Received: 3 September 2022 | Revised: 5 April 2023 | Accepted: 10 July 2023

DOI: 10.1111/obr.13620

REVIEW

OBESITY Reviews WILEY

Effects of bariatric surgery and dietary interventions for obesity on brain neurotransmitter systems and metabolism: A systematic review of positron emission tomography (PET) and single-photon emission computed tomography (SPECT) studies

Alhanouf S. Al-Alsheikh[1,2] | Shahd Alabdulkader[1,3] | Alexander D. Miras[1,4] | Anthony P. Goldstone[5]

[1]Department of Metabolism, Digestion and Reproduction, Imperial College London, Hammersmith Hospital, London, UK

[2]Department of Community Health Sciences, College of Applied Medical Sciences, King Saud University, Riyadh, Saudi Arabia

[3]Department of Health Sciences, College of Health and Rehabilitation Sciences, Princess Nourah Bint Abdulrahman University, Riyadh, Saudi Arabia

[4]School of Medicine, Faculty of Life and Health Sciences, Ulster University, Londonderry, UK

[5]PsychoNeuroEndocrinology Research Group, Division of Psychiatry, Department of Brain Sciences, Imperial College London, Hammersmith Hospital, London, UK

Correspondence
Dr. Tony Goldstone, Room 2S5B, 2nd Floor Commonwealth Building, Department of Brain Sciences, Imperial College London, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK.
Email: tony.goldstone@imperial.ac.uk

Funding information
UK Medical Research Council; BBSRC; National Institute for Health and Care Research (NIHR); Wellcome Trust; NIHR Biomedical Research Centre; NIHR Imperial Clinical Research Facility; King Saud University; Princess Nourah Bint Abdulrahman University

Summary

This systematic review collates studies of dietary or bariatric surgery interventions for obesity using positron emission tomography and single-photon emission computed tomography. Of 604 publications identified, 22 met inclusion criteria. Twelve studies assessed bariatric surgery (seven gastric bypass, five gastric bypass/sleeve gastrectomy), and ten dietary interventions (six low-calorie diet, three very low-calorie diet, one prolonged fasting). Thirteen studies examined neurotransmitter systems (six used tracers for dopamine DRD2/3 receptors: two each for ^{11}C-raclopride, ^{18}F-fallypride, ^{123}I-IBZM; one for dopamine transporter, ^{123}I-FP-CIT; one used tracer for serotonin 5-HT$_{2A}$ receptor, ^{18}F-altanserin; two used tracers for serotonin transporter, ^{11}C-DASB or ^{123}I-FP-CIT; two used tracer for μ-opioid receptor, ^{11}C-carfentanil; one used tracer for noradrenaline transporter, ^{11}C-MRB); seven studies assessed glucose uptake using ^{18}F-fluorodeoxyglucose; four studies assessed regional cerebral blood flow using ^{15}O-H_2O (one study also used arterial spin labeling); and two studies measured fatty acid uptake using ^{18}F-FTHA and one using ^{11}C-palmitate. The review summarizes findings and correlations with clinical outcomes, eating behavior, and mechanistic mediators. The small number of studies using each tracer and intervention, lack of dietary intervention control groups in any surgical studies, heterogeneity in time since intervention and degree of weight loss, and small sample sizes hindered the drawing of robust conclusions across studies.

KEYWORDS
dopamine, gastric bypass, opioid, sleeve gastrectomy

Abbreviations: VSG, vertical sleeve gastrectomy; RYGB, Roux-en-Y gastric bypass; PET, positron emission tomography; SPECT, single-photon emission computed tomography; fMRI, functional magnetic resonance imaging; BGU, brain glucose uptake; rCBF, regional cerebral blood flow; BMI, body mass index; NIH, National Institutes for Health; VLCD, very low calorie diet; LCD, low-calorie diet; T2DM, type 2 diabetes mellitus; BP, binding potential; ^{123}I-IBZM, ^{123}I-iodobenzamide; DRD2/3, dopamine D2/3 receptors; ^{123}I-FP-CIT, ^{123}I-N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl) nortropane; ^{11}C-PHNO, ^{11}C-4-propyl-9-hydroxynaphthoxazine; DAT, dopamine transporter; 5-HT, serotonin; 5-HT$_{2C}$R, serotonin 2C receptor; 5-HT$_{2A}$R, serotonin 2A receptor; SERT, serotonin transporter; ^{11}C-DASB, ^{11}C-3-amino-4-(2-dimethylaminomethyl-phenylsulfanyl)-benzonitrile; MOR, μ-opioid receptors; ROIs, regions of interest; NAT, noradrenaline transporter; ^{11}C-MRB, ^{11}C-methylreboxetine; ^{18}F-FTHA, ^{18}F-fluoro-6-thia-heptadecanoic acid; ^{15}O-H_2O, ^{15}O-water; ASL, arterial spin labeling; GLP-1, glucagon-like peptide-1; PYY, peptide YY; FPG, fasting plasma glucose; FFA, free fatty acid; aROIs, anatomical regions of interest.

