

Results from mixed model RMANOVA for appeal ratings for group (HOMA-IR>2.5 vs. HOMA-IR<2.5) as between-subject factor or HOMA-IR, and ED energy density (low and high energy food picture) and HE food subcategory (chocolate, sweet, savoury) as within subject factors. [a] cohort C only had HE food picture appeal ratings.

Abbreviations: EB: Endobarrier, **nOB:** non-obesity**, OB:** obesity, **RYGB:** Roux-En Y gastric bypass, **ED:** energy density, **HOMA-IR:** homeostasis model of assessment-insulin resistance

Cohort A *(pre-RYGB/EB)*			95% confidence interval				
	Post-hoc contrast	**Mean ± SEM**	**lower**	**upper**	**df**	**F**	**P**
	LE: HOMA-IR>2.5 vs. HOMA-IR<2.5	-0.40 ± 0.31	-1.03	0.22	(1,70.30)	1.64	0.20
	HE: HOMA-IR>2.5 vs. HOMA-IR<2.5	-0.62 ± 0.31	-1.25	0.01	(1,70.30)	3.91	**0.05***
	HOMA-IR<2.5: HE vs. LE	0.43 ± 0.26	-0.09	0.95	(1,47)	2.82	0.10
	HOMA-IR>2.5: HE vs. LE	0.22 ± 0.13	-0.04	0.47	(1,47)	2.95	0.09
	Savoury: HOMA-IR>2.5 vs. HOMA-IR<2.5	-0.50 ± 0.35	-1.19	0.20	(1,58.13)	2.06	0.16
	Sweet: HOMA-IR>2.5 vs. HOMA-IR<2.5	-0.70 ± 0.35	-1.40	-0.01	(1,58.13)	4.10	**0.05***
	Chocolate: HOMA-IR>2.5 vs. HOMA-IR<2.5	-0.65 ± 0.35	-1.35	0.04	(1,58.13)	3.52	0.07
Cohort B *(nOB/OB)*							
	LE: HOMA-IR>2.5 vs. HOMA-IR<2.5	-0.18 ± 0.29	-0.75	0.40	(1,134.21)	0.38	0.54
	HE: HOMA-IR>2.5 vs. HOMA-IR<2.5	-0.14 ± 0.29	-0.71	0.44	(1,134.21)	0.23	0.64
	HOMA-IR<2.5: HE vs. LE	0.05 ± 0.29	-0.13	0.22	(1,92.48)	0.26	0.61
	HOMA-IR>2.5: HE vs. LE	0.09 ± 0.29	-0.39	0.56	(1,92.13)	0.13	0.72
	Savoury: HOMA-IR>2.5 vs. HOMA-IR<2.5	-0.12 ± 0.26	-0.63	0.40	(1,135.70)	0.20	0.66
	Sweet: HOMA-IR>2.5 vs. HOMA-IR<2.5	-0.19 ± 0.26	-0.70	0.33	(1, 135.56)	0.50	0.48
	Chocolate: HOMA-IR>2.5 vs. HOMA-IR<2.5	-0.18 ± 0.26	-0.70	0.33	(1, 135.56)	0.50	0.48
Cohort C *(OB)*							
	HOMA-IR<2.5	3.45 ± 0.21	3.02	3.88			
	HOMA-IR>2.5	3.56 ± 0.29	2.95	4.17			

Table 5.9 Post-hoc analysis for effect of HOMA-IR group on food appeal ratings
Results from post-hoc pairwise comparisons for group*ED interaction. Between-subject factor (HOMA-IR above 2.5 vs. HOMA-IR below 2.5), and within-group factor ED energy density (LE: low energy and HE:high energy food picture). Significant results in bold *P<0.05
Abbreviations: EB: Endobarrier, **nOB:** non-obesity, **OB:** obesity, **RYGB:** Roux-En Y gastric bypass, **df:** degree of freedom, **HOMA-IR:** homeostasis model of assessment-insulin resistance

	Cohort A (pre-RYGB/EB)		*Cohort B* (nOB/OB)		*Cohort C* (OB)	
Appeal rating	**r**	**P**	**r**	**P**	**r**	**P**
High-energy	-0.17	0.25	-0.09	0.37	-0.06	0.78
Low-energy	-0.27	0.06	-0.19	0.07	-	-
High-energy subcategories						
Chocolate	-0.20	0.18	-0.07	0.50	-	-
Sweet	-0.21	0.15	-0.08	0.47	-	-
Savoury	0.01	0.97	-0.04	0.73	-	-

Table 5.10 Spearman's correlation between HOMA-IR levels and food appeal ratings for HE and LE food picture in all cohorts

Spearman's correlations between BMI levels and appeal ratings for HE food vs. objects and LE foods vs. objects, and HE subcategory (chocolate, sweet, savoury) food. Data presented as r Spearman's correlation coefficient, *P<0.05

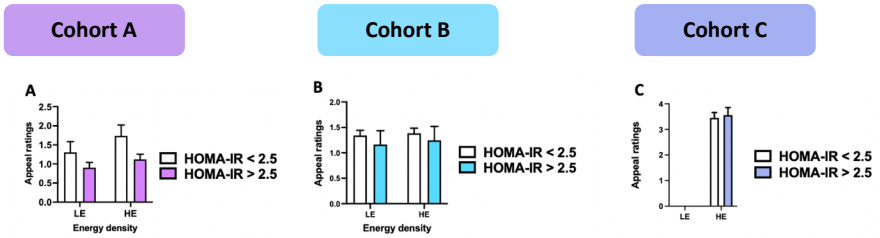


Figure 5.3 Food appeal rating during evaluation fMRI task for HE and LE food picture
Comparison between groups within each cohort for food picture (HE vs. object and LE vs. object) appeal rating during scanning
Abbreviations: HOMA-IR: homeostasis model of assessment-insulin resistance, LE: low-energy, HE: high energy

5.4.4 Leeds food preference questionnaire (cohort A only)

Explicit liking: For explicit liking of HF, LF, sweet and savoury foods, there was not significant interaction effect for: (i) group*sweet*fat content [F(2,138)=0.80, P=0.45], in mixed model RMANOVA analysis, allowing for analysis separately by sweet and fat categories**.** There was a significant interaction effect for: (ii) group*fat content (independent of sweet category) [F(2,138)=3.69, P=0.03] **Table 5.11.** Further post-hoc analysis showed a higher explicit liking to HF vs. LF within HOMA-IR > 2.5 group (effect size mean ± SEM 5.19 ± 1.96 (95% CI 1.32, 9.07), P=0.009) **Table 5.12**. **Figure 5.4**

Implicit wanting: For implicit wanting of HF, LF, sweet and savoury foods, there was a significant interaction effect for: (i) group*sweet*fat content [F(2,184)=5.84, P=0.003], in mixed model RMANOVA analysis **Table 5.11**. Further post-hoc analysis did not show a significant difference between groups, but rather differences in savoury HF and sweet HF food within groups **Table 5.12 Figure 5.4**

	Explicit liking		**Implicit wanting**	
Interaction	**(df) F**	**P**	**(df) F**	**P**
group*sugar*fat	(2,138)0.80	0.45	(2,184)5.84	**0.003****
group* sugar	(1,138)0.13	0.72	(1,184)0.78	0.38
group*fat	(2,138)3.69	**0.027****	(2,184)8.13	**<0.001****
group	(1, 46)2.43	0.13	(1,184)0	1.00

Table 5.11 RMANOVA for effect of HOMA-IR>2.5 group on explicit liking and implicit wanting using Leeds food preference questionnaire LFPQ Cohort A (n=46)
Results from RMANOVA for explicit liking and implicit wanting for groups (HOMA-IR<2.5 vs. HOMA-IR>2.5) as between-subject factor, and sugar (sweet and savoury) and fat (high fat and low fat) content as within subject factors. Significant results in bold *P<0.05, ****P<0.001

Explicit liking [a]			95% confidence interval				
	Post-hoc contrast	**Mean ± SEM**	**lower**	**upper**	**df**	**F**	**P**
	LF: HOMA-IR>2.5 vs. HOMA-IR<2.5	8.58 ± 6.78	-5.00	22.16	(1, 57.35)	1.60	0.21
	HF: HOMA-IR>2.5 vs. HOMA-IR<2.5	11.41 ± 6.78	-2.17	24.99	(1, 57.35)	2.83	0.10
	HOMA-IR<2.5: HF vs LF	2.36 ± 3.97	-5.49	10.21	(1, 138)	0.35	0.55
	HOMA-IR>2.5: HF vs LF	5.19 ± 1.96	1.32	9.07	(1, 138)	7.03	**0.009****
Implicit wanting [b]							
	LF: Savoury: HOMA-IR>2.5 vs. HOMA-IR<2.5	1.44 ± 9.21	-16.73	19.60	(1,48)	0.02	0.88
	LF: Sweet: HOMA-IR>2.5 vs. HOMA-IR<2.5	6.70 ± 9.21	-11.47	24.87	(1,48)	0.53	0.47
	HF: Savoury: HOMA-IR>2.5 vs. HOMA-IR<2.5	-5.54 ± 9.21	-23.71	12.63	(1,48)	0.36	0.55
	HF: Sweet: HOMA-IR>2.5 vs. HOMA-IR<2.5	-2.60 ± 9.21	-20.76	15.57	(1,48)	0.08	0.78
	HOMA-IR<2.5: Savoury: HF vs LF	22.88 ± 11.68	-0.16	45.92	(1,48)	3.84	**0.052***
	HOMA-IR<2.5: Sweet: HF vs LF	-0.20 ± 11.68	-23.25	22.84	(1,48)	0.00	0.99
	HOMA-IR>2.5: Savoury: HF vs LF	28.14 ± 5.76	16.78	39.51	(1,48)	23.87	**<0.001****
	HOMA-IR>2.5: Sweet: HF vs LF	2.74 ± 5.76	-8.62	14.11	(1,48)	0.23	0.64
	HOMA-IR<2.5: LF: sweet vs savoury	11.28 ± 11.68	-11.76	34.32	(1,48)	0.93	0.34
	HOMA-IR<2.5: HF: sweet vs savoury	-11.80 ± 11.68	-34.84	11.24	(1,48)	1.02	0.31
	HOMA-IR>2.5: LF: sweet vs savoury	4.30 ± 5.76	-7.06	15.67	(1,48)	0.56	0.46
	HOMA-IR>2.5: HF: sweet vs savoury	-21.10 ± 5.76	-32.46	-9.73	(1,48)	13.41	**<0.001****

Table 5.12 Post-hoc analysis for effect of HOMA-IR group on explicit liking and implicit wanting using Leeds food preference questionnaire LFPQ Cohort A (n=46)

[a]Results from post-hoc pairwise comparisons for group*fat interaction for explicit liking. [b]Results from post-hoc pairwise comparisons for group*sugar*fat interaction. For implicit wanting. Between-subject factor (HOMA-IR>2.5 vs. HOMA-IR<2.5), and and sugar (sweet and savoury) and fat (high fat and low fat) content as within subject factors. Significant results in bold *P<0.05, ***P<0.001

Abbreviations: LF: low-fat, **HF:** high-fat, **df:** degree of freedom**, HOM-IR:** homeostasis model of assessment-insulin resistance

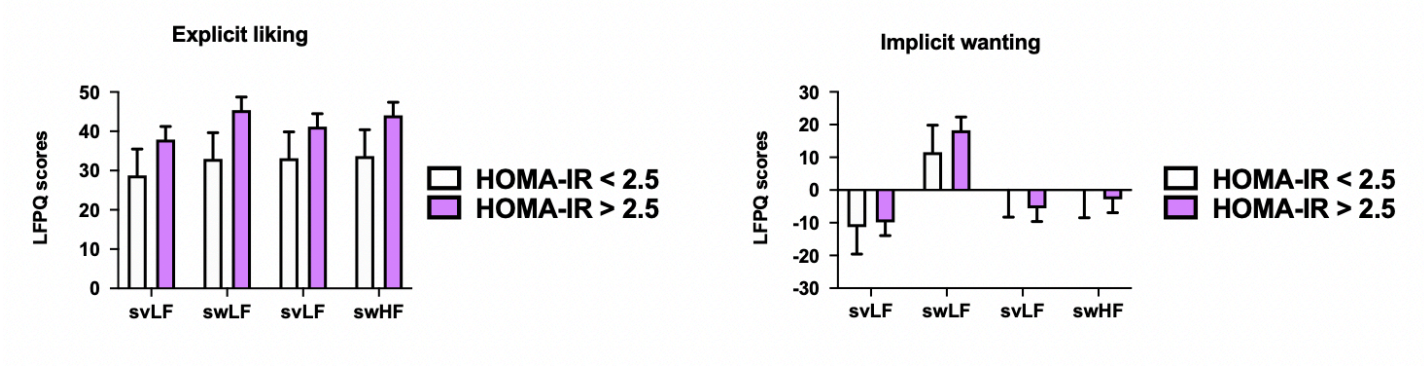


Figure 5.4 Explicit liking and implicit wanting scores from LFPQ in cohort A n=46

Comparison between participants of lower and higher HOMA-IR in explicit liking ad implicit wanting score for four food categories (savoury low-fat, sweet low-fat, savoury low-fat, sweet low-fat)

Abbreviations: LFPQ: Leeds food preference questionnaire, HOMA-IR: homeostasis model of assessment-insulin resistance, svLF: savoury low-fat food, swLF: sweet low-fat food, svLF: savoury low-fat, swHF: sweet high-fat food

5.4.5 Taste ratings

Pleasantness

Cohort A (pre-RYGB/EB) **n=45**: for pleasantness taste ratings, there was a significant interaction effect for group*sweet*fat content [F(2,134.49)=6.66, P=0.002] in mixed model RMANOVA analysis. Further post-hoc analysis showed a higher rating for sweet LF (yogurt) in HOMA-IR above 2.5 compared HOMA-IR below 2.5 group **Table 5.13 and 5.14 Figure 5.5-A**

cohort B (nOB/OB) **n=76***:* for pleasantness and tastiness ratings, there was not a significant difference between participants with HOMA-IR below 2.5 and HOMA-IR above 2.5 in Mann-whitney test **Table 5.15**

cohort C (OB) **n=24** for pleasantness taste ratings, there was a significant interaction effect for group*sweet*fat content [F(2,96)=4.55, P=0.013] in mixed model RMANOVA analysis. Further post-hoc analysis did not show a significant difference between groups, but rather higher ratings for sweet HF (ice-cream) compared to sweet LF (yogurt) within groups **Table 5.13 and 5.14 Figure 4.5-B**

Creaminess

Cohort A (pre-RYGB/EB) **n=46**: for creaminess taste ratings, there was a significant interaction effect forgroup*sweet*fat content [F(2,138)=33.97, P<0.001 in mixed model RMANOVA analysis. Further post-hoc analysis did not show a significant difference between groups, but rather higher ratings for savoury HF (chicken of cream soup) compared to savoury LF (chicken broth soup), and sweet LF (yogurt) compared savoury LF (chicken broth soup) within groups **Table 5.13 Figure 5.5-A**.

Similarly in *cohort C (OB)* **n=24** for creaminess taste ratings, there was a significant interaction effect for group*sweet*fat content [F(2,72)=10.71, P<0.001] in mixed model RMANOVA analysis. Further post-hoc analysis did not show a significant difference between groups, but rather higher ratings for savoury HF (chicken of cream soup) compared to savoury LF (chicken broth soup), and sweet LF (yogurt) compared to savoury LF (chicken broth soup) within groups **Table 5.13 Figure 5.5-B**.