1 | BACKGROUND

1.1 | Introduction

In many parts of the world, obesity has reached pandemic proportions; the number of deaths because of obesity-related health issues is rising at an unprecedented pace, and controlling obesity remains a daunting challenge. The obesity epidemic has tripled since 1975; in 2016, 39% of adults had overweight, and 13% had obesity globally.[1] The last report from the National Health Service in 2020 estimated that obesity might affect one in every four adults in the United Kingdom (25% of the population).[2]

Obesity surgery is the most effective long-term treatment for obesity.[3,4] As the number of obesity surgery operations has increased in the last decade, elucidating the mechanisms of action is crucial and a key research goal that may help optimize surgical outcomes by improving patient selection.[5] Moreover, understanding the mechanism of action by which each procedure reduces energy intake may eventually facilitate novel non-surgical approaches, including medications.[3,5] Vertical sleeve gastrectomy (VSG) and Roux-en-Y gastric bypass (RYGB) are currently the most commonly performed obesity surgeries worldwide.[4,6] Both procedures result in sustained weight reduction with no significant difference in terms of weight loss (20–25%) between the two groups after 5 years post-surgery.[7,8] Although both operations decrease gastric volume, the changes in appetitive gut hormones reduce energy intake by affecting the brain, which produces sustained weight loss.[3] Moreover, changes in taste, food preference, food hedonics, and food cue reactivity have been seen in some studies after RYGB and VSG surgery.[5,9] However, this depends on the particular outcome measures used. After bariatric surgery, reductions in food cue reactivity in brain reward systems using functional magnetic resonance imaging (fMRI) paradigms, motivation to work, and liking and wanting of high-energy (HE) over low-energy (LE) foods have been found, though preferential reductions in actual intake of HE over LE foods in the laboratory setting have not been reported.[5,10–20] In patients with obesity, hyperactivity of the brain in areas associated with reward and hypoactivity in areas associated with cognitive control have been reported.[21–24]

Non-surgical interventions usually consist of dietary changes and behavioral therapy, with the primary goal of reducing energy intake, increasing physical activity, and various pharmacotherapies.[4] Although non-surgical interventions may achieve weight loss, most of the non-pharmacotherapy methods lead to weight regain over the long-term because of compensatory adaptations in body weight regulation, which promote rapid weight regain efficiently.[25]

Functional neuroimaging techniques, such as positron emission tomography (PET), single-photon emission computed tomography (SPECT), fMRI, magnetoencephalography, and electroencephalography, are recently developed tools to investigate the brain centers involved in the control of appetite signals, eating behavior, and the pathophysiology of obesity.[26] These techniques offer insight into the brain by providing objective and sensitive information, accelerating scientific progress, and facilitating hypothesis testing.[27] In brief, PET is an imaging technique that provides semi-quantitative and quantitative measurements of biochemical processes by measuring the density of various neuroreceptor subtypes. These neuroreceptors include dopamine, opioids, noradrenaline, and serotonin.[28] PET also measures the transporter availability of certain neurotransmitters and physiological process including measurement of the brain glucose uptake (BGU), fatty acid uptake, and regional cerebral blood flow (rCBF) which reflect local neuronal activity.[26] These measurements rely partly on the use of a pharmacological or physiological compound labeled with a positron-emitting radioisotope, such as ^{18}F, ^{11}C, and ^{15}O.

Like PET, SPECT is another imaging method providing information about biochemical and physiological processes. SPECT radiotracers are elements or pharmacological compounds that include radioactive isotopes such as iodine-123 (^{123}I).[26] Only PET and SPECT can provide information on a molecular level because specific molecules can be labeled to allow their detection.[29]

This systematic review will discuss how these neural systems are dysregulated in human obesity and the effects of dietary and surgical weight loss interventions. This will help understand the mechanisms that lead to overeating and the development of obesity, and the mechanisms behind weight loss, by comparing the differences post-intervention with pre-intervention, or participants with versus without obesity, in brain area related to reward processing, homeostatic control of eating behavior, inhibitory control, executive function, and cognition. Moreover, it evaluates the association of changes in brain tracer uptake with clinical outcomes, behavioral changes, and appetitive gut hormones.

To our knowledge, there is no systematic review that has previously investigated the effect of surgical and other non-pharmacological interventions on the brain, other than one conducted in 2013 that examined the impact of obesity surgery on the brain which included only three PET studies (19 PET/SPECT studies have been conducted after 2013).[30] Therefore, this systematic review will identify all the available evidence to evaluate and summarize the finding and help identify any literature gaps.

1.2 | Aims and objectives

i. Identify PET or SPECT studies in patients with overweight/obesity examining effects of bariatric surgery or dietary interventions in longitudinal or cross-sectional design.
ii. Summarize and critically review the findings from the studies identified.
iii. Examine the following issues:
   a. how heterogeneity in study design, methodology, protocol, and analysis might explain discrepancies between studies.
   b. associations of brain PET/SPECT findings with clinical outcomes, eating behavior measures, and potential mechanistic

mediators, for example, gut hormones. This review includes predictive studies that focus on assessing the effects of an intervention on clinical outcomes, eating behavior measures, and potential mechanistic mediators. Cross-sectional studies that looked only at correlations among PET/SPECT and clinical features, eating behavior measures and mechanistic mediators, in participants *before* any intervention, and studies that only looked at pharmacological interventions are out of the scope of this review.

A systematic review was completed of studies investigating the impact of bariatric surgery and dietary intervention on brain function using PET/SPECT scans. A comprehensive search of the literature was undertaken to obtain information on both longitudinal and cross-sectional human studies.

2 | METHODS

2.1 | Inclusion and exclusion criteria

The studies selected for the review included the following criteria.

2.1.1 | Inclusion criteria

i. Longitudinal and cross-sectional human studies.
ii. Studies published in English.
iii. Articles published between January 1980 and April 2021.
iv. Studies conducted on adolescents or adults aged 16 years and older, of either sex.
v. Participants in the intervention group should be diagnosed with overweight (body mass index, BMI > 25 kg/m^2) or obesity with BMI > 30 kg/m^2.
vi. Assessments of obesity surgery (RYGB, VSG, one anastomosis gastric bypass, gastric banding, vertical band gastroplasty, biliary-pancreatic diversion, and gastric balloon) and dietary interventions.
vii. Studies using brain PET/SPECT scanning, including tracers assessing neurotransmitter systems, rCBF, glucose uptake, or uptake of other metabolites.

2.1.2 | Exclusion criteria

i. Studies performed on children <16 years old.
ii. Studies conducted on animals.
iii. Reviews and meetings abstracts.
iv. PET/SPECT studies that just assessed the impact of interventions on peripheral tracer binding (such as the heart, gastrointestinal tract, or adipose tissue).
v. PET/SPECT studies that only included a pharmacological intervention.

2.2 | Database search

An electronic database search was performed to find the articles to form the evidence base for this review. A comprehensive search was performed across multiple databases and journals using PubMed, Web of Science, PsycINFO, MEDLINE, and EMBASE databases within OVID. Reference lists were also examined from individual papers and relevant review articles.

2.2.1 | Keywords/terms used

The detailed keywords and terms used are provided in Data S1 Methods.

2.3 | Data extraction

A complete description of all data extraction is available in Data S1 Methods.

2.4 | Methodological quality assessment

The reviewer assessed the methodological quality of the articles by using the National Institutes of Health (NIH) Quality Assessment Tool for the following: (i) observational cohort and cross-sectional studies, (ii) before–after (pre-post) studies with no control group, (iii) controlled intervention studies (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools), including appraisal criteria specific to the study design. For instance, studies were rated based upon the following criteria: exposure-related considerations (timeline relative to outcome measurement, frequency of measure, and categorization of exposure levels); methodological validity of exposure and outcome measurements; participation and post-baseline follow-up rates; adjustment for confounding variables; outcome assessor blinding; and explicitness of aims, sample, and study setting. The summary score of each study was calculated based on applicable questions for that particular study, expressed as a percentage ranging from 0% to 100%. These were categorized into three categories of quality assessment: poor (0–33.3%), fair (33.4–66.6%), good (66.7–100%), which were equated to high, low, and very low risk of bias.[31]

3 | RESULTS

3.1 | Search results and selection of studies

Using the keywords, 604 articles were identified and 480 of these were screened after duplicates were removed. From these articles, 458 were excluded with only 22 studies meeting the inclusion criteria (Figure 1).