Ideal creaminess

Cohort A (pre-RYGB/EB) **n=46**: for ideal creaminess taste ratings, there was a significant interaction effect for group*sweet*fat content [F(1,138)=14.08, P<0.001] in mixed model RMANOVA analysis. Further post-hoc analysis did not show a significant difference between groups, but rather higher ratings for savoury HF (chicken of cream soup) compared to savoury LF (chicken broth soup), and sweet LF (yogurt) compared to savoury LF (chicken broth soup) within groups **Table 5.13 Figure 5.5-A**

cohort C (OB) **n=24** for ideal creaminess taste ratings, there was a significant interaction effect for group*sweet*fat content [F(2,72)=6.11, P=0.004] in mixed model RMANOVA analysis. Further post-hoc analysis did not show a significant difference between groups, but rather higher ratings for savoury HF (chicken of cream soup) compared to savoury LF (chicken broth soup), and sweet LF (yogurt) compared to savoury LF (chicken broth soup) within groups **Table 5.13 Figure 5.5-B**

Sweetness

Cohort A (pre-RYGB/EB) **n=45**: for sweetness taste ratings, there was a significant interaction effect for group*fat content [F(2,45)=96.62, P<0.001] in mixed model RMANOVA analysis. Further post-hoc analysis did not show a significant difference between groups, but rather differences in ratings for sweet HF (ice-cream) compared to sweet LF (yogurt) within groups **Table 5.13 and 5.14 Figure 5.5-A**

cohort C (OB) **n=24** : for sweetness taste ratings, there was a significant interaction effect for group*fat content [F(2,48)=10.17, P<0.001] in mixed model RMANOVA analysis. Further post-hoc analysis showed a higher ratings for sweet HF (ice-cream) in participants with participants with HOMA-IR below 2.5 compared to participants with HOMA-IR above 2.5 **Table 5.13 and 5.14 Figure 5.5-B**

Ideal sweetness

Cohort A (pre-RYGB/EB) **n=45**: for ideal sweetness taste ratings, there was a significant interaction effect for group*sweet content [F(2,45)=51.16, P<0.001] in mixed model

RMANOVA analysis. Further post-hoc analysis showed higher ratings for sweet LF (yogurt) in participants with HOMA-IR above 2.5 compared to participants with HOMA-IR below 2.5 group **Table 5.13 and 5.14 Figure 5.5-A**

cohort C (OB) **n=24** for ideal sweetness taste ratings, there was a significant interaction effect for group*sweet content [$F(2,24)=9.19$, $P<0.001$] in mixed model RMANOVA analysis. Further post-hoc analysis did not show a significant difference between groups, but rather differences in ratings for sweet HF (ice-cream) compared to sweet LF (yogurt) within participants with HOMA-IR below 2.5 **Table 5.13 and 5.14 Figure 5.5-B**

Spearman's correlation between HOMA-IR levels and taste ratings: creaminess, ideal creaminess, pleasantness, sweetness, and ideal sweetness revealed positive correlation between HOMA-IR and sweet LF (yogurt) creaminess, pleasantness, and sweetness in *cohort A* only, but no significant correlation seen in *cohort B and cohort C* **Table 5.16**

		Cohort A *(pre-RYGB/EB)* n=46		Cohort C *(OB)* n=24	
Taste ratings	**Interaction**	**(df) F**	**P**	**(df) F**	**P**
Pleasantness[#]	group*sugar*fat	(2,134.49) 6.66	0.002	(2,96) 4.55	**0.013**[*]
	group*sugar	(1,134.37) 3.24	0.08	(1,96) 4.09	**0.046**[*]
	group*fat	(2,134.49) 5.79	0.004	(2,96) 1.40	0.25
	group	(1, 44.996) 0.74	0.39	(1,96) 0.08	0.78
	HOMA-IR *sugar*fat	(1,134.67) 2.77	0.10	(1,96) 4.78	**0.03**[*]
	HOMA-IR *sugar	(1,134.36) 1.27	0.26	(1,96) 2.22	0.14
	HOMA-IR*fat	(1,134.67) 6.09	**0.015**[***]	(1,96) 1.00	0.32
	HOMA-IR	(1,44.93) 3.10	0.41	(1,96) 0.20	0.66
Creaminess	group*sugar*fat	(2,138) 33.97	**<0.001**[****]	(2,72) 10.71	**<0.001**[****]
	group*sugar	(1,138) 0.05	0.83	(1,72) 0.16	0.691
	group*fat	(2,138) 58.39	**<0.001**[****]	(2,72) 54.07	**<0.001**[****]
	group	(1,46) 1.20	0.28	(1,24) 0.77	0.39
	HOMA-IR *sugar*fat	(1,135) 52.73	**<0.001**[****]	(1,96) 5.64	**0.02**[**]
	HOMA-IR *sugar	(1,135) 4.22	**0.042**[*]	(1,96) 0.06	0.81
	HOMA-IR*fat	(1,135) 64.55	**<0.001**[****]	(1,96) 23.61	**<0.001**[****]
	HOMA-IR	(1,45) 6.53	**0.014**[**]	(1,96) 0.94	0.33
Ideal creaminess	group*sugar*fat	(1,138) 14.08	**<0.001**[****]	(2,72) 6.11	0.004[***]
	group*sugar	(1,138) 0.12	0.73	(1,72) 0.64	0.43
	group*fat	(2,138) 16.24	**<0.001**[****]	(2,72) 12.19	**<0.001**[****]
	group	(1,46) 0.13	0.72	(1,24) 0.15	0.70
	HOMA-IR *sugar*fat	(1,135) 18.39	**<0.001**[****]	(1,96) 4.88	**0.03**[*]
	HOMA-IR *sugar	(1,135) 0.18	0.68	(1,96) 0.21	0.65
	HOMA-IR*fat	(1,135) 25.42	**<0.001**[****]	(1,96) 11.48	**<0.001**[****]
	HOMA-IR	(1,45) 0.11	0.75	(1,96) 0.56	0.46
Sweetness	group*fat	(2,45) 96.62	**<0.001**[****]	(2,48) 10.17	**<0.001**[****]

	group	(1,45) 0.90	0.35	(1,48) 0.92	0.34
	HOMA-IR*fat	(1,90) 128.40	**<0.001******	(1,48) 4.10	**0.05***
	HOMA-IR	(1,90) 6.41	**0.013****	(1,48) 1.09	0.30
Ideal sweetness	group*fat	(2,45) 51.16	**<0.001******	(2,24) 9.19	**0.001*****
	group	(1,45) 5.79	**0.02*****	(1,24) 0.27	0.61
	HOMA-IR*fat	(1,90) 43.59	**<0.001******	(1,48) 3.69	0.06
	HOMA-IR	(1,90) 1.27	0.26	(1,48) 0.67	0.42

Table 5.13 Mixed model RMANOVA for effect of HOMA-IR (categorical HOMA-IR>2.5 vs. HOMA-IR<2.5, and continuous HOMA-IR levels) and on taste ratings. Cohort A (n=46), and cohort C (n=24)
Results from mixed model RMANOVA for taste ratings, including: creaminess, ideal creaminess, pleasantness, sweetness, and ideal sweetness for group (HOMA-IR>2.5 vs. HOMA-IR<2.5) as between-subject factor, and and sugar (sweet and savoury) and fat (high fat and low fat) content as within subject factors, $^{\#}$n=45.Significant results in bold **P<0.01, ***P<0.001.
Abbreviations: HOMA-IR: homeostasis model of assessment-insulin resistance

		Cohort A *(pre-RYGB/EB)* ***n=46***						Cohort C *(OB)* ***n=24***					
Taste ratings	**Interaction**	Mean ± SEM	95% confidence interval		df	F	P	Mean ± SEM	95% confidence interval		df	F	P
			upper	**lower**					upper	lower			
Pleasantness	Savoury: LF HOMA-IR>2.5 vs. HOMA-IR<2.5	-3.56 ± 7.28	**-17.93**	10.82	(1,173.91)	0.24	0.63	8.38 ± 8.18	**-7.86**	24.61	(1,96)	1.05	0.31
	Savoury: HF HOMA-IR>2.5 vs. HOMA-IR<2.5	-1.74 ± 7.28	**-16.11**	12.64	(1,173.91)	0.06	0.81	10.50 ± 8.18	**-5.73**	26.73	(1,96)	1.65	0.20
	Sweet: LF: HOMA-IR>2.5 vs. HOMA-IR<2.5	20.71 ± 7.30	**6.30**	35.12	(1,173.91)	8.05	**0.005****	-8.63 ± 8.18	**-24.86**	7.61	(1,96)	1.11	0.29
	Sweet: HF: HOMA-IR>2.5 vs. HOMA-IR<2.5	-1.11 ± 7.28	**-15.48**	13.27	(1,173.91)	0.02	0.88	-5.56 ± 8.18	**-21.80**	10.67	(1,96)	0.46	0.50
	HOMA-IR<2.5: Savoury: HF vs LF	-1.88 ± 8.86	**-19.40**	15.65	(1,134.30)	0.05	0.83	-6.00 ± 6.677	**-19.25**	7.25	(1,96)	0.81	0.371
	HOMA-IR<2.5: Sweet: HF vs LF	34.63 ± 8.86	**17.10**	52.15	(1,134.30)	15.27	**<0.001****	16.94 ± 6.68	**3.68**	30.19	(1,96)	6.43	**0.013**
	HOMA-IR>2.5: Savoury: HF vs LF	-0.05 ± 4.12	**-8.20**	8.10	(1,134.30)	0	0.99	-3.88 ± 9.44	**-22.62**	14.87	(1,96)	0.17	0.68
	HOMA-IR>2.5: Sweet: HF vs LF	12.81 ± 4.12	**4.60**	21.019	(1,135.05)	9.52	**0.002**	20.00 ± 9.44	**1.26**	38.74	(1,96)	4.49	**0.037**
	HOMA-IR<2.5: LF: sweet vs savoury	-28.75 ± 8.86	**-46.28**	-11.22	(1,134.30)	10.53	**0.001**	-1.75 ± 6.68	**-15.00**	11.50	(1,96)	0.07	0.79
	HOMA-IR<2.5: HF: sweet vs savoury	7.75 ± 8.86	**-9.78**	25.28	(1,134.30)	0.77	0.38	21.19 ± 6.68	**7.93**	34.44	(1,96)	10.0	**0.002**
	HOMA-IR>2.5: LF: sweet vs savoury	-4.48 ± 4.151	**-12.69**	3.73	(1,135.05)	1.17	0.28	-18.75 ± 9.44	**-37.49**	-0.01	(1,96)	3.94	**0.05**
	HOMA-IR>2.5: HF: sweet vs savoury	8.38 ± 4.151	**0.23**	16.53	(1,134.30)	4.13	**0.044**	5.13 ± 9.44	**-13.62**	23.87	(1,96)	0.30	0.59
Creaminess	Savoury: LF HOMA-IR>2.5 vs. HOMA-IR<2.5	0.69 ± 6.63	-12.41	13.79	(1,148.54)	0.01	0.92	6.00 ± 7.69	-9.28	21.28	(1,92.94)	0.61	0.44

	Savoury: HF HOMA-IR>2.5 vs. HOMA-IR<2.5	7.92 ± 6.63	-5.18	21.02	(1,148.54)	1.43	0.23	-10.81 ± 7.69	-26.09	4.47	(1,92.94)	1.98	0.16
	Sweet: LF: HOMA-IR>2.5 vs. HOMA-IR<2.5	9.15 ± 6.63	-3.95	22.25	(1,148.54)	1.91	0.17	-1.31 ± 7.69	-16.59	13.97	(1,92.94)	0.03	0.87
	Sweet: HF: HOMA-IR>2.5 vs. HOMA-IR<2.5	1.95 ± 6.63	-11.16	15.05	(1,148.54)	0.09	0.77	-9.31 ± 7.69	-24.59	5.97	(1,92.94)	1.47	0.23
	HOMA-IR<2.5: Savoury: HF vs LF	34.38 ± 7.22	20.10	48.65	(1,138)	22.66	**<0.001******	56.56 ± 5.94	44.71	68.41	(1,72)	90.54	**<0.001******
	HOMA-IR<2.5: Sweet: HF vs LF	11.63 ± 7.22	-2.65	25.90	(1,138)	2.59	0.11	22.13 ± 5.94	10.28	33.98	(1,72)	13.85	**<0.001******
	HOMA-IR>2.5: Savoury: HF vs LF	41.61 ± 3.31	35.05	48.16	(1,138)	157.67	**<0.001******	39.75 ± 8.41	22.99	56.51	(1,72)	22.36	**<0.001******
	HOMA-IR>2.5: Sweet: HF vs LF	4.42 ± 3.31	-2.13	10.97	(1,138)	1.78	0.184	14.13 ± 8.41	-2.63	30.88	(1,72)	2.82	0.10
	HOMA-IR<2.5: LF: sweet vs savoury	28.8 ± 7.22	14.47	43.03	(1,138)	15.85	**<0.001******	33.31 ± 5.94	21.46	45.16	(1,72)	31.41	**<0.001******
	HOMA-IR<2.5: HF: sweet vs savoury	6.00 ± 7.22	-8.28	20.28	(1,138)	0.69	0.407	-1.13 ± 5.94	-12.98	10.73	(1,72)	0.04	0.85
	HOMA-IR>2.5: LF: sweet vs savoury	37.20 ± 3.31	30.66	43.76	(1,138)	126.12	**<0.001******	26.00 ± 8.41	9.24	42.76	(1,72)	9.57	**0.003****
	HOMA-IR>2.5: HF: sweet vs savoury	0.00 ± 3.31	-6.53	6.58	(1,138)	0	0.994	0.38 ± 8.41	-16.38	17.13	(1,72)	0.002	0.965
Ideal creaminess	Savoury: LF HOMA-IR>2.5 vs. HOMA-IR<2.5	2.91 ± 4.93	-6.82	12.63	(1,170.61)	0.35	0.56	1.38 ± 6.74	-12.01	14.76	(1,95.92)	0.04	0.84
	Savoury: HF HOMA-IR>2.5 vs. HOMA-IR<2.5	0.78 ± 4.93	-8.95	10.50	(1,170.61)	0.03	0.88	-4.06 ± 6.74	-17.45	9.32	(1,95.92)	0.36	0.55
	Sweet: LF: HOMA-IR>2.5 vs. HOMA-IR<2.5	2.28 ± 4.93	-7.45	12.00	(1,170.61)	0.21	0.65	1.00 ± 6.74	-12.39	14.39	(1,95.92)	0.02	0.88
	Sweet: HF: HOMA-IR>2.5 vs. HOMA-IR<2.5	-1.68 ± 4.93	-11.40	8.05	(1,170.61)	0.12	0.73	7.00 ± 6.74	-6.39	20.39	(1,95.92)	1.08	0.30
	HOMA-IR<2.5: Savoury: HF vs LF	20.50 ± 5.80	9.04	31.96	(1,138)	12.51	**0.001*****	28.062 ± 5.46	17.18	38.95	(1,72)	26.42	**<0.001******
	HOMA-IR<2.5: Sweet: HF vs LF	3.88 ± 5.30	-7.59	15.34	(1,138)	0.45	0.51	2.875 ± 5.46	-8.01	13.76	(1,72)	0.28	0.6

	HOMA-IR>2.5: Savoury: HF vs LF	18.37 ± 2.66	13.11	23.63	(1,138)	47.70	**<0.001******	22.625 ± 7.72	7.23	38.02	(1,72)	8.59	**0.005****
	HOMA-IR>2.5: Sweet: HF vs LF	-0.08 ± 2.66	-5.34	5.18	(1,138)	0.001	0.98	8.875 ± 7.72	-6.52	24.27	(1,72)	1.32	0.25
	HOMA-IR<2.5: LF: sweet vs savoury	15.00 ± 5.80	3.54	26.462	(1,138)	6.70	**0.011**	19.625 ± 5.46	8.74	30.51	(1,72)	12.92	**0.001*****
	HOMA-IR<2.5: HF: sweet vs savoury	-1.63 ± 5.80	-13.09	9.837	(1,138)	0.08	0.78	-5.563 ± 5.46	-16.45	5.32	(1,72)	1.04	0.31
	HOMA-IR>2.5: LF: sweet vs savoury	14.37 ± 2.66	9.11	19.627	(1,138)	29.18	**<0.001******	19.250 ± 7.72	3.86	34.64	(1,72)	6.22	**0.015****
	HOMA-IR>2.5: HF: sweet vs savoury	-4.08 ± 2.66	-9.34	1.18	(1,138)	2.35	0.13	5.5 ± 7.72	-9.89	20.89	(1,72)	0.51	0.48
Sweetness	LF: HOMA-IR>2.5 vs. HOMA-IR<2.5	5.98 ± 5.36	-4.68	16.632	(1,89.40)	1.24	0.27	6.44 ± 8.89	-11.43	24.31	(1,46.71)	0.53	0.47
	HF: HOMA-IR>2.5 vs. HOMA-IR<2.5	1.51 ± 5.36	-9.15	12.166	(1,89.40)	0.08	0.78	-18.50 ± 8.89	-36.37	-0.63	(1,46.71)	4.33	**0.043***
	HOMA-IR<2.5: HF vs LF	42.25 ± 6.59	28.98	55.519	(1,45)	41.13	**<0.001******	32.31 ± 7.26	17.72	46.90	(1,24)	19.83	**<0.001******
	HOMA-IR<2.5: HF vs LF	37.78 ± 3.06	31.61	43.954	(1,45)	152.12	**<0.001******	7.38 ± 10.26	-13.26	28.01	(1,24)	0.52	0.48
Ideal sweetness	LF: HOMA-IR>2.5 vs. HOMA-IR<2.5	13.87 ± 4.90	4.12	23.609	(1,87.66)	7.70	**0.006*****	7.00 ± 5.71	-4.48	18.48	(1,46.71)	1.50	0.23
	HF: HOMA-IR>2.5 vs. HOMA-IR<2.5	4.13 ± 4.90	-5.62	13.873	(1,87.66)	0.71	0.40	-2.5 ± 5.71	-13.98	8.98	(1,46.71)	0.19	0.66
	HOMA-IR<2.5: HF vs LF	32.25 ± 5.75	20.67	43.833	(1,45)	31.45	**<0.001******	17.38 ± 4.26	8.59	26.16	(1,24)	16.67	**<0.001******
	HOMA-IR<2.5: HF vs LF	22.51 ± 2.67	17.13	27.9	(1,45)	70.88	**<0.001******	7.88 ± 4.26	-4.55	20.30	(1,24)	1.71	0.20

Table 5.14 Post-hoc analysis for effect of HOMA-IR group on taste ratings. Cohort A (n=46), and cohort C (n=24)

Results from mixed model RMANOVA for taste ratings, including: creaminess, ideal creaminess, pleasantness, sweetness, and ideal sweetness for group (HOMA-IR<2.5 vs. HOMA-IR>2.5) as between-subject factor, and and sugar (sweet and savoury) and fat (high fat and low fat) content as within subject factors. Significant results in bold **P<0.01, ***P<0.001

Abbreviations: HOMA-IR: homeostasis model of assessment-insulin resistance, LF: low-fat, HF: high-fat

		Cohort B *(nOB/OB)* n=76		
		Mean rank	**Test statistic**	**P**
Tastiness	HOMA-IR <2.5	38.93	273.00	0.65
	HOMA-IR >2.5	35.33		
Pleasantness	HOMA-IR <2.5	39.42	240.00	0.32
	HOMA-IR >2.5	31.67		

Table 5.15 Mann-Whitney test for effect of HOMA-IR>2.5 group on taste ratings for cohort B (n=76)
Results from Mann-Whitney for taste ratings, including: tastiness and pleasantness for group (HOMA-IR<2.5 vs. HOMA-IR>2.5).

		Cohort A *(pre-RYGB/EB)*		***Cohort B*** *(nOB/OB)*		***Cohort C*** *(OB)*	
Taste category	**Food category**	**r**	**P**	**r**	**P**	**r**	**P**
Creaminess	chicken broth soup *Savoury low-fat*	-0.21	0.16	-	-	-0.19	0.38
	chicken cream soup Savoury high-fat	-0.16	0.27	-	-	-0.19	0.37
	yogurt Sweet low-fat	0.01	0.93	-	-	-0.24	0.26
	ice-cream *Sweet high-fat*	0.01	0.95	-	-	0.18	0.40
Ideal creaminess	chicken broth soup *Savoury low-fat*	-0.32	**0.029***	-	-	-0.24	0.26
	chicken cream soup Savoury high-fat	0.07	0.65	-	-	0.31	0.14
	yogurt Sweet low-fat	-0.12	0.43	-	-	-0.21	0.33
	ice-cream *Sweet high-fat*	-0.25	0.10	-	-	0.38	0.07
Pleasantness	chicken broth soup *Savoury low-fat*	-0.12	0.42	-0.12	0.31	0.06	0.78
	chicken cream soup Savoury high-fat	-0.12	0.43	-	-	-0.05	0.81
	yogurt Sweet low-fat	-0.11	0.49	-	-	0.14	0.50
	ice-cream *Sweet high-fat*	0.20	0.19	-	-	0.08	0.73
Sweetness	*yogurt Sweet low-fat*	0.06	0.67	-	-	-0.13	0.55
	ice-cream *Sweet high-fat*	-0.02	0.89	-	-	0.09	0.67
Ideal sweetness	*yogurt Sweet low-fat*	-0.08	0.62	-	-	0.09	0.67
	ice-cream *Sweet high-fat*	-0.19	0.20	-	-	0.15	0.48
Tasty[a]				-0.1	0.39		

Table 5.16 Spearman's correlation between HOMA-IR levels and taste ratings in all cohorts

Spearman's correlations between HOMA-IR levels and taste ratings including creaminess, ideal creaminess, pleasantness, sweetness, ideal sweetness. Data presented as r Spearman correlation coefficient, *P<0.05, **P<0.01,***P<0.001. [a] taste rating in cohort B included pleasantness and tastiness for one savoury dish for *ad libitum meal*

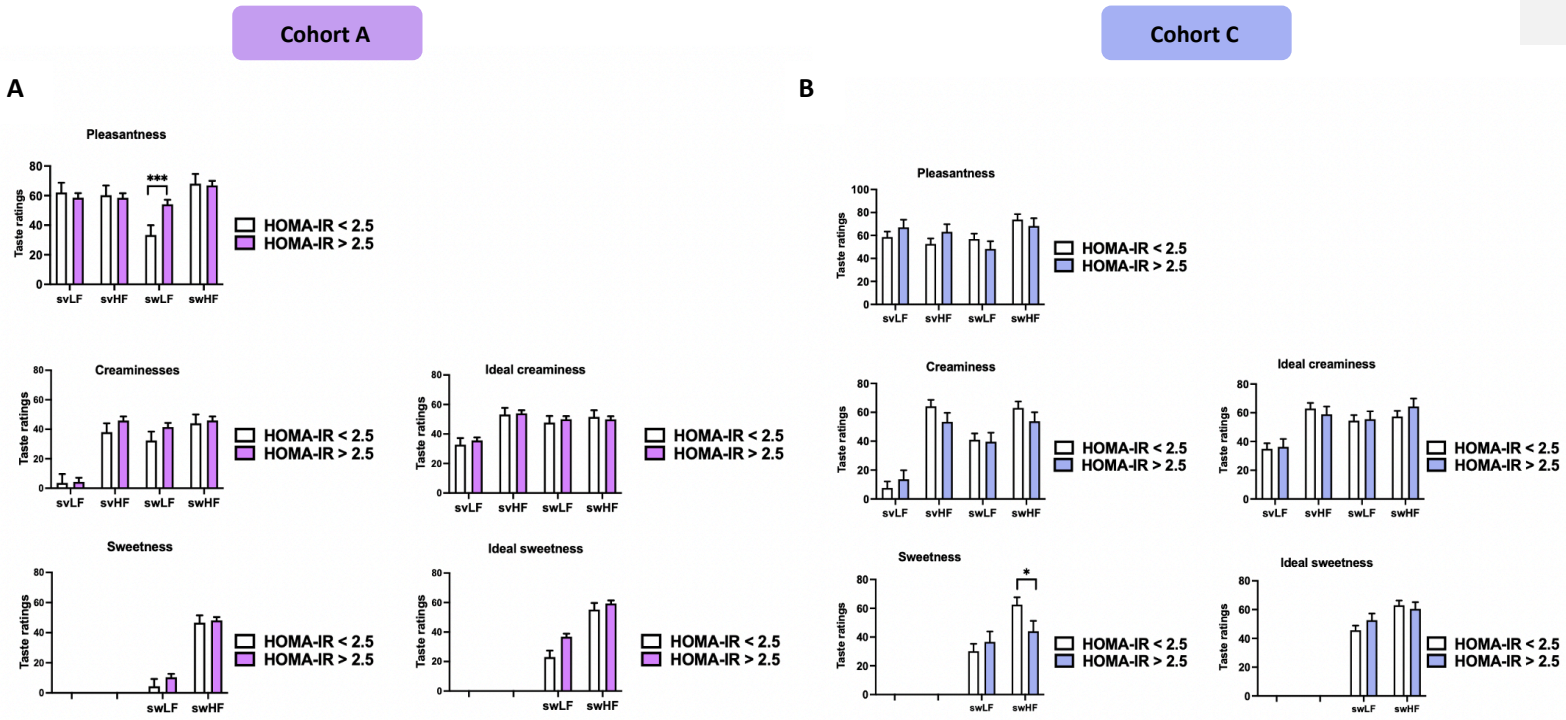


Figure 5.5 Taste rating scores in cohort A (n=46) and cohort C (n=24)
Comparison between HOMA-IR>2.5 groups in taste ratings, including: pleasantness, creaminess, ideal creaminess, sweetness, and ideal sweetness) for four dishes (svLF: chicken broth soup, svHF: chicken cream soup, swLF: yogurt, swHF: ice-cream). Data presented as mean ± SEM. Statistics from mixed model repeated measures ANOVA, with sweet and fat content as within subject factors: post-hoc test *P<0.05, P<0.01,***P<0.005, ****P<0.0001.
Abbreviations: **HOM-IR:** homeostasis model of assessment-insulin resistance, **svLF:** savoury low-fat, **svHF:** savoury high-fat, **swLF**: sweet low-fat, **swHF:** sweet high-fat

5.4.6 ad libitum lunch and energy intake

Total energy in take (kcal):

Cohort A (pre-RYGB/EB) **n=46**: for total energy intake (kcal) from *ad libitum* meal, there was a significant interaction effect for group*sweet*fat content [F(2,138)=3.60, P=0.03] in mixed model RMANOVA analysis, Energy intake of sweet HF (ice-cream) was higher in HOMA-IR above 2.5 group compared to HOMA-IR below 2.5 (effect size mean ± SEM -137.13 ± 62.49 (95% CI -260.42, -13.83), P=0.03)**Table 5.17 and 5.18 Figure 5.6-A**

Cohort B (nOB/OB) **n=87***:* for total energy intake and % of REE kcal from *ad libitum* meal, there was not a significant difference between HOMAIR below 2.5 and HOMA-IR above 2.5 in Mann-whitney test **Table 5.19**

Cohort C (OB) **n=24**, for total energy intake (kcal) from *ad libitum* meal, there was not a significant interaction effect for group*sweet*fat content [F(2,72)=0.36, P=0.70] in mixed model RMANOVA analysis, allowing for analysis separately by sweet and fat categories. There was a significant interaction effect for group*fat content (independent of sweet category) [F(2,72)=20.05, P<0.001]. This was driven by a higher energy intake from HF (ice-cream and chicken cream soup) compared to LF foods (yogurt and chicken broth soup) (independent of sweet content) within both HOMA-IR below 2.5 (effect size mean ± SEM 226.51 ± 40.10 (95% CI 146.57306.45), P<0.001), and HOMA-IR above 2.5 (effect size mean ± SEM 162.43 ± 56.71 (95% CI 49.38, 275.49), P=0.005 **Table 5.17 and 5.18 Figure 5.6-A**

Percentage of REE

Cohort A (pre-RYGB/EB) **n=46**: for % of REE from *ad libitum* meal, there was a significant interaction effect for group*sweet*fat content [F(2,135)=4.36, P=0.015] in mixed model RMANOVA analysis. % of Further post-hoc analysis showed a higher intake of sweet HF (yogurt) in HOMA-IR above 2.5 group [effect size -18.01 ± 5.09 (95% CI -28.05,-7.96), P<0.001] compared to HOMA-IR below 2.5 group **Table 5.17 and 5.18 Figure 5.6-B**

cohort C (OB) **n=24**, for % of REE from *ad libitum* meal, there was not a significant interaction effect for group*sweet*fat content [F(2,72)=0.37, P=0.69] in mixed model RMANOVA

analysis, allowing for analysis separately by sweet and fat categories. There was a significant interaction effect for group*fat content (independent of sweet category) [F(2,72)=20.82, P<0.001]. This was driven by a higher energy intake from HF (ice-cream and chicken cream soup) (independent of sweet content) within both HOMA-IR below 2.5 (effect size mean ± SEM 12.27 ± 2.16 (95% CI 7.97, 16.57), P<0.001), and HOMA-IR above 2.5 (effect size mean ± SEM 9.31 ± 3.05 (95% CI 3.23, 15.39), P<0.001) **Table 5.17 and 5.18 Figure 5.6-B**

% of total kcal

Cohort A (pre-RYGB/EB) **n=46**: for percentage of total energy intake (kcal) from *ad libitum* meal, there was a significant interaction effect for group*sweet*fat content [F(1,184)=6.35, P=0.002] in mixed model RMANOVA analysis. Further post-hoc analysis showed higher % of total kcal of sweet HF (ice-cream) in participants with HOMA-IR above 2.5 group [effect size -15.72 ± 7.44 (95% CI -30.40,-1.04), P=0.04] compared to participants with HOMA-IR below 2.5 **Table 5.17 and 5.18 Figure 5.6-C**

Cohort C **n=24** for percentage of total energy intake (kcal) from *ad libitum* meal, there was not a significant interaction effect for group*sweet*fat content [F(2,96)=0.86, P=0.43] in mixed model RMANOVA analysis, allowing for analysis separately by sweet and fat categories. There was a significant interaction effect for group*fat content (independent of sweet category) [F(2,96)=20.36, P<0.001]. This was driven by a higher energy intake from HF (ice-cream and chicken cream soup) compared to LF foods (yogurt and chicken broth soup) (independent of sweet content) within both HOMA-IR below 2.5 (effect size mean ± SEM 21.95 ± 4.34 (95% CI 13.34, 30.56), P<0.001), and HOMA-IR above 2.5 (effect size mean ± SEM 23.83 ± 6.13 (95% CI 11.65, 36.00), P<0.001**Table 5.17 and 5.18 Figure 5.6-A**

Spearman's correlation between HOMA-IR levels and food intake: absolute energy intake, % REE, and % kcal revealed negative correlation between HOMA-IR and sweet HF (ice-cream) ideal creaminess in *cohort A* **Table 5.20**