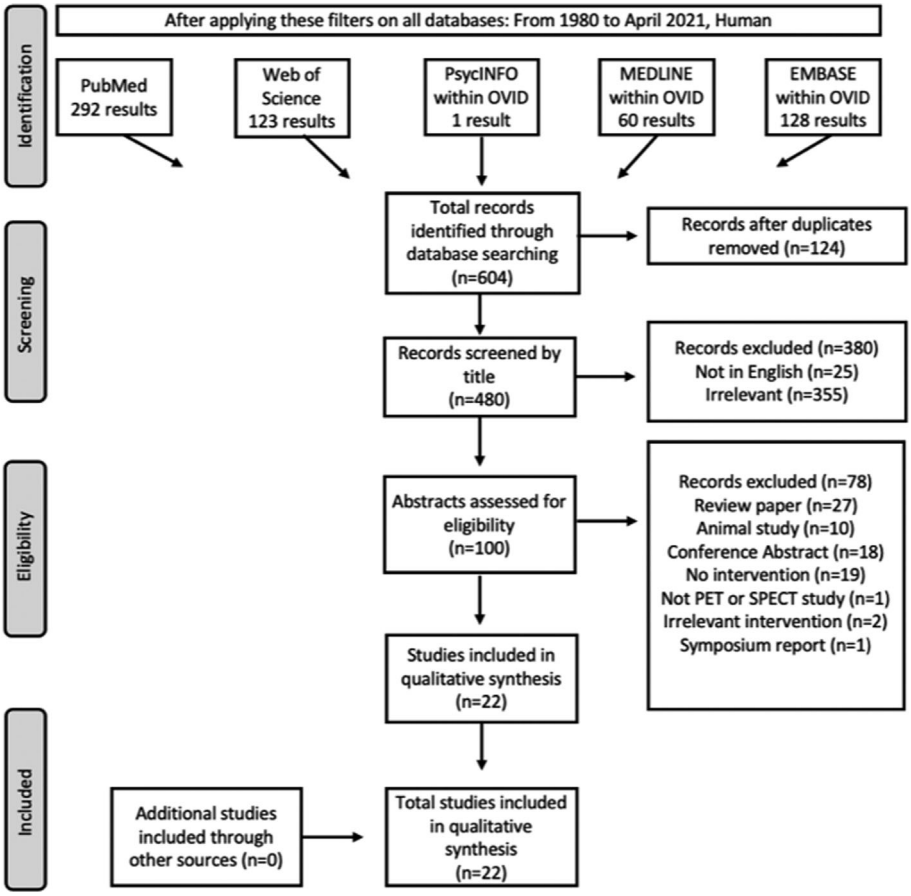

FIGURE 1 PRISMA flow diagram for included studies.

Nineteen of these studies used PET scans,[32–50] whereas three studies used SPECT scans.[51–53]

3.2 | Study summary

3.2.1 | PET/SPECT tracers

A complete description of all PET/SPECT tracers is available in S1 Results. Radioactive tracers used to investigate neurotransmitter systems are illustrated in Figure 2. Radioactive tracers used to investigate brain metabolism are illustrated in Figure 3.

3.2.2 | Country

The country where the studies were conducted are provided in Table 1 and summarised in Data S1 Results: 3.2.2. Country.

3.2.3 | Study design

Study summaries are presented in Table 1.

Of the included studies, 18 (81.8%) were of a longitudinal design[32–37,39–43,46,47,49–53] with 11 of these (61.1%) including a surgical intervention and seven (38.9%) a dietary intervention. No studies included a control dietary intervention in the same publication as the surgical intervention. Out of the four (18.2%) cross-sectional studies, one included a surgical intervention[38] and three a dietary intervention.[44,45,48]

Among the different types of interventions, 12 studies (54.5%) assessed the effect of surgery: seven included RYGB surgery[32,37,38,40,50–52] and five included a mixed RYGB/VSG surgery group.[33,34,39,41,49] There were no studies that assessed only VSG surgery and no studies included one anastomosis gastric bypass, gastric banding, biliopancreatic diversion or gastric balloon.

Among the 10 studies (45.5%) assessing dietary interventions, three included very low-calorie diet (VLCD),[35,36,46] six low-calorie diet (LCD),[42,44,45,47,48,53] and one study assessed total fasting for 3 weeks.[43]

3.3 | Demographic data

Demographic data for individual studies are given in Table 2.

3.4 | Study protocols and analysis

Study protocols and PET/SPECT protocols and analysis are summarized in Tables S1–S3.