		Cohort A *(pre-RYGB/EB)* n=46		Cohort C *(OB)* n=24	
Energy intake	**Interaction**	**(df) F**	**P**	**(df) F**	**P**
Total kcal	group*sugar*fat	(2,138) 3.60	**0.03***	(2,72) 0.36	0.70
	group*sugar	(1,138) 0.76	0.39	(1,72) 0.04	0.84
	group*fat	(2,138) 28.78	**<0.001******	(2,72) 20.05	**<0.001******
	group	(2,138) 0.21	0.65	(1,24) 1.93	0.18
	HOMA-IR *sugar*fat	(1,184) 0.70	0.41	(1,96) 1.54	0.22
	HOMA-IR *sugar	(1,184) 1.88	0.17	(1,96) 0.29	0.59
	HOMA-IR*fat	(1,184) 28.11	**<0.001******	(1,96) 15.10	**<0.001******
	HOMA-IR	(1,184) 3.11	0.08	(1,96) 0.21	0.65
% REE	group*sugar*fat	(2,135) 4.36	**0.015****	(2,72) 0.37	0.69
	group*sugar	(1,135) 1.16	0.28	(1,72) 0.01	0.92
	group*fat	(2,135) 25.61	**<0.001******	(2,72) 20.82	**<0.001******
	group	(1,45) 3.00	0.09	(1,24) 1.55	0.23
	HOMA-IR *sugar*fat	(1,135) 0.87	0.35	(1,96) 1.40	0.24
	HOMA-IR *sugar	(1,135) 1.32	0.25	(1,96) 0.31	0.58
	HOMA-IR*fat	(1,135) 19.49	**<0.001******	(1,96) 15.44	**<0.001******
	HOMA-IR	(1,45) 6.35	**0.02***	(1,96) 0.34	**0.56**
% kcal	group*sugar*fat	(1,184) 6.35	**0.002*****	(2,96) 0.86	0.43
	group*sugar	(1,184) 1.09	0.30	(1,96) 0.02	0.88
	group*fat	(2,184) 28.68	**<0.001******	(2,96) 20.36	**<0.001******
	group	(1,184) 0	1.00	(1,96) 0.00	1.00
	HOMA-IR *sugar*fat	(1,84) 2.60	0.11	(1,96) 1.74	0.19
	HOMA-IR *sugar	(1,184) 3.70	**0.056**	(1,96) 1.27	0.26
	HOMA-IR*fat	(1,184) 34.99	**<0.001******	(1,96) 20.75	**<0.001******
	HOMA-IR	(1,184) 0	1.00	(1,96) 0.00	1.00

Table 5.17 Mixed model RMANOVA for effect of HOMA-IR group (categorical and continuous) on energy intake from *ad libitum* meal. Cohort A (n=46), and Cohort C (n=24)

Results from mixed model RMANOVA for energy intake, including: absolute energy intake (kcal), percentage of estimated 24-hour resting energy expenditure (%kcal of REE), percentage of total meal energy intake (%kcal) for group (HOMA-IR>2.5 vs. HOMA-IR <2.5) as between-subject factor, and sugar

(sweet and savoury) and fat (high fat and low fat) content as within subject factors. Significant results in bold **P<0.01, ***P<0.001

		Cohort A *(pre-RYGB/EB)* n=46						Cohort C *(OB)* n=24					
Energy intake	**Post-hoc contrast**	Mean ± SEM	**95% CI**		df	F	P	Mean ± SEM	95% CI		df	F	P
			lower	**upper**					lower	upper			
Total kcal	Savoury: LF HOMA-IR>2.5 vs. HOMA-IR<2.5	1.45 ± 62.49	-121.85	124.75	(1, 183.48)	0.001	0.98	-16.60 ± 49.32 [a]	-114.93	81.72	(1,71.41)	0.11	0.74
	Savoury: HF HOMA-IR>2.5 vs. HOMA-IR<2.5	22.45 ± 62.49	-100.85	145.74	(1, 183.48)	0.13	0.72	-80.68 ± 49.32 [a]	-179.01	17.64	(1,71.41)	2.68	0.11
	Sweet: LF: HOMA-IR>2.5 vs. HOMA-IR<2.5	53.91 ± 62.49	-69.39	177.20	(1, 183.48)	0.74	0.39	-	-	-	-	-	-
	Sweet: HF: HOMA-IR>2.5 vs. HOMA-IR<2.5	-137.13 ± 62.49	-260.42	-13.83	(1, 183.48)	4.82	**0.03** **	-	-	-	-	-	-
	HOMA-IR<2.5: Savoury: HF vs LF	-48.00 ± 79.07	-204.35	108.36	(1,138)	0.37	0.55	226.51 ± 40.10 [a]	146.57	306.45	(1,72)	31.90	**<0.001** ****
	HOMA-IR<2.5: Sweet: HF vs LF	223.11 ± 79.07	66.76	379.47	(1,138)	7.96	**0.005** ***	-	-	-	-	-	-
	HOMA-IR>2.5: Savoury: HF vs LF	4.46 ± 36.28	-67.28	76.20	(1,138)	0.02	0.90	162.43 ± 56.71[a]	49.38	275.49	(1,72)	8.20	**0.005** ***
	HOMA-IR>2.5: Sweet: HF vs LF	63.54 ± 36.28	-8.20	135.29	(1,138)	3.07	0.08	-	-	-	-	-	-
	HOMA-IR<2.5: LF: sweet vs savoury	108.61 ± 79.07	-47.74	264.97	(1,138)	1.89	0.17	-	-	-	-	-	-
	HOMA-IR<2.5: HF: sweet vs savoury	379.73 ± 79.07	223.37	536.08	(1,138)	23.06	**<0.001** ****	-	-	-	-	-	-
	HOMA-IR>2.5: LF: sweet vs savoury	129.61 ± 36.28	57.87	201.35	(1,138)	12.76	**<0.001** ****	-	-	-	-	-	-
	HOMA-IR>2.5: HF: sweet vs savoury	188.69 ± 36.28	116.95	260.43	(1,138)	27.05	**<0.001** ****	-	-	-	-	-	-
% REE	Savoury: LF HOMA-IR>2.5 vs. HOMA-IR<2.5	-1.98 ± 5.09	-12.03	8.06	(1,175.60)	0.15	0.70	-0.89 ± 2.67 [a]	-6.217	4.43	(1,70.53)	0.11	0.74
	Savoury: HF HOMA-IR>2.5 vs. HOMA-IR<2.5	-2.75 ± 5.09	-12.79	7.30	(1,175.60)	0.29	0.59	-3.85 ± 2.67 [a]	-9.177	1.47	(1,70.53)	2.08	0.15

	Sweet: LF: HOMA-IR>2.5 vs. HOMA-IR<2.5	-4.33 ± 5.09	-7.21	12.88	(1,175.60)	0.31	0.58	-	-	-	-	-	-
	Sweet: HF: HOMA-IR>2.5 vs. HOMA-IR<2.5	20.04 ± 5.09	-28.05	-7.96	(1,175.60)	12.52	**<0.001******	-	-	-	-	-	-
	HOMA-IR<2.5: Savoury: HF vs LF	8.90 ± 6.30	-3.57	21.36	(1,135)	1.99	0.16	12.27 ± 2.16 [a]	7.97	16.57	(1,72)	32.34	**<0.001******
	HOMA-IR<2.5: Sweet: HF vs LF	33.26 ± 6.30	20.80	45.73	(1,135)	27.84	**<0.001******	-	-	-	-	-	-
	HOMA-IR>2.5: Savoury: HF vs LF	8.13 ± 2.71	2.78	13.48	(1,135)	9.03	**0.003****	9.31 ± 3.05 [a]	3.23	15.39	(1,72)	9.31	**0.003****
	HOMA-IR>2.5: Sweet: HF vs LF	12.42 ± 2.71	7.07	17.77	(1,135)	21.08	**<0.001******	-	-	-	-	-	-
	HOMA-IR<2.5: LF: sweet vs savoury	-4.33 ± 6.30	-16.80	8.14	(1,135)	0.47	0.49	-	-	-	-	-	-
	HOMA-IR<2.5: HF: sweet vs savoury	20.04 ± 6.30	7.57	32.50	(1,135)	10.10	**0.002*****	-	-	-	-	-	-
	HOMA-IR>2.5: LF: sweet vs savoury	0.49 ± 2.71	-4.87	5.84	(1,135)	0.47	0.86	-	-	-	-	-	-
	HOMA-IR>2.5: HF: sweet vs savoury	4.78 ± 2.71	-0.57	10.13	(1,135)	10.10	0.08	-	-	-	-	-	-
% kcal	Savoury: LF HOMA-IR>2.5 vs. HOMA-IR<2.5	0.30 ± 7.44	-14.38	14.97	(1,184)	0.002	0.97	-0.94 ± 5.31 [a]	-11.48	9.60	(1,96)	0.03	0.86
	Savoury: HF HOMA-IR>2.5 vs. HOMA-IR<2.5	7.47 ± 7.44	-7.21	22.15	(1,184)	1.00	0.32	-0.94 ± 5.31 [a]	-9.60	11.48	(1,96)	0.03	0.86
	Sweet: LF: HOMA-IR>2.5 vs. HOMA-IR<2.5	7.94 ± 7.44	-6.736	22.617	1.14	1,184	0.29	-	-	-	-	-	-
	Sweet: HF: HOMA-IR>2.5 vs. HOMA-IR<2.5	-15.72 ± 7.44	-30.396	-1.043	4.47	1,184	**0.04***	-	-	-	-	-	-
	HOMA-IR<2.5: Savoury: HF vs LF	7.03 ± 9.56	-11.839	25.891	0.54	1,184	0.46	21.95 ± 4.34 [a]	13.34	30.56	(1,96)	25.62	**<0.001******
	HOMA-IR<2.5: Sweet: HF vs LF	48.85 ± 9.56	29.98	67.71	26.10	1,184	**<0.001******	-	-	-	-	-	-
	HOMA-IR>2.5: Savoury: HF vs LF	14.20 ± 4.39	5.54	22.86	10.48	1,184	**0.001**	23.83 ± 6.13 [a]	11.65	36.00	(1,96)	15.10	**<0.001******
	HOMA-IR>2.5: Sweet: HF vs LF	25.19 ± 4.39	16.53	33.84	32.96	1,184	**<0.001******	-	-	-	-	-	-

	HOMA-IR<2.5: LF: sweet vs savoury	-10.07 ± 9.59	-28.93	8.80	(1,184)	1.11	0.29	-	-	-	-	-	-
	HOMA-IR<2.5: HF: sweet vs savoury	31.75 ± 9.59	12.89	50.62	(1,184)	11.03	**0.001*****	-	-	-	-	-	-
	HOMA-IR>2.5: LF: sweet vs savoury	-2.42 ± 9.59	-11.08	6.23	(1,184)	0.31	0.58	-	-	-	-	-	-
	HOMA-IR>2.5: HF: sweet vs savoury	8.56 ± 9.59	-0.09	17.22	(1,184)	3.81	**0.05***	-	-	-	-	-	-

Table 5.18 Post-hoc analysis for effect of HOMA-IR on energy intake from *ad libitum* meal. Cohort A (n=47), and cohort C (n=24)

Results from mixed model RMANOVA for food intake, including: including: absolute energy intake (kcal), percentage of estimated 24-hour resting energy expenditure (%kcal of REE), percentage of total meal energy intake (%kcal) for group (HOMA-IR>2.5 vs. HOMA-IR<2.5) as between-subject factor, and and sugar (sweet and savoury) and fat (high fat and low fat) content as within subject factors. [a] in cohort C: group*sugar*fat interaction did not reach significance, hence post-hoc contrasts were reported for group*fat interaction independent of sweet, post-hoc contrasts are: LF: HOMA-IR>2.5 vs. HOMA-IR<2.5and HF: HOMA-IR>2.5 vs. HOMA-IR<2.5, HOMA-IR<2.5: HF vs. LF, HOMA-IR>2.5: HF vs. LF, respectively, Significant results in bold **P<0.01, ***P<0.001. **Abbreviations: df:** degrees of freedom, **CI:** confidence intervals. **LF:** low-fat, **HF:** high-fat

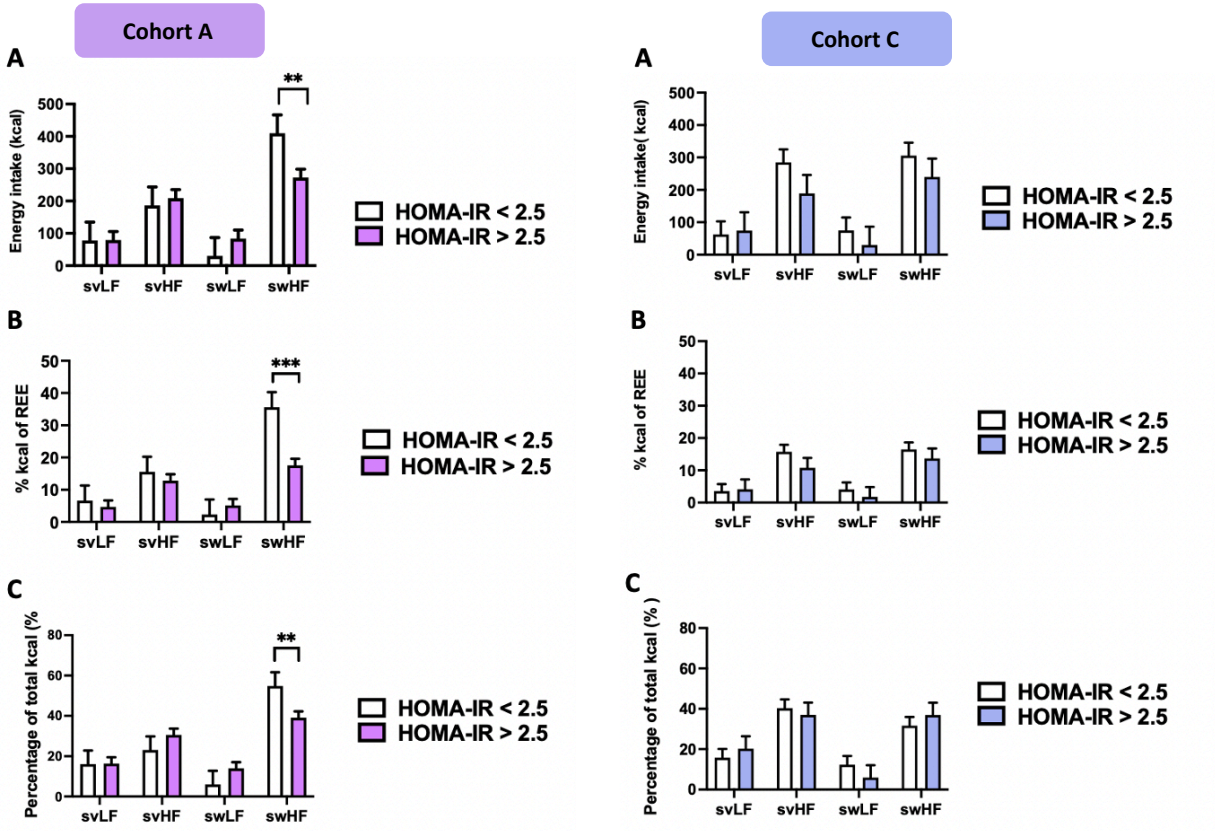


Figure 5.6 Energy intake in cohort A (n=47) and cohort C (n=24)

Comparison between HOMA-IR>2.5 and HOMA-IR<2.5 groups in energy intake, including: (A) absolute energy intake (kcal), (B) percentage of estimated 24-hour resting energy expenditure (REE), (C) percentage of total meal energy intake for four dishes (svLF: chicken broth soup, svHF: chicken cream soup, swLF: yogurt, swHF: ice-cream). Data presented as mean ± SEM. Statistics from mixed model repeated measures ANOVA, with sweet and fat content as within subject factors: post-hoc test *P<0.05, P<0.01,***P<0.005, ****P<0.0001.

Abbreviations: svLF: savoury low-fat, **svHF:** savoury high-fat, **swLF:** sweet low-fat, **swHF:** sweet high-fat

		Cohort B *(nOB/OB)* n=76		
		Mean rank	**Test statistic**	**P**
Total kcal	HOMA-IR <2.5	39.0	267.0	0.58
	HOMA-IR >2.5	34.7		
% REE kcal	HOMA-IR <2.5	39.5	233.0	0.27
	HOMA-IR >2.5	30.9		

Table 5.19 Mann-Whitney test for effect of HOMA-IR>2.5 group on energy intake in cohort B (n=76)
Results from Mann-Whitney for food intake including absolute energy intake (kcal), percentage of estimated 24-hour resting energy expenditure (%kcal of REE) for groups (HOMA-IR>2.5 vs. HOMA-IR<2.5)

		Cohort A (pre-RYGB/EB)		Cohort B (nOB/OB)		Cohort C (OB)	
Energy intake	**Food category**	**r**	**P**	**r**	**P**	**r**	**P**
Absolute energy intake	chicken broth soup *Savoury low-fat*	-0.04	0.81	-0.19[a]	0.11	0.13	0.55
	chicken cream soup Savoury high-fat	0.03	0.83	-	-	-0.14	0.51
	yogurt Sweet low-fat	0.07	0.63	-	-	0.15	0.49
	ice-cream *Sweet high-fat*	-0.33	**0.026**[*]	-	-	-0.12	0.57
% REE	chicken broth soup *Savoury low-fat*	-0.14	0.36	-0.30[a]	0.01	0.11	0.60
	chicken cream soup Savoury high-fat	-0.03	0.84	-	-	-0.16	0.44
	yogurt Sweet low-fat	0.02	0.91	-	-	0.13	0.55
	ice-cream *Sweet high-fat*	-0.42	**0.004**[**]	-	-	-0.13	0.54
% kcal	chicken broth soup *Savoury low-fat*	0.03	0.84	-	-	-	-
	chicken cream soup Savoury high-fat	0.18	0.23	-	-	-	-
	yogurt Sweet low-fat	0.16	0.28	-	-	-	-
	ice-cream *Sweet high-fat*	-0.27	0.07	-	-	-	-

Table 5.20 Spearman's correlation between HOMA-IR levels and energy intake in all cohorts
Spearman's correlations between HOMA-IR levels and energy intake, including: absolute energy intake (kcal), percentage of estimated 24-hour resting energy expenditure (%kcal of REE), percentage of total meal energy intake (%kcal). Data presented as r Spearman correlation coefficient, *P<0.05, **P<0.01,***P<0.001. [a] cohort B was offered one savoury dish

5.4.7 Progressive ratio task and appetite ratings

For total number of completed clicks and breakpoint (last completed click to earn an M&M), there were no difference between participants with HOMA-IR above 2.5 and HOMA-IR below 2.5 in *cohort A and cohort C* **Table 5.21**

Moreover, there was no difference in appetite ratings (hunger and fullness), measured by visual analogue scales, between participants with HOMA-IR above 2.5 and HOMA-IR below 2.5 in *cohort A and cohort C* **Table 5.22**

	Cohort A *(pre-RYGB/EB)* **n=47**				**Cohort C** *(OB)* **n=23**			
	HOMA-IR<2.5	**HOMA-IR>2.5**	**test statistic**	**P**	***HOMA-IR<2.5***	**HOMA-IR>2.5**	**test statistic**	**P**
Breakpoint	28.8	22.7	137.0	0.19	12.6	10.8	50.5	0.52
Total clicks	27.1	23.16	154.0	0.42	12.9	10.4	47.0	0.39

Table 5.21 Mann-Whitney test for effect of HOMA-IR>2.5 groups on progressive ratio task in cohort A(n=47) and cohort C (n=23)
Results from Mann-Whitney for progressive ratio task PRT including breakpoint and total clicks for groups (HOMA-IR>2.5 vs. HOMA-IR<2.5). Data presented as mean rank and test statistic

	Cohort A *(pre-RYGB/EB)* **n=48**				**Cohort B** *(nOB/OB)* **n=93**				**Cohort C** *(OB)* **n=24**			
Appetite ratings	***HOMA-IR<2.5***	**HOMA-IR>2.5**	**Test statistic**	**P**	***HOMA-IR<2.5***	**HOMA-IR>2.5**	**Test statistic**	**P**	***HOMA-IR<2.5***	**HOMA-IR>2.5**	**Test statistic**	**P**
Hunger	27.15	23.8	163.5	0.51	47.7	41.8	394.0	0.50	11.1	15.3	0.19	0.19
Fullness	21.3	25.3	222.0	0.43	45.6	57.8	570.0	0.15	13.7	10.1	0.26	0.26

Table 5.22 Mann-Whitney test for effect on HOMA-IR>2.5 group on appetite ratings

5.4.8 Eating behaviour questionnaires

Participants with HOMA-IR above 2.5 compared to participants with HOMA-IR below 2.5 in *cohort B*, showed higher scores of restraint eating measured by DEBQ, TFEQ, and EDEQ **Table 5.23.** However, no differences in restraint eating scores between participants with severe and non-severe obesity in *cohort A and cohort C.*

Participants from three cohorts were combined to examine the correlation between BMI levels and eating behaviours. Higher HOMA-IR levels correlated positively with higher restraint, disinhibition, and emotional eating scores **Table 5.24.**

	Cohort A *(pre-RYGB/EB)* **n=48**				**Cohort B** *(nOB/OB)* **n=93**				**Cohort C** *(OB)* **n=24**			
Food restraint	***HOMA-IR<2.5***	**HOMA-IR>2.5**	**Test statistic**	**P**	***HOMA-IR<2.5***	**HOMA-IR>2.5**	**Test statistic**	**P**	***HOMA-IR<2.5***	**HOMA-IR>2.5**	**Test statistic**	**P**
DEBQ	22.9	24.9	206.0	0.70	43.8	71.1	716.5	**0.002*****	15.3	8.1	29.0	**0.023****
TFEQ	25.1	24.3	184.0	0.89	42.0	66.8	556.0	**0.005****	15.4	7.8	26.5	**0.013****
EDE	25.4	24.3	181.5	0.83	44.1	68.9	691.5	**0.004****	-	-	-	-

Table 5.23 Comparison of restraint eating scores between groups in all cohorts

	Cohort A *(pre-RYGB/EB)* **Cohort B** *(nOB/OB)* **Cohort C** *(OB)*	
Eating behaviour questionnaire	**r**	**P**
DEBQ		
Restraint	0.33	**<0.001******
Emotional	0.22	**0.004*****
External	0.02	0.80
TFEQ		
Restraint	0.04	0.63
Disinhibition	0.29	**<0.001******
Hunger	0.22	**0.005****
EDEQ		
Restraint	0.30	**<0.001******
Weight	0.55	**<0.001******
Eating	0.46	**<0.001******
BDI-II	0.53	**<0.001******
BIS	0.18	**0.036**
BES	-0.06	0.62

Table 5.24 Spearman's correlation between HOMA-IR levels and eating behaviour questionnaires in all cohorts combined

Correlations between HOMA-IR levels and eating behaviour questionnaire. Data presented as r Spearman correlation coefficient, **P<0.01,***P<0.001.

5.5 Discussion

This chapter aims to investigate the effect of BMI in obesity on food cue reactivity and other aspects of eating behavior by comparing the findings from three cohorts including participants with obesity. Findings across cohorts for each outcome measure are summarized in **Table 5.25**.

	Cohort A n=47		Cohort B n=93		Cohort C n=25	
Measure	**HOMA-IR>2.5 vs. *HOMA-IR<2.5***	***Corr w/ HOMA-IR***	**HOMA-IR>2.5 vs. *HOMA-IR<2.5***	***Corr w/ HOMA-IR***	**HOMA-IR>2.5 vs. *HOMA-IR<2.5***	***Corr w/ HOMA-IR***
Food cue reactivity	**Legend:** ↑ higher in participants with HOMA-IR >2.5, ↓ lower in participants HOMA-IR >2.5, → no difference between groups, **"o"** no significant correlation between HOMA-IR and outcome, **()**exploratory analysis interaction group*ED not significant					
fROI						
HE	→	-ve av 6 ROIs, insula, caudate	→	o	(↓) NAcc	o
LE	→	o	→	o	n/a [a]	n/a [a]
HE vs. LE	↓ HE>LE av 6 ROIs, NAcc		↑HE>LE av 6 ROIs, amygdala		n/a [a]	n/a [a]
Whole brain						
HE	→	o	→	o	→	o
LE	→	o	→	o	n/a [a]	n/a [a]
HE vs. LE	→	o	→	o	n/a [a]	n/a [a]
Food appeal ratings	(↓) HE, → LE,HE>LE	o HE, LE	→ HE, LE, HE>LE	o HE, LE	→ HE	o HE
Food intake						
Total energy	↓ sweet HF [b]	-ve sweet HF [b]	→ [c]	o[c]	→ [b]	o [b]
Intake (kcal % REE)	↓ sweet HF [b]	-ve sweet HF [b]	→ [c]	-ve[c]	→ [b]	o [b]
Intake as % total kcal	↓ sweet HF [b]	o [b]	n/a	n/a	→ [b]	o [b]
Taste ratings						
Pleasantness	↑ sweet LF	+ve sweet LF	→[c]	o[c]	→	o
Creaminess	→	+ve sweet LF	n/a	n/a	→	o
Ideal creaminess	→	o	n/a	n/a	→	o
Sweetness	→	+ve sweet LF +ve sweet HF	n/a	n/a	↓ sweet HF	o
Ideal sweetness	↑ LF		n/a	n/a	→	+ve sweet LF
LFPQ						
Explicit Liking	→	n/a	n/a	n/a	→	n/a
Implicit wanting	→	n/a	n/a	n/a	→	n/a
PRT						→
Break point	→	n/a	n/a	n/a	→	n/a
Total clicks	→	n/a	n/a	n/a	→	n/a
Appetite ratings						
Hunger	→	n/a	→	n/a	→	n/a
Fullness	→	n/a	→	n/a	→	n/a

Table 5.25 Summary of all outcome measures across cohorts based on HOMA-IR

[a] fMRI paradigm in cohort C included only HE food pictures, [b] energy intake from four dishes (savoury HF/LF and sweet HF/LF), [c] energy intake from *ad libitum* meal and taste ratings from one savoury dish, [d]effect of group*fat independent of sweetness

Abbreviations: av 6 ROIs: average BOLD signal in six functional regions of interest (amygdala, insula, OFC, putamen, NAcc, caudate), **HE:** high energy, **LE:** low energy**, corr.:** correlation, **HOMA-IR:** homeostasis model of assessment-insulin resistance; **HF:** high fat, **LF:** low fat**, -ve:** negative correlation with BMI; **+ve:** positive correlation with BMI; **LFPQ:** Leeds Food Preference Questionnaire; **fROI:** functional regions of interest; **NAcc:** nucleus accumbens; **OFC:** orbitofrontal cortex; **PRT:** progressive ratio task; **n/a:** data/analysis for outcome measure is not available

5.5.1 Food cue reactivity to HE and LE food pictures

Hypothesis 1: Higher insulin resistance is associated with higher BOLD signal to HE vs. LE food picture

Results: Higher HOMA-IR was associated with higher BOLD signal to HE vs. LE

Summary of results

Findings from *cohort B* support my hypothesis, where participants with HOMA-IR above 2.5 showed higher BOLD signal to HE vs. LE food picture in average 6 ROIs, and in amygdala when exploratory individual ROI analysis was performed.

Unexpectedly, opposite findings from *cohort A,* where participants with HOME-IR above 2.5 showed lower BOLD signal to HE vs. LE food picture in average 6 ROIs, and in NAcc when exploratory individual fROI analysis was performed. Similarly, HOMA-IR levels negatively correlated with BOLD signal to HE food picture in average 6 ROIs, insula, and caudate.

In all cohorts, there was no difference between groups in BOLD signal to HE vs. LE food picture in whole brain analysis.

While findings from my analysis were not replicable in the two cohorts, findings from *cohort B* are similar with cross-sectional (71) and interventional studies (70, 193, 281). The following is a summary of the literature discussing insulin and food cue reactivity

Cross-sectional fMRI studies and insulin resistance

In a cross-sectional study, participants with obesity and insulin resistance (n=25, mean of BMI = 32.6 kg/m^2 and HOMA-IR = 3.8) and participants with normal weight (n=25, mean of BMI = 22.9 kg/m^2 and HOMA-IR = 2.5) were instructed to refrain from food intake ~2 hours before scanning session. Participants with obesity and insulin resistance compared to participants with normal weight, showed higher BOLD signal to favorite-food cue in amygdala, insula, putamen and PHG. Also, HOMA-IR positively correlated with BOLD to favorite-food cue in striatum and insula (71). Indeed, participants in this cross-sectional study had obesity and insulin resistance, which might be problematic in interpreting these results because BMI and insulin resistance can be correlated; thus, we cannot dismantle these two factors to explain

the difference in food cue reactivity. These findings suggest that in obesity and insulin resistance, the brain is less responsive to the inhibitory effect of insulin despite exaggerated insulin levels, resulting in higher BOLD signal to favorite food cues. They also agree with findings from *cohort B*, but not from *cohort A.*

In another cross-sectional fMRI study comparing participants with obesity and prediabetes (n=26, mean BMI = 38.4 kg/m^2 and HOMA-IR = 3.91) to participants with obesity and no prediabetes (n=11, mean BMI = 35.5 kg/m^2 and HOMA-IR = 3.48), lower BOLD signal to highly vs. less desirable food in putamen (but not amygdala, insula, and OFC) was seen in participants with obesity and prediabetes in the fasted state. After a meal, participants with obesity and prediabetes compared to participants with obesity and no prediabetes, showed lower BOLD signal to food vs. no food in insula (but not amygdala, putamen, and OFC) using SVC analysis (210). These findings were consistent with another cross-sectional study from the same research group (282). Findings from these studies may suggest a diminished reward response to food in insulin resistance, which may also predispose patients with obesity and prediabetes to overconsumption of highly desirable foods to compensate for reward deficiency. The hypothesis and findings from these studies are contrary to my hypothesis. Moreover, participants from the above study in both groups were with obesity.

Central insulin infusion fMRI studies

In a cross-over, double-blind study, intranasal insulin was utilized to study the effect of central insulin on food cue reactivity (70). After an overnight fast, participants with normal insulin sensitivity (n= 28, mean BMI = 23.6 kg/m^2 and HOMA-IR = 1.2) and participants with insulin resistance (n=20, mean BMI = 29.4 kg/m^2 and HOMA-IR = 2.4) had two scanning sessions: placebo and intranasal insulin. Insulin resistance was determined by a cut-off point of HOMA-IR >2.0 (70). During fMRI food valuation task in the placebo session, there was no difference between those with normal insulin sensitivity and those with insulin resistance, where both groups showed higher BOLD signal to food pictures in VTA, amygdala, insula and OFC using corrected whole brain and fROI analysis (70). During intranasal session, lower BOLD signal to food cues in VTA and NAcc in normal insulin sensitivity group, and opposite effect of intranasal insulin in the same regions in insulin resistance group. Findings from this study support the hypothesis that insulin resistance may have an inhibitory effect on insulin action on BOLD signal and agree with my findings from *cohort B.*

fMRI studies after oral glucose tolerance test in insulin resistance participants

To examine the effect of insulin sensitivity on food cue reactivity in women with polycystic ovary syndrome (PCOS), insulin sensitivity (resistant vs. sensitive) was assessed by HOMA2-IR score > 1.7 during two conditions, two groups included: women in insulin-sensitive group (n=8, mean BMI = 30.8 kg/m^2 and HOMA2-IR = 0.9) and women in insulin-resistance group (n=11, mean BMI = 40.0 and HOMA2-IR = 2.3) (281). After a 5-hour fast and in drinking water condition compared to glucose condition, higher BOLD signal to HE food picture in insula in insulin-sensitive women; and in midbrain, VTA, NAcc, putamen, hippocampus, amygdala in insulin-resistant women. After 75 g glucose challenge in insulin resistant women compared to insulin-sensitive women, higher BOLD signal to HE food picture in dlPFC, mPFC, caudate, insula using corrected SVC analysis (281). No changes in BOLD signal to HE food pictures during glucose challenge in insulin sensitive-women. During glucose challenge compared to water condition in insulin resistance women compared to insulin sensitive women, a greater BOLD signal to HE food in fusiform and insula. Furthermore, HOMA-IR levels positively correlated with BOLD signal to HE food picture in mPFC, OFC, anterior cingulate, VTA, and to HE vs. LE in OFC, midbrain, hippocampus, amygdala (281). These findings are in agreement with my findings in *cohort B*, where higher BOLD signal to HE vs. LE in higher HOMA-IR group

Commented [AS6]: significant interaction of group and condiyion

in average 6 ROIs and insula using fROI analysis, suggesting an unfavorable effect of insulin resistance on food cue reactivity in several region in the brain.