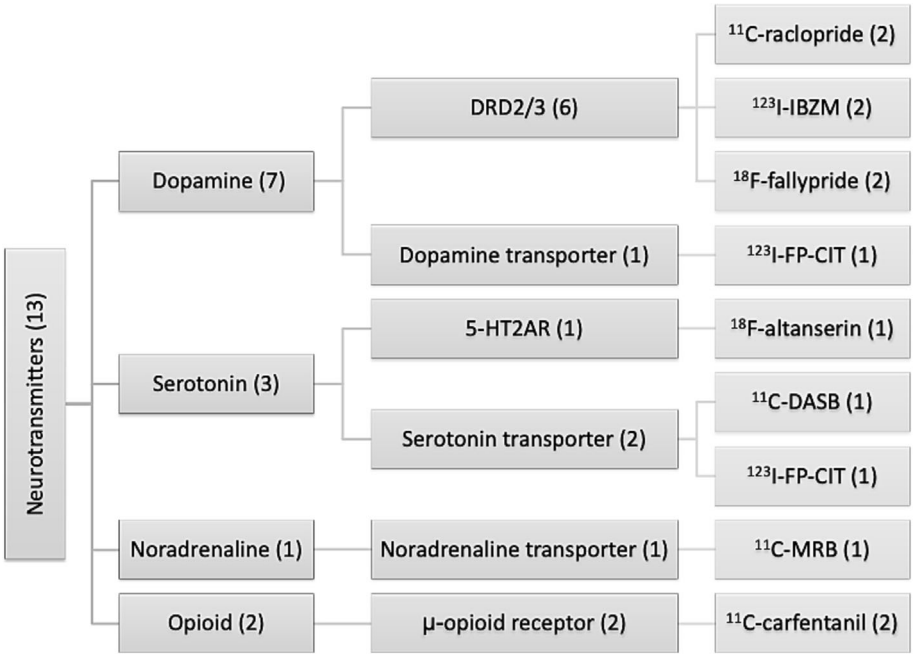

FIGURE 2 Summary of radioactive tracers used to investigate neurotransmitter systems. Number in brackets indicates number of studies.

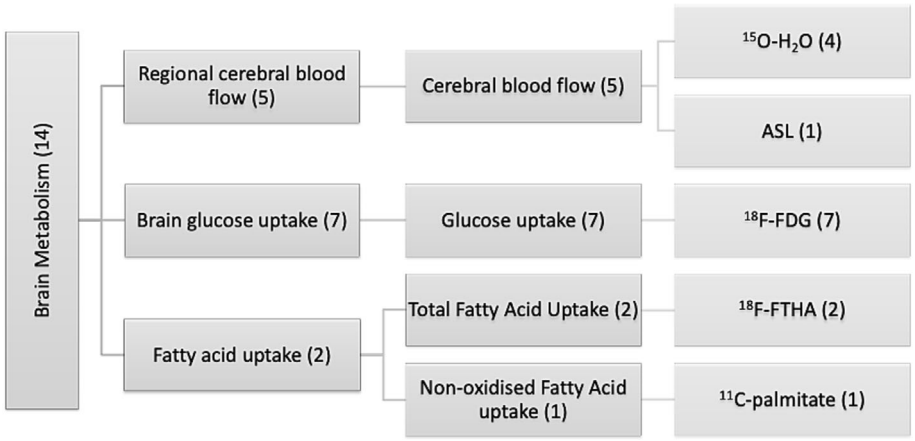

FIGURE 3 Summary of radioactive tracers used to investigate brain metabolism. Number in brackets indicates number of studies.

A complete description of study protocols is available in Data S1 Results: 3.4.1. Nutritional status, 3.4.2. Menstrual cycle, 3.4.3. Mood assessment, 3.4.4. PET paradigm and stimulus type, and 3.4.5. PET/SPECT analysis methodology.

Quality of data and risk of bias is summarized in Table S4 and described in Data S1 Results: 3.4.6. Quality of data.

3.5 | PET/SPECT study findings

Study findings are summarized in Table S5. A complete description of study findings is available in Data S1 Results: 3.5.1. Dopamine neurotransmitter system, 3.5.2. Serotonin neurotransmitter system, 3.5.3. Opioid neurotransmitter system, 3.5.4. Noradrenaline neurotransmitter system, 3.5.5. Regional cerebral blood flow, 3.5.6. Brain glucose uptake, and 3.5.7. Brain fatty acid uptake.

3.6 | Correlations

Association of PET/SPECT findings with clinical outcomes are summarized in Table S6 and described in Data S1 Results: 3.6.1. Clinical outcomes.

Behavioral measures and their association with PET/SPECT findings are summarized in Tables S7 and S8, and described in Data S1 Results: 3.6.2. Behavioral outcomes and 3.6.3. Mood assessment.

Blood mechanistic measures and the association with PET/SPECT findings are summarized in Tables S9 and S10, and described in Data S1 Results: 3.6.4. Mechanistic outcomes.

4 | DISCUSSION

This literature review of PET/SPECT studies examining neurotransmitter systems and rCBF and metabolite uptake in surgical and non-

TABLE 1 Study summaries.