Similar findings from the PREVIEW study (Prevention of Diabetes through Lifestyle Intervention and Population Studies in Europe and around the World) that aimed to examine the relationship of insulin resistance and food cue reactivity in participants with obesity/overweight and impaired glycemia (n= 35, mean BMI = 32.3 and HOMA-IR 3.9) (193). After an overnight fast and during oral glucose tolerance test OGTT, they reported a positive correlation between HOMA-IR and BOLD signal to HE/LE food in insula, cingulate gyrus and NAcc, this correlation remained significant after adjusting for BMI and age (193).

To the best of my knowledge, there is no evidence in the literature that examined the effect metformin or thiazolidinedione on insulin sensitivity in relation to food cue reactivity. The literature is more focused on the effect of these medications on clinical outcomes (i.e., glucose, HbA1c, body weight)

There are a few possible explanations for variability between studies in the literature and findings from my analysis: In *cohort A* both groups had similar BMI levels (42.5 and 39.3 kg/m^2 P=0.58), whilst participants in HOMA-IR above 2.5 group had higher BMI than participants with HOMA-IR above 2.5 group in *cohort B,* (27.6 vs. 38.2 kg/m^2, P=0.001), hence maybe the synergistic effect of BMI and insulin resistance drives the difference between groups in this cohort.

Insulin resistance is highly correlated with BMI, in one study in women with PCOS (281), adding BMI as a nuisance covariate reduced the significance level of BOLD signal in some of the regions.

Moreover, the average of HOMA-IR varied across studies from 2.4 (70), 2.9 (281), 3.8 (71), and 3.9 (193, 210). This is comparable to the average of HOMA-IR in *cohort A* (median HOMA-IR = 4.3) and *cohort B* (median HOMA-IR = 3.7).

Lastly, Participants were either scanned after OGTT (70, 193, 281), or in pre-meal state (71), or fasted (70, 210), whilst participants in my analysis, were fasted in *cohort A and cohort B.*

Hypothesis 2: Higher insulin resistance is associated with lower BOLD signal to LE food picture

Results: Higher HOMA-IR was not associated with lower BOLD signal to LE food picture

Summary of results

BOLD signal to LE food pictures in average 6 ROIs did not differ between participants with HOMA-IR above and below 2.5 in *cohort A and cohort B* in fROI and whole brain analysis. Similarly, no correlation between HOMA-IR and BOLD signal to LE in fROI and whole brain analysis

Unfortunately, when I searched the literature for the effect of insulin resistance on LE food cue reactivity, to my knowledge, only two studies examined this contrast. Other studies focused on HE food or food (HE/LE) cue reactivity in relation to insulin resistance. The effect of insulin infusion on BOLD signal to LE was examined in a cross-sectional study including participants with normal weight (283). Findings for LE food contrast for infused insulin or saline were reported in supplementary file; however, only figures were included in the file with no further explanation of the results (283)

In the previously mentioned study of women with PCOS (281), after a 5-hour fast and in drinking water condition compared to glucose condition, higher BOLD signal to LE food picture in insula midbrain, putamen, hippocampus, amygdala and caudate in insulin-resistant women. After 75 g glucose challenge compared to water condition, higher BOLD signal to LE food picture in OFC, caudate, putamen, insula, hippocampus, amygdala and VTA in insulin resistant women using SVC analysis (281). Furthermore, in women with insulin resistance compared to women with normal insulin sensitivity, a greater increase in BOLD signal to LE food picture in dlPFC, mPFC, caudate, insula (281). The interaction between insulin sensitivity and condition revealed a greater BOLD signal to LE food in midbrain and insula in insulin resistant women during glucose challenge. Lastly, insulin resistance positively correlated with BOLD signal to LE food picture in dlPFC, mPFC, OFC, brainstem, anterior cingulate and insula. These findings suggest an association between insulin resistance and alterations in BOLD signal to LE food pictures in brain regions involved in reward- and appetite- control, it may also suggest that peripheral insulin resistance reflect brain insulin resistance to a degree.

Commented [AS7]: Food task effect. The whole brain contrast map for food condition (HC and LC combined) relative to the NF condition, including both the INS and SAL groups (all 34 subjects) showed that food condition increased activity in the striatum (dorsal, ventral), ventromedial prefrontal cortex (VmPFC), dorsolateral PFC (DLPFC), insula, amygdala, hypothalamus and occipital lobe compared to the NF condition (Figure 3a). A similar brain response was observed when the whole brain contrast included only the HC (Figure 3b) and LC food pictures relative to the NF pictures (Supplementary Figures 1 and 2)

Commented [AS8]: Food task effect. The whole brain contrast map for food condition (HC and LC combined) relative to the NF condition, including both the INS and SAL groups (all 34 subjects) showed that food condition increased activity in the striatum (dorsal, ventral), ventromedial prefrontal cortex (VmPFC), dorsolateral PFC (DLPFC), insula, amygdala, hypothalamus and occipital lobe compared to the NF condition (Figure 3a). A similar brain response was observed when the whole brain contrast included only the HC (Figure 3b) and LC food pictures relative to the NF pictures (Supplementary Figures 1 and 2)

While food cue reactivity findings from *cohort A* was not as expected, they are in the same direction and consistent with findings from other behavioral measures that will be discussed later. For example, findings from *ad libitum* lunch; unexpectedly showed higher energy intake in those with lower HOMA-IR compared to higher HOMA-IR group, suggesting an inherent characteristic in this cohort other than HOMA-IR contributed to these findings. The two groups in this cohort were also unbalanced due to differences in recruitment and inclusion criteria. Participants of *cohort A* were a combination of: (1) patients with obesity (higher BMI but not with T2DM) who were in the waiting list for obesity surgery (RYGB), and (2) participants for Endobarrier study who were with T2DM but lower BMI levels. Based on that, participants in lower HOMA-IR group were with higher BMI and a few of them had T2DM (n=4/9), and participants in higher HOMA-IR group were with lower BMI and most of them had T2DM (n=32/38).

This discrepancy does not seem to be due to restraint or eating behaviour, nor BMI because both measures were similar between groups. Another possible factor is glucose levels. When differences between groups were examined for fasting glucose levels, participants with higher HOMA-IR had higher fasting glucose levels compared to participants with lower HOMA-IR in *cohort A*. Higher glucose levels may have suppressed BOLD signal in higher HOMA-IR group (217).

5.5.2 Appeal rating to LE and HE food picture during scanning

Higher BOLD signal to HE vs. LE food picture was not accompanied by higher appeal ratings for HE or LE food pictures between participants with higher or lower HOMA-IR in *cohort B*, nor in *cohort A and cohort C*.

In a cross-over, double blind study, participants with normal insulin sensitivity and insulin resistance were instructed to rate the liking of food pictures using a four-point rating scale during scanning session (70). During intranasal session, preference ratings of food vs. non-food picture were reduced in participants with normal insulin sensitivity compared to participants with insulin resistance. Moreover, during intranasal insulin session, participants with insulin resistance showed a trend to increased preference ratings for food vs. non-food pictures (70). These findings support BOLD signal findings from the same study, suggesting the inhibitory effect of insulin resistance on insulin action in the brain.

In acute insulin infusion and during fMRI scanning, participants with normal weight were instructed to rate liking and wanting of HE, LE, and non-food pictures (283). Higher ratings for HE and LE food pictures compared to non-food pictures in insulin and saline conditions; however, there was no difference in liking and wanting ratings between HE and LE food pictures; nor between insulin and saline condition (283). While these findings agree with findings from my analysis, participants from the latter study were not with insulin resistance.

5.5.3 Ratings of explicit liking and implicit wanting (LFPQ), motivation PRT and taste ratings

There was no difference between HOMA-IR groups in explicit liking or implicit wanting ratings using Leeds Food Preference Questionnaire in *cohort A*, or in progressive ratio task in *cohort A and cohort C*. Participants with higher HOMA-IR showed higher scores in explicit liking for HF food (chicken cream soup and ice-cream) compared to LF food (chicken broth and yogurt), and higher scores in implicit wanting for savoury HF vs. savoury LF (chicken cream soup vs. chicken broth soup) and for HF sweet vs. HF savoury (ice-cream vs. chicken cream soup).

Higher pleasantness ratings were expected to be seen for HF sweet food (ice-cream); however, the only significant difference between participants with higher HOMA-IR and participants with lower HOMA-IR, is for LF sweet food (yogurt) in *cohort A.* The difference in pleasantness ratings between groups of higher and lower HOMA-IR was not seen in *cohort B and cohort C* for all four dishes. In general, there was no difference between groups of higher and lower HOMA-IR in creaminess and sweetness ratings for all four dishes

In an intranasal insulin infusion study, participants with normal weight (n=15, mean BMI = 22.7 kg/m^2 and HbA_{1c} = 33.15 mmol/mol) and participants with overweight or obesity (n=12, mean BMI = 31.3 kg/m^2 and HbA_{1c} = 34.20 mmol/mol) were asked to rate HE savoury and sweet food pictures after intranasal or placebo application (68). There was no difference between groups (normal weight vs. overweight/obesity) or between conditions (insulin vs. placebo) in explicit liking and wanting ratings for HE savoury and sweet food (68).

The former studies are different than my analysis in the following:
1) The first study aimed to examine the effect of insulin infusion on liking and wanting in participants with normal weight (283), while my analysis aimed to compare liking and wanting ratings between participants with higher and lower HOMA-IR;
2) Liking and wanting ratings were obtained for HE, LE, and non-food pictures during scanning session (283), or pictures of HE savoury and sweet food were rated outside the scanner on a scale of 1-9 (68); while in my analysis participants were asked to complete Leeds Food Preference Questionnaire task on a laptop
3) The second study divided participants based on BMI levels (normal weight vs. overweight/obesity) and included HbA_{1c} as a measure of glycemic control

To my knowledge, explicit liking and implicit wanting were not examined in insulin resistance population. However, findings from previous chapter showed an increase in explicit liking for HF sweet food in participants with severe obesity compared to participants with non-severe obesity which may suggest a stronger effect of BMI in this measure than HOMA-IR.

5.5.4 Food intake from ad libitum lunch meal

Hypothesis: higher HOMA-IR is associated with higher food intake, especially high fat and sweet/ or lower low fat and savoury food

Result: Participants with lower HOMA-IR compared to participants with higher HOMA-IR had higher food intake of sweet HF

It was unexpected to find that participants with lower HOMA-IR compared to participants with higher HOMA-IR, had higher total energy intake from sweet HF (ice-cream) at the *ad libitum* meal in *cohort A,* despite *lower* pleasantness ratings in this cohort. These findings are in the same direction as food cue reactivity findings, perhaps suggesting another factor within lower HOMA-IR group driving the difference. No difference between groups of lower and higher HOMA-IR in any *ad libitum* energy intake measures in *cohort B* and *cohort C.*

Insulin is known as a satiety hormone that reduces food intake via it's anorexigenic action on hypothalamic receptors (284). As well as affecting the hypothalamus, central insulin modulates activity and connections of cortical and limbic regions, thus regulating reward response to food intake (64). In previous studies, intranasal insulin either reduced food intake in participants with obesity (285, 286) or did not affect food intake in postmenopausal and young women with normal weight (287).

For example, in one interventional study, food intake was assessed by *ad libitum* breakfast meal in two conditions: intranasal insulin and placebo in participants with normal weight (men: n=14, BMI = 22.9 kg/m^2, women: n=18, BMI = 21.4 kg/m^2) (285). When intranasal insulin compared to placebo condition, food intake was reduced only in men; while there was no difference in food intake between intranasal insulin and placebo condition in women (285). This effect was also seen in another interventional study in which 15 participants with normal weight (mean BMI 22.2 kg/m^2) were tested twice: intranasal insulin and placebo, and total energy intake was measured by *ad libitum* breakfast buffet meal 40 minutes after insulin or placebo administration (286). Total energy intake was significantly lower in intranasal insulin condition compared to placebo (286). Most studies in the literature demonstrated the anorexigenic effect of exogenous insulin on food intake in participants with normal weight and normal insulin sensitivity; however, the same effect may not be seen in participants with

Commented [AS9]: Intranasal insulin suppresses food intake via enhancement of brain energy levels in humans

Commented [AS10]: Rosemarie Krug, Christian Benedict, Jan Born, Manfred Hallschmid, Comparable Sensitivity of Postmenopausal and Young Women to the Effects of Intranasal Insulin on Food Intake and Working Memory, *The Journal of Clinical Endocrinology & Metabolism*, Volume 95, Issue 12, 1 December 2010, Pages E468–E472, https://doi.org/10.1210/jc.2010-0744

Commented [AS11]: Intranasal insulin suppresses food intake via enhancement of brain energy levels in humans

Commented [AS12]: Intranasal insulin suppresses food intake via enhancement of brain energy levels in humans

insulin resistance. This assumption is based on the fact that in insulin resistance, central insulin action in the brain is disrupted, which may result in higher preference for palatable food and overeating (68, 70, 280)

5.5.5 Eating behaviour questionnaires

Hypothesis: HOMA-IR levels is positively correlated with restraint, emotional, disinhibition and external eating

As expected, higher HOMA-IR levels positively correlated with eating behaviours assessed by eating behaviour questionnaires including dietary restraint, emotional, external, hunger and disinhibition eating. Moreover, participants with higher HOMA-IR compared with participants with lower HOMA-IR, had higher restraint scores measured by DEBQ and TFEQ questionnaires in *cohort B and cohort C.*

In a cross-sectional study, 487 participants were included across three BMI categories (lean: n=173, BMI range 18.5-24.9 kg/m^2), (overweight: n=159, BMI range 25-29.9 kg/m^2), and (obesity: n=155, BMI > 30 kg/m^2)(288). The study aimed to examine sex-differences in dietary restrain and its association with insulin resistance. In men with obesity, dietary restraint positively correlated with HOMA-IR levels; however, this correlation was not seen in women with obesity (288). Findings from this study suggested an association between restrained eating, modulated by gender and obesity, and insulin resistance.

Eating behaviours such as higher restraint and higher responsivity to food cues may contribute to overconsumption of food; hence, these behaviours may exacerbate metabolic dysfunction such as insulin resistance, especially when accompanied with obesity.

5.6 Strengths and limitations

The present analysis aimed to examine the effect of insulin resistance measured by HOMA-IR, on several eating behaviour measures in three cohorts. To the best of my knowledge, there are not many studies in the literature that focused on HOMA-IR as an independent measure for comparing between groups in eating behaviour. One of the limitations in this analysis is the unbalance between groups within cohorts such as sample size and the presence of T2DM.

5.7 Conclusion

Insulin modulates homeostatic and hedonic network in the brain, influencing eating behaviour. Thus, it was expected to find an alteration in food cue reactivity and eating behaviour measures in participants with higher insulin resistance. In line with my hypothesis, participants with higher HOMA-IR showed higher food cue reactivity in regions involved in reward processing compared with participants with lower HOMA-IR in *cohort B* only. Unfortunately, there was not any other behavioural findings (energy intake and liking ratings) from this cohort to support fMRI findings. These findings were not reproduced in either of the other cohorts mainly due to differences in participants characteristics.

In conclusion, there is not consistent finding on the value of insulin resistance as a marker of food cue reactivity in obesity. This further suggests that insulin resistance is not a cause of obesity and consequently overeating (289).

Further examination of the value of insulin resistance in obesity to determine eating behaviour is needed. Ideally, a longitudinal fMRI study examining the effect of enhanced insulin sensitivity on food cue reactivity, in BMI-matched, insulin resistance and normal insulin sensitivity participants. This will allow to understand the mechanistic role of insulin resistance in food cue reactivity in obesity.

Chapter 6 General discussion and conclusion

6.1 Summary of main findings and general discussion

Previous fMRI studies aimed to examine the difference in BOLD signal between patients with obesity and individuals with normal weight, or the difference in BOLD signal in individuals with obesity before and after weight loss (dietary intervention or surgery). Brain regions that are usually targeted in eating behaviour-related fMRI studies included limbic, striatal, and frontal regions, these regions were identified as regions involved in reward processing. The activation in these regions represents not just the reward value of food, but also emotional and cognitive responses. This thesis is aimed to conduct a systematic review on food cue reactivity in patients before and after obesity surgery, and then to further examine the value of BMI and insulin resistance as markers of food cue reactivity in three cohorts predominately consisting of patients with obesity.

6.1.1 Changes in food cue reactivity after obesity surgery

Weight loss after obesity surgery can be explained by several mechanisms, and the available evidence strongly supports that the reduction in hunger and increase in fullness are the key mechanisms (177). It also suggests that the change in food preferences away from high palatable food is partially mediated by reductions in high-energy food cue reactivity. By preforming a comprehensive review of the literature for fMRI studies after obesity surgery, I was able to compare findings from three types of obesity surgery: RYGB, VSG, and AGB. Most of longitudinal fMRI studies were conducted to compare changes in food cue reactivity after RYGB (77.3% of studies), with less evidence from fMRI studies after VSG and AGB operations.

Reductions in BOLD signal to high-energy food pictures in caudate, amygdala, putamen, NAcc, insula, and OFC were frequently observed after RYGB surgery. While studies performed fMRI session either in fasted or fed state or both, reductions in BOLD signal in brain regions involved in reward processing were more pronounced in the fasted state. These findings suggest an interaction between less hunger and reduced reward responses to food after surgery **Figure 6.1**. I was surprised to observe this, as I was expecting that the interaction between fullness and reduced reward responses to food would be more pronounced, considering that anorexigenic hormones are at maximum concentrations after a meal.

In VSG surgery, changes in BOLD signal to food pictures were often seen in dlPFC. The direction of these changes was time-dependent, with an initial decrease shortly after surgery, and an increase in BOLD signal at 1 year after surgery. It is still not clear from the available evidence whether VSG surgery alter reward responsivity in patients with obesity, but it suggests transient changes in cognitive restraint towards food. **Figure 6.1**.

High-energy food vs. non-food cues	
Fasted	***Fed***
RYGB n=3 studies	**RYGB n=4 studies**
NAcc 2/2 no change	**NAcc** 3/3 no change
Caudate 1/2 decrease	**Caudate** 4/4 no change
Putamen 2/2 no change	**Putamen** 1/4 decrease
Amygdala 1/3 decrease	**Amygdala** 4/4 no change
Hippocampus 1/1 no change	**Hippocampus** 3/4 no change
Insula 2/2 no change	**Insula** 4/4 no change
OFC 1/3 decrease	**OFC** 4/4 no change

High-energy vs. low-energy food cues	
Fasted	***Fed***
RYGB n=3 studies	**RYGB n=4 studies**
NAcc 3/3 no change	**NAcc** 1/4 decrease
Caudate 2/2 no change	**Caudate** 4/4 no change
Putamen 2/2 no change	**Putamen** 4/4 no change
Amygdala 3/3 no change	**Amygdala** 4/4 no change
Hippocampus 3/3 no change	**Hippocampus** 4/4 no change
	PHG 1/4 decrease
Insula 1/3 decrease	**Insula** 4/4 no change
	ACC 1/4 decrease
OFC 3/3 no change	**OFC** 4/4 no change
dlPFC 1/2 decrease	**dlPFC** 1/4 decrease, 1/4 increase
VSG n=3 studies	**VSG n=2 studies**
NAcc 3/3 no change	**NAcc** 2/2 no change
Caudate 2/2 no change	**Caudate** 2/2 no change
Putamen 2/2 no change	**Putamen** 2/2 no change
Amygdala 3/3 no change	**Amygdala** 2/2 no change
Hippocampus 3/3 no change	**Hippocampus** 2/2 no change
PHG 2/2 no change	**PHG** 1/2 decrease
Insula 3/3 no change	**Insula** 2/2 no change
OFC 3/3 no change	**OFC** 2/2 no change
dlPFC 2/3 decrease	**dlPFC** 1/2 increase

Figure 6.1 Summary of changes in BOLD signal in brain regions involved in reward processing in RYGB and VSG longitudinal studies

The associations between changes in BOLD signal and changes in clinical, behavioural, and hormonal outcomes were also examined across studies. It was unexpected to see that weight loss was not associated with changes in food cue reactivity. This in contrast with the behavioural literature, which demonstrates that food preference changes do not happen in everyone, but are associated with greater weight loss in those that they do (128). The main reason underlying this discrepancy are probably methodological.

While consistent reductions in unhealthy eating behaviours (e.g. emotional eating, high-energy food liking and wanting) were seen after obesity surgery across studies, direct correlations with changes in BOLD signal were variable and inconsistent. Eating behaviour measures were predominantly assessed by self-reported questionnaires or indirect measures including appeal and appetite ratings. Direct measures of food intake such as ad libitum buffet meals and residential stays might reveal more valid and reproducible findings.

Hormonal mediators were also measured in some of fMRI studies after surgery, and as expected a marked post-prandial increase in GLP-1 was observed after RYGB surgery, and a decrease in fasting ghrelin was seen after VSG surgery. Decreased BOLD signal to food correlated with an increase in GLP-1 and PYY plasma levels, thus in line with the findings of Goldstone *et al* (160), in supporting a potential causative role of satiety gut hormones in reduced food cue reactivity after RYGB.

Promising evidence from my review for preferential reduction in high-energy vs. low-energy food cue reactivity, in line with other behavioural measures such as food intake and appeal ratings. This further expands the efficacy of obesity surgery beyond metabolic and physiologic benefits, and indeed promotes drug development. Methodological variations across studies and fMRI inherent methodological differences limited conclusion regarding changes in food cue reactivity after obesity surgery.

6.1.2 Food cue reactivity and BMI in obesity

Obesity is defined as a body mass index ≥ 30 kg/m^2, and it is commonly associated with heightened reactivity to food cues (143, 254), and higher intake from sweet high fat food (268, 269). However, even this widely accepted belief is not consistently supported by the

available behavioural and neuroimaging literature. My analysis aimed to test the value of BMI as a predictor or marker of heightened levels in brain responses to high-energy and low-energy food pictures, food appeal ratings, food intake, and associated-eating behaviours in obesity. Additionally, I aimed to examine whether there is a differential food cue reactivity between high- and low- energy food pictures in obesity. It is important in the context of obesity, to examine the hypothesis whether patients with obesity have higher attention and salience specifically for high-energy and food in general, or lower low-energy food salience. This will further expand our understanding of mechanisms of food preferences and food choices, and consequently aid in designing treatment interventions. Since weight loss and dietary advice usually focus on the avoidance of high energy food choices, early life interventions may focus on improving the salience and appearance of low-energy foods to set higher brain response to these foods. The novelty in my approach was to perform these analyses in 3 different cohorts to check the reproducibility of my findings. The clinical value of this approach would be to use BMI, instead of cumbersome research methodologies, to personalize treatments for obesity.

My findings revealed a lower BOLD signal to low-energy food pictures in participants with severe obesity compared to participants with non-severe obesity. Furthermore, the reduction in BOLD signal to high-energy vs. low-energy food picture was mainly driven by the reduction in BOLD signal to low-energy food picture instead of an increase in BOLD signal to high-energy food picture. While this finding was not replicated in other two cohorts (maybe due to methodological differences), it raises the possibility of a novel mechanism underlying food preferences in obesity. It suggests that patients with obesity are more likely to consume fatty foods not purely because they are perceived as more rewarding, but also because low-energy foods are of very little reward value indeed, and this gets worse with increasing BMI. Another important finding is that BOLD signal to high-energy vs. non-food pictures was not higher in participants with higher BMI compared to participants with lower BMI in FROI and whole brain analysis in all cohorts.

Findings from eating behaviour fMRI studies are more meaningful when accompanied by other measures of eating behaviour. My neuroimaging analyses were complemented by additional eating behaviour measures including food appeal ratings, food intake, taste rating,

explicit liking and implicit wanting scores, and assessment of eating behaviours and psychological traits. While findings from fROI and whole brain analysis were in agreement with my initial hypothesis, findings from other measures were not necessarily significant or in the same direction. For example, energy intake when corrected for percentage of estimated 24-hour resting energy expenditure (REE) was either higher, lower, or not different between groups of higher and lower BMI across cohorts. There was no difference between groups in active food appeal rating during scanning, implicit wanting scores, progressive ratio task, and pleasantness ratings in all three cohorts.

The differences between groups appear to be due to the heterogeneity in participants characteristics across the 3 cohorts. For example, *cohort A* included patients with obesity and T2DM who were in the waiting list for obesity surgery and findings from this cohort were not replicated in *cohort B* that included participants with normal weight and overweight, hence diluting the effect of BMI on outcome measures, neither in *cohort C* where patients with obesity did not have T2DM and were actively dieting.

In this chapter, I examined the association of BMI with food cue reactivity because BMI is a readily available marker of obesity. The variability in findings from this chapter also demonstrated that BMI is a crude measure at the individual or small-group level that provides very little information on muscle mass and fat distribution (290). Having investigated the relationship between BMI and food cue reactivity, I chose HOMA-IR as another potential useful marker. HOMA-IR is a marker of insulin resistance and more specifically hepatic insulin resistance. It is strongly correlates with waist circumference and therefore visceral adiposity which is a risk factor for the development of metabolic complications of obesity (291-293)

6.1.3 Food cue reactivity and insulin resistance in obesity

Insulin resistance is a common phenotype in patients with obesity and a risk factor for T2DM and metabolic syndrome. HOMA-IR is a readily available measurement of hepatic insulin resistance; thus, if associated with food cue reactivity, it can be used easily in the clinical setting. Evidence from fMRI studies demonstrated altered food cue reactivity in patients with insulin resistance, giving rise to the model of "brain insulin resistance". In brain insulin resistance, insulin anorexigenic effect is inhibited in brain regions involved in appetite and food intake, and consequently contribute to overeating (64). Acute insulin infusion reduced BOLD signal to high-energy food pictures in individuals with normal weight (66, 67, 280). Therefore, I sought the re-analyze all three datasets and divide groups within each cohort based on HOMA-IR value above 2.5. This allowed to examine whether higher HOMA-IR levels better explain food cue reactivity in obesity.

In food cue reactivity analysis in *cohort B*, participants with HOMA-IR above 2.5 compared to participants with HOMA-IR below 2.5 showed *higher* BOLD signal to HE vs. LE food pictures; however, findings from *cohort A* were in the opposite direction. The discrepancy in *cohort A* can be explained in part by differences in participant characteristics, as mentioned earlier participants in this cohort included patients with obesity who were taking part in two clinical studies (RYGB and Endobarrier studies) including different inclusion/exclusion criteria and this created an imbalance between groups. One of the factors that I investigated to explain this discrepancy is higher fasting plasma glucose in participants with HOMA-IR above 2.5 which may have suppressed BOLD signal in this group.

The findings in *cohort B* are in line with the model of brain insulin resistance, where insulin action is inhibited in brain regions involved in appetite and food intake. Insulin role as an anorexigenic hormone act on hypothalamic and cortical receptors to suppress appetite and reduce food intake (64). There are two hypotheses under investigation in the literature; the first: suggests *a higher* in BOLD signal to high-energy food pictures in brain regions involved in reward processing in insulin resistance due to brain insulin resistance (70, 71), as observed in *cohort B.* The second hypothesis: suggests *a lower* in BOLD signal in brain regions involved in reward processing in insulin resistance due to diminished reward sensitivity (210, 282), as observed in *cohort A.* The latter hypothesis suggests a further explanation for lower BOLD

signal in participant with higher HOMA-IR in *cohort A,* where reward sensitivity may be lower in this cohort and it was further reflected on lower consumption of sweet high-fat food from *ad libitum* meal. Finally, my analysis did not reveal any significant differences between groups across cohorts in BOLD signal to low-energy food pictures.

I did not observe consistent differences in behavioural outcomes when comparing groups based on HOMA-IR; the effect of insulin resistance was either in the opposite direction of my hypothesis, or not present at all. In conclusion, findings from two sets of analyses suggested that in obesity, BMI might act as a better marker for food cue reactivity. This conclusion is supported by significant differences in BOLD signal to high-energy and low-energy food pictures, in fROI and whole brain analysis, accompanied by differences in other eating behaviour measures between groups of non-severe and severe-obesity.

6.2 Conclusion and future directions

Findings from previous chapters demonstrated that obesity surgery and BMI level alter food cue reactivity, specifically in areas related to food reward processing, hence eating behaviour. My thesis included a comprehensive systematic review of fMRI studies after three types of obesity surgery: RYGB, VSG, and LAGB. It also included a cross-sectional examination of food cue reactivity in three cohorts by testing two commonly used clinical markers in obesity. Indeed, pathological overeating can be attributed to a dysfunctional reward system in obesity, thus it is crucial to explore markers that can explain eating behaviour in this heterogenous condition.

The reward-based eating behaviour is predominantly controlled by the interaction of networks in the brain including regions involved in reward processing, decision making, executive control, memory formation, and incentive valuation. However, the challenge is to identify markers within obesity that determine abnormalities in the reward system. While my work examined BMI and HOMA-IR, there are other biological and psychological markers need to be examined to pinpoint eating behaviour determinants in obesity. Hence, it would be interesting to reanalysis data by using another psychological marker such as restraint, impulsivity, and reward sensitivity. Furthermore, the utilization of existing data from these cohort instead of cumbersome research studies, and the application of more advanced statistical methods to create a predictive model for eating behaviour in obesity.

In order to understand weight loss mechanism after obesity surgery, and whether alteration in food cue reactivity mediates food preference, a multi-center fMRI study including collaboration with other research teams and using high standard fMRI methodology will allow to further understand obesity surgery manipulation of the reward system. This includes scanning at early and late timepoints after surgery, including two nutritional states, applying proper statistical analysis, investigating the role of satiety hormones in food cue reactivity, and most importantly complementing neuroimaging studies with other direct eating behavioural measures.

Obesity surgery, specifically RYGB surgery, holds convincing evidence from fMRI and non-

fMRI studies that changes in food preferences, mediated by neural and hormonal factors, occur in a sub-group of patients. This function can be clinically translated into a better response to surgery. Once, these neural and hormonal factors are identified, then we can use a multi-model approach to predict surgery outcome. Patients can be then treated with either an adjunct treatment to surgery or with another non-surgical treatment.