Author, year	Journal	Country	Tracer	Target	Design	Bariatric surgery	Non-surgical dietary intervention	Control group	Group (s)	Task
DOPAMINE										
^{11}C-raclopride										
Steele, 2010	Obes Surg	USA	^{11}C-raclopride	DRD2/3	long.	Yes (mix)	o	Yes (CS)	RYGB, NWC	o
Karlsson, 2016[a]	Mol Psychiatry	Finland	^{11}C-raclopride	DRD2/3	long.	Yes (mix)	o	Yes (CS)	RYGB/VSG, NOC	o
^{18}F-fallypride										
Dunn, 2010	Brain Res	USA	^{18}F-fallypride	DRD2/3	long.	Yes (mix)	o	o	RYGB/VSG	o
Dunn, 2017	Obesity	USA	^{18}F-fallypride	DRD2/3	long.	o	Yes	o	OB-VLCD	o
^{123}I-IBZM										
de Weijer, 2014[b]	Diabetologia	Netherlands	^{123}I-IBZM	DRD2/3	long.	Yes	o	o	RYGB	o
van der Zwaal, 2016[b]	Eur Neuropsychopharmacol	Netherlands	^{123}I-IBZM	DRD2/3	long.	Yes	o	Yes (CS)	RYGB, NOC	o
^{123}I-FP-CIT										
Versteeg, 2017[c]	FASEB J	Netherlands	^{123}I-FP-CIT	DAT	long.	o	Yes	o	OB-LCD-BR, OB-LCD-D[d]	o
SEROTONIN										
^{123}I-FP-CIT										
Versteeg, 2017[c]	FASEB J	Netherlands	^{123}I-FP-CIT	SERT	long.	o	Yes	o	OB-LCD-BR, OB-LCD-D[d]	o
^{18}F-altanserin and ^{11}C-DASB										
Haahr, 2015	J Neurosci	Denmark	^{11}C-DASB, ^{18}F-altanserin	SERT, 5-HT$_{2A}$R	long.	Yes	o	Yes (CS)	RYGB, NWC	o
NORADRENALINE										
^{11}C-MRB										
Vettermann, 2018	Eur J Nucl Med Mol Imaging	Germany	^{11}C-MRB	NAT	long.	o	Yes	Yes (CS)	OB-LCD, NOC-NT	o
OPIOID										
^{11}C-carfentanil										
Karlsson, 2016[a]	Mol Psychiatry	Finland	^{11}C-carfentanil	MOR	long.	Yes (mix)	o	Yes (CS)	RYGB/VSG, NOC	o
Burghardt, 2015	J Clin Endocrinol Metab	USA	^{11}C-carfentanil	MOR	long.	o	Yes	Yes (CS)	OB-VLCD, NWC	o
GLUCOSE METABOLISM										
^{18}F-FDG										
Hunt, 2016	Diab Care	UK	^{18}F-FDG	GU	CS	Yes	o	Yes (CS)	RYGB, OB, NWC	o
Rebelos, 2019	Diabetes Obes Metab	Finland	^{18}F-FDG	GU	long.	Yes (mix)	o	Yes (CS)	RYGB/VSG, NOC	o
Marques, 2014	J Clin Endocrinol Metab	Brazil	^{18}F-FDG	GU	long.	Yes	o	Yes (CS)	RYGB, NWC	o
Tuulari, 2013	Diabetes	Finland	^{18}F-FDG	GU	long.	Yes (mix)	o	Yes (CS)	RYGB/VSG, NOC	o
Guzzardi, 2018	Eur Eat Disord Rev	Italy	^{18}F-FDG	GU	long.	o	Yes	o	OW-LCD (low vs. high YFAS)[e]	Yes
Redies, 1989[a]	Am J Physiol	Canada	^{18}F-FDG	GU	long.	o	Yes	o	OB-fast[f]	o
Almby, 2021	Diabetes	Sweden	^{18}F-FDG	GU	long.	Yes	o	o	RYGB	o

TABLE 1 (Continued)

Author, year	Journal	Country	Tracer	Target	Design	Bariatric surgery	Non-surgical dietary intervention	Control group	Group (s)	Task
CEREBRAL BLOOD FLOW										
^{15}O-H_2O										
Redies, 1989[a]	Am J Physiol	Canada	^{15}O-H_2O	CBF	long.	o	Yes	o	OB-fast	o
Delparigi, 2004[b]	Int J Obesity	USA	^{15}O-H_2O	CBF	CS	o	Yes	Yes (CS)	post-OB-LCD[j], OB, NWC	o
Delparigi, 2007[b]	Int J Obesity	USA	^{15}O-H_2O	CBF	CS	o	Yes	Yes (CS)	post-OB-LCD[j], OB	o
Le, 2007[b]	Am J Clin Nutr	USA	^{15}O-H_2O	CBF	CS	o	Yes	Yes (CS)	post-OB-LCD[j], OB, NWC	o
ASL										
Almby, 2021	Diabetes	Sweden	ASL	CBF	long.	Yes	o	o	RYGB	o
FATTY ACID METABOLISM										
^{18}F-FTHA and ^{11}C-palmitate										
Kami, 2010	Diabetes	Finland	^{18}F-FTHA, ^{11}C-palmitate	total FAU non-oxidized FAU	long.	o	Yes	Yes (CS)	MS-VLCD, NOC	o
Rebelos, 2020	Diabetes Obes Metab	Finland	^{18}F-FTHA	total FAU	long.	Yes (mix)	o	Yes (CS)	RYGB/VSG, NOC	o

Abbreviations: ^{11}C-DASB, ^{11}C-3-amino-4-(2-dimethylaminomethyl-phenylsulfanyl)-benzonitrile; ^{11}C-MRB, ^{11}C-methylreboxetine; ^{123}I-FP-CIT, ^{123}I-N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropane; ^{123}I-IBZM, ^{123}I-iodobenzamide; ^{15}O-H_2O, ^{15}O-water; ^{18}F-FDG, ^{18}F-fluorodeoxyglucose; ^{18}F-FTHA, ^{18}F-fluoro-6-thia-heptadecanoic acid; 5-HT_{2A}R, serotonin 2A receptor; ASL, arterial spin labeling; BMI, body mass index; BR, breakfast; CBF, cerebral blood flow; CHO, carbohydrate; CS, cross-sectional; D, dinner; DAT, dopamine transporter; DRD2/3, dopamine receptor D2/3; FAU, fatty acid uptake; GU, glucose uptake; HEC, hyperinsulinemic euglycemic clamp; HOC, hyperinsulinemic hypoglycemic clamp; LCD, low-calorie diet; long., longitudinal; mix, mixed group; MOR, μ-opioid receptor; MS, metabolic syndrome; n/a, not applicable; NAT, noradrenaline transporter; NOC, non-obese control; NT, no treatment; NWC, normal weight control (lean); o, no; OB, obesity; OW, overweight; PET, positron emission tomography; REE, resting energy expenditure; RYGB, Roux-en-Y gastric bypass; SERT, serotonin transporter; SPECT, single-photon emission computerized tomography; SST, somatostatin; UK, United Kingdom; USA, United States of America; VLCD, very low-calorie diet; VSG, vertical sleeve gastrectomy; YFAS, Yale Food Addiction Scale.

[a]Same datasets.

[b]Overlapping datasets.

[c]Same dataset and tracer (SERT binding at 2 h, DAT binding at 3 h).

[d]50% of total 24-h energy requirements (calculated from 1.33 × REE using indirect calorimetry) with 35% at lunch, and either 50% at breakfast, 15% at dinner (LCD-BR) or 15% at breakfast, 50% at dinner (LCD-D).

[e]1600 kcal/day (30% fat, 50% CHO, 20% protein).

[f]Fasted for 3 weeks.

[g]With diet and exercise BMI fallen from >35 to ≤25 kg/m^2 and weight stable ≥ 3 months.

[h]But no localization reported.

TABLE 1 (Continued)

Author, year	Paradigm	Nutritional state interaction	Other state intervention	Association PET/SPECT with clinical outcome	Appetite ratings	Other eating behavior measures	Association PET/SPECT with appetite/ behavior	Assessment nausea or dumping symptoms	Mechanistic blood measures	Association PET/SPECT with mechanistic measures	Exclusion criteria: use of psychotropic medication
DOPAMINE											
^{11}C-raclopride											
Steele, 2010	n/a	o	o	o	o	o	o	o	o	o	Yes
Karlsson, 2016[a]	n/a	o	o	Yes	o	Yes	Yes	o	Yes	Yes	Yes
^{18}F-fallypride											
Dunn, 2010	n/a	o	o	o	o	Yes	o	o	Yes	o	Yes
Dunn, 2017	n/a	o	o	o	o	o	o	o	Yes	Yes	Yes
^{123}I-IBZM											
de Weijer, 2014[b]	n/a	o	o	Yes	o	o	o	o	Yes	Yes	Yes
van der Zwaal, 2016[b]	n/a	o	o	Yes	o	Yes	Yes	o	Yes	Yes	Yes
^{123}I-FP-CIT											
Versteeg, 2017[c]	n/a	o	o	o	Yes	o	o	o	Yes	o	Yes
SEROTONIN											
^{123}I-FP-CIT											
Versteeg, 2017[c]	n/a	o	o	o	Yes	o	o	o	Yes	o	Yes
^{18}F-altanserin and ^{11}C-DASB											
Haahr, 2015	n/a	o	o	Yes	Yes	o	Yes	o	Yes	Yes	Yes
NORADRENALINE											
^{11}C-MRB											
Vettermann, 2018	n/a	o	o	Yes	o	Yes	o	o	o	o	Yes
OPIOID											
^{11}C-carfentanil											
Karlsson, 2016[a]	n/a	o	o	Yes	o	Yes	Yes	o	Yes	Yes	Yes
Burghardt, 2015	n/a	Yes	o	Yes	Yes	o	Yes	o	o	o	Yes
GLUCOSE METABOLISM											
^{18}F-FDG											
Hunt, 2016	n/a	Yes	± SST/insulin infusion	o	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Rebelos, 2019	n/a	o	± HEC	Yes[h]	o	o	o	o	Yes	Yes[h]	Yes
Marques, 2014	n/a	o	o	o	o	o	o	o	Yes	o	Yes
Tuulari, 2013	n/a	o	o	o	o	o	o	o	Yes	o	Yes
Guzzardi, 2018	Food cue reactivity, Taste, Food odor	o	o	Yes	Yes	Yes	Yes	o	Yes	Yes	Yes
Redies, 1989[a]	n/a	o	o	o	o	o	o	o	Yes	o	o
Almby, 2021	n/a	o	HEC vs. HOC	o	o	o	o	o	Yes	o	Yes