Following on from this, understanding pathological eating behaviour mechanisms will facilitate and improve on treatment options for patients. Multimodal phenotyping approach including genetic, hormonal, and neural markers can be assessed to optimize obesity treatment and predict intervention outcome.

Chapter 7 Appendices

Appendix 1

Literature search strategies

Search terms and databases

Unless otherwise stated, search terms are free text terms; MeSH = Medical subject heading (MEDLINE medical index term); exp = exploded MeSH; the dollar sign ($) stands for any character(s); the question mark (?) substitutes one or no characters; tw = text word; pt = publication type; sh = MeSH; adj = adjacent (i.e. number of words within range of search term).

Database: Ovid MEDLINE

Search Strategy:

1 exp obesity/
2 Overweight/
3 over?weight.ti,ab.
4 over weight.ti,ab.
5 overeating.ti,ab.
6 exp Weight Loss/
7 weight loss.ti,ab.
8 weight reduc$.ti,ab.
9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10 bariatric surg$.ti,ab.
11 exp bariatric surgery/
12 obesity surg$.ti,ab.
13 (surg$ adj5 bariatric).ti,ab.
14 exp gastric bypass/
15 gastric band$.ti,ab.
16 exp gastroenterostomy/
17 gastrectomy.ti,ab.
18 AGB.ti,ab.
19 lap band$.ti,ab.
20 malabsorptive surg$.ti,ab.
21 OAGB.ti,ab.
22 SAGB.ti,ab.

23 L?VSG.ti,ab.

24 malabsorptive procedure$.ti,ab.

25 "Roux-en-Y".ti,ab.

26 obesity/su

27 exp Obesity, Morbid/su [Surgery]

28 RYGB.ti,ab.

29 gastric sleeve.ti,ab.

30 (gastroplasty or gastro?gastostomy or "gastric bypass" or "gastric surgery" or "restrictive surgery").ti,ab.

31 stomach balloon.ti,ab.

32 gastric balloon.ti,ab.

33 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32

34 9 and 33

35 26 or 27 or 34

36 fMRI.ti,ab.

37 exp fmri/

38 functional magnetic resonance imaging.ti,ab.

39 neural response?.ti,ab.

40 BOLD signal.ti,ab.

41 food cue$.ti,ab.

42 reward.ti,ab.

43 36 or 37 or 38 or 39 or 40 or 41 or 42

44 34 and 43

45 limit 44 to humans

Database: Pubmed

Literature search was performed in 4 steps following PICO strategy

((((obese adults) OR "obesity")) AND ((((((((((gastric bypass) OR ("gastric bypass"[MeSH Terms] OR ("gastric"[All Fields] AND "bypass"[All Fields]) OR "gastric bypass"[All Fields])) OR mini gastric bypass) OR vertical sleeve gasterectomy) OR vertical sleeve gastrectomy) OR roux-en-y gastric bypass) OR "RYGB") OR adjustable gastric band) OR one-anastomosis gastric

bypass) OR single-anastomosis gastric bypass)) AND (((((((blood oxygen level dependent BOLD) OR fMRI) OR functional imaging) OR bold signal) OR reward) OR eating behavior) OR food cues)

P (obese adults) OR "obesity"

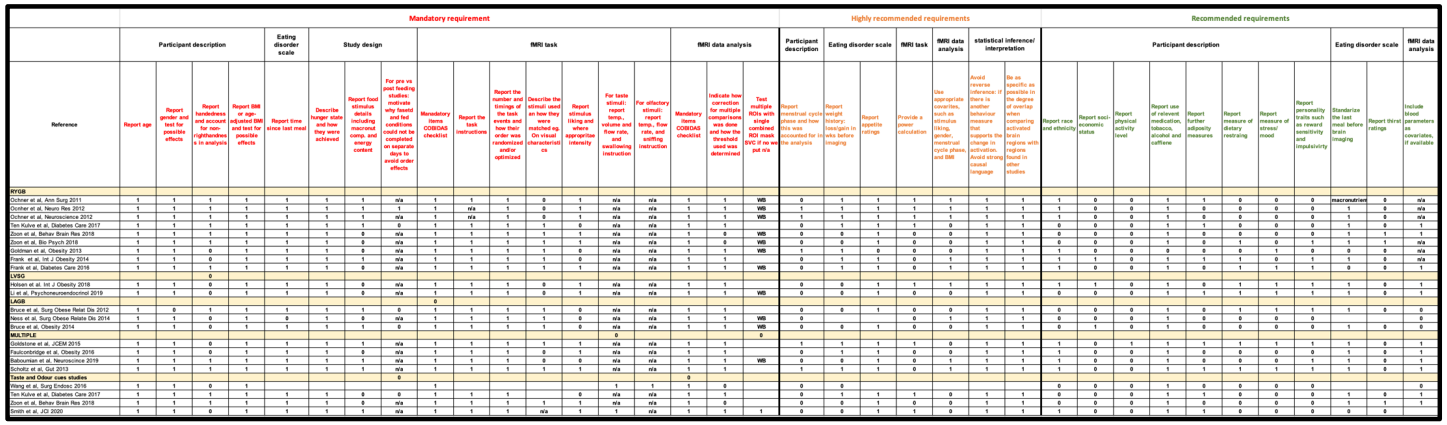
I (((((((((gastric bypass) OR ("gastric bypass"[MeSH Terms] OR ("gastric"[All Fields] AND "bypass"[All Fields]) OR "gastric bypass"[All Fields])) OR mini gastric bypass) OR vertical sleeve gasterectomy) OR vertical sleeve gastrectomy) OR roux-en-y gastric bypass) OR "RYGB") OR adjustable gastric band) OR one-anastomosis gastric bypass) OR single-anastomosis gastric bypass

O ((((((blood oxygen level dependent BOLD) OR fMRI) OR functional imaging) OR bold signal) OR reward) OR eating behavior) OR food cues

((((obese adults) OR "obesity")) AND ((((((((((gastric bypass) OR ("gastric bypass"[MeSH Terms] OR ("gastric"[All Fields] AND "bypass"[All Fields]) OR "gastric bypass"[All Fields])) OR mini gastric bypass) OR vertical sleeve gasterectomy) OR vertical sleeve gastrectomy) OR roux-en-y gastric bypass) OR "RYGB") OR adjustable gastric band) OR one-anastomosis gastric bypass) OR single-anastomosis gastric bypass)) AND (((((((blood oxygen level dependent BOLD) OR fMRI) OR functional imaging) OR bold signal) OR reward) OR eating behavior) OR food cues) OR gustatory) OR olfactory) OR taste) OR smell) OR odour)

Appendix 2

Quality assessment for fMRI studies adapted from Smeets *et al* (147)



	Mandatory requirement																		Highly recommended requirements						Recommended requirements																
	Participant description				Eating disorder scale	Study design			fMRI task								fMRI data analysis				Participant description	Eating disorder scale	fMRI task	fMRI data analysis	statistical inference/ interpretation		Participant description										Eating disorder scale		fMRI data analysis	
Reference	Report age	Report gender and test for possible effects	Report handedness and account for non-righthandedness in analysis	Report BMI or age-adjusted BMI and test for possible effects	Report time since last meal	Describe hunger state and how they were achieved	Report food stimulus details including macronut comp. and energy content	For pre vs post feeding studies: motivate why fasetd and fed conditions could not be completed on separate days to avoid order effects	Manadatory items COBIDAS checklist	Report the task instructions	Report the number and timings of the task events and how their order was randomized and/or optimized	Describe the stimuli used an how they were matched eg. On visual characteristics	Report stimulus liking and where appropriate intensity	For taste stimuli: report temp., volume and flow rate, and swallowing instruction	For olfactory stimuli: report temp., flow rate, and sniffing instruction	Mandatory items COBIDAS checklist	Indicate how correction for multiple comparisons was done and how the threshold used was determined	Test multiple ROIs with single combined ROI mask SVC if no we put n/a	Report menstrual cycle phase and how this was accounted for in the analysis	Report weight history; (weigain in wks before imaging	Report appetite ratings	Provide a power calculation	Use appropriate covarites, such as stimulus liking, gender, menstrual cycle phase, and BMI	Avoid reverse inference: if there is another behaviour measure that supports the change in activation. Avoid strong causal language	Be as specific as possible in the degree of overlap when comparing activated brain regions with regions found in other studies	Report race and ethnicity	Report socioeconomic status	Report physical activity level	Report use of relevent medication, tobacco, alcohol and caffiene	Report further adiposity measures	Report measure of dietary rewtraing	Report measure of stress/ mood	Report personality traits such as reward sensitivity and impulsivity	Standarize the last meal before brain imaging	Report thirst ratings	Include blood parameters as covariates, if available
HYOB																																								
Ochner et al, Ann Surg 2011	1	1	1	1	1	1	1	n/a	1	1	1	0	1	n/a	n/a	1	1	WB	0	1	1	1	1	1	1	1	0	0	1	1	0	0	0	macronutrient	0	n/a
Ochner et al, Neuro Res 2012	1	1	1	1	1	1	1	1	1	n/a	1	0	1	n/a	n/a	1	1	WB	1	1	1	1	1	1	1	1	0	0	1	0	0	0	0	1	0	n/a
Ochner et al, Neuroscience 2012	1	1	1	1	1	1	1	n/a	1	n/a	1	0	1	n/a	n/a	1	1	WB	1	1	1	1	1	1	1	1	0	0	1	0	0	0	0	1	0	n/a
Ten Kulve et al, Diabetes Care 2017	1	1	1	1	1	1	1	0	1	1	1	1	0	n/a	n/a	1	1		0	1	1	1	0	1	1	0	0	0	1	0	0	0	0	1	0	1
Zoon et al, Behav Brain Res 2018	1	1	1	1	1	1	0	n/a	1	1	1	1	1	n/a	n/a	1	0	WB	0	0	1	0	0	1	1	0	0	0	1	0	0	0	0	1	1	1
Zoon et al, Bio Psych 2018	1	1	1	1	1	1	0	n/a	1	1	1	1	1	n/a	n/a	1	0	WB	0	0	1	0	0	1	1	0	0	0	1	0	1	0	1	1	1	n/a
Goldman et al, Obesity 2013	1	1	0	1	1	1	0	n/a	1	1	1	1	0	n/a	n/a	1	1	WB	1	1	0	0	0	1	1	1	0	0	0	0	0	1	0	0	0	n/a
Frank et al, Int J Obesity 2014	1	1	0	1	1	1	1	n/a	1	1	1	1	0	n/a	n/a	1	1		0	1	1	0	1	1	1	1	0	0	1	1	1	0	1	1	0	n/a
Frank et al, Diabetes Care 2016	1	1	1	1	1	1	0	n/a	1	1	1	1	1	n/a	n/a	1	1	WB	0	1	1	0	1	1	1	1	0	0	1	0	1	1	1	0	0	1
UVSG			0																																				
Holsen et al, Int J Obesity 2018	1	1	0	1	1	1	0	n/a	1	1	1	0	1	n/a	n/a	1	1		0	0	1	1	1	1	1	1	0	0	1	1	0	1	1	1	0	1
O et al, Psychoneuroendocrinol 2019	1	1	0	1	1	1	0	n/a	1	1	1	0	1	n/a	n/a	1	1	WB	0	0	1	0	0	1	1	0	0	0	1	1	1	1	1	1	0	1
LAGB									0																														
Bruce et al, Surg Obese Relat Dis 2012	1	0	1	1	1	1	1	0	1	1	1	1	0	n/a	n/a	1	1		0	0	1	0	0	1	1	0	0	0	0	1	0	1	1	1	0	0
Nesic et al, Surg Obese Relate Dis 2014	1	1	0	1	0	1	0	n/a	1	1	1	1	0	n/a	n/a	1	1	WB	0	0	1	0	0	1	1	1	0	0	0	1	0	0	0	0	0	0
Bruce et al, Obesity 2014	1	1	0	1	1	1	1	0	1	1	1	1	0	n/a	n/a	1	1	WB	0	0	1	0	0	1	1	0	1	0	1	0	0	0	0	1	0	0
MULTIPLE														0				0																				
Goldstone et al, JCEM 2015	1	1	0	1	1	1	1	n/a	1	1	1	1	1	n/a	n/a	1	1		1	1	1	1	0	1	1	1	0	1	1	1	1	1	1	1	0	1
Faulconbridge et al, Obesity 2016	1	1	0	1	1	1	0	n/a	1	1	1	0	1	n/a	n/a	1	1		0	1	1	0	0	1	1	1	0	0	1	0	0	0	0	1	0	1
Sabouinian et al, Neuroscience 2019	1	1	1	1	1	1	1	n/a	1	1	1	0	0	n/a	n/a	1	1	WB	0	0	1	0	1	1	1	1	0	0	1	0	0	0	1	1	0	1
Scholtz et al, Gut 2013	1	1	1	1	1	1	1	n/a	1	1	1	1	1	n/a	n/a	1	1		1	1	1	0	1	1	1	1	0	0	1	0	1	1	1	1	0	1
Taste and Odour cues studies								0								0																						
Wang et al, Surg Endosc 2016	1	1	0	1					1					1	1	1	0		0	0																		0
Ten Kulve et al, Diabetes Care 2017	1	1	1	1	1	1	0	0	1	1	1		0	n/a	n/a	1	1		0	1	1	1	0	1	1	0	0	0	1	1	0	0	0	1	0	1
Zoon et al, Behav Brain Res 2018	1	1	1	1	1	1	0	n/a	1	1	1	1	1	n/a	n/a	1	0		0	0	1	0	0	1	1	0	0	0	1	0	0	0	0	1	1	1
Smith et al, JCI 2020	1	1	0	1	1	1	1	n/a	1	1	1	n/a	1	1	n/a	1	1	1	0	0	1	1	0	1	1	1	0	0	1	0	1	0	0	0	0	0

Mandatory requirements:

- Report age
- Report gender and test for possible effects
- Report handedness and account for non-righthandness in analysis
- Report BMI or age-adjusted BMI and test for possible effects
- Report time since last meal
- Describe hunger state and how they were achieved
- Report food stimulus details including macronut comp. and energy content
- For pre vs post feeding studies: motivate why fasetd and fed conditions could not be completed on separate days to avoid order effects
- Manadatory items COBIDAS checklist
- Report the task instructions

- Report the number and timings of the task events and how their order was randomized and/or optimized
- Describe the stimuli used an how they were matched eg. On visual characteristics
- Report stimulus liking and where appropritae intensity
- For taste stimuli: report temp., volume and flow rate, and swallowing instruction
- For olfactory stimuli: report temp., flow rate, and sniffing instruction
- Mandatory items COBIDAS checklist
- Indicate how correction for multiple comparisons was done and how the threshold used was determined
- Test multiple ROIs with single combined ROI mask

Highly recommended requirements

- Report menstrual cycle phase and how this was accounted for in the analysis
- Report weight history: loss/gain in wks before imaging
- Report appetite ratings
- Provide a power calculation
- Use appropriate covarites, such as stimulus liking, gender, menstrual cycle phase, and BMI
- Avoid reverse inference: if there is another behaviour measure that supports the change in activation.
- Avoid strong causal language
- Be as specific as possible in the degree of overlap when comparing activated brain regions with regions found in other studies

Recommended requirements

- Report race and ethnicity
- Report soci-economic status
- Report physical activity level

- Report use of relevent medication, tobacco, alcohol and caffiene
- Report further adiposity measures
- Report measure of dietary restraing
- Report measure of stress/ mood
- Report personality traits such as reward sensitivity and impulsivirty
- Standarize the last meal before brain imaging
- Report thirst ratings
- Include blood parameters as covariates, if available

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