TABLE 1 (Continued)

Author, year	Paradigm	Nutritional state interaction	Other state intervention	Association PET/SPECT with clinical outcome	Appetite ratings	Other eating behavior measures	Association PET/SPECT with appetite/ behavior	Assessment nausea or dumping symptoms	Mechanistic blood measures	Association PET/SPECT with mechanistic measures	Exclusion criteria: use of psychotropic medication
CEREBRAL BLOOD FLOW											
^{15}O-H_2O											
Redies, 1989[a]	n/a	o	o	o	o	o	o	o	Yes	o	o
Delparigi, 2004[b]	Taste	Yes	o	o	Yes	o	Yes	o	Yes	Yes	Yes
Delparigi, 2007[b]	Taste	Yes	o	o	Yes	Yes	Yes	o	Yes	Yes	Yes
Le, 2007[b]	o	Yes	o	o	Yes	o	o	o	Yes	o	Yes
ASL											
Almby, 2021	n/a	o	HEC vs. HOC	o	o	o	o	o	Yes	o	Yes
FATTY ACID METABOLISM											
^{18}F-FTHA and ^{11}C-palmitate											
Karmi, 2010	n/a	o	o	Yes	o	o	o	o	Yes	o	Yes
Rebelos, 2020	n/a	o	o	Yes	o	o	o	o	Yes	Yes	Yes

Abbreviations: ^{11}C-DASB, ^{11}C-3-amino-4-(2-dimethylaminomethyl-phenylsulfanyl)-benzonitrile; ^{11}C-MRB, ^{11}C-methylreboxetine; ^{123}I-FP-CIT, ^{123}I-N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropane; ^{123}I-IBZM, ^{123}I-iodobenzamide; ^{15}O-H_2O, ^{15}O-water; ^{18}F-FDG, ^{18}F-fluorodeoxyglucose; ^{18}F-FTHA, ^{18}F-fluoro-6-thia-heptadecanoic acid; 5-HT_{2A}R, serotonin 2A receptor; ASL, arterial spin labeling; BMI, body mass index; BR, breakfast; CBF, cerebral blood flow; CHO, carbohydrate; CS, cross-sectional; D, dinner; DAT, dopamine transporter; DRD2/3, dopamine receptor D2/3; FAU, fatty acid uptake; GU, glucose uptake; HEC, hyperinsulinemic euglycemic clamp; HOC, hyperinsulinemic hypoglycemic clamp; LCD, low-calorie diet; long., longitudinal; mix, mixed group; MOR, μ-opioid receptor; MS, metabolic syndrome; n/a, not applicable; NAT, noradrenaline transporter; NOC, non-obese control; NT, no treatment; NWC, normal weight control (lean); o, no; OB, obesity; OW, overweight; PET, positron emission tomography; REE, resting energy expenditure; RYGB, Roux-en-Y gastric bypass; SERT, serotonin transporter; SPECT, single-photon emission computerized tomography; SST, somatostatin; UK, United Kingdom; USA, United States of America; VLCD, very low-calorie diet; VSG, vertical sleeve gastrectomy; YFAS, Yale Food Addiction Scale.

[a]Same datasets.

[b]Overlapping datasets.

[c]Same dataset and tracer (SERT binding at 2 h, DAT binding at 3 h).

[d]50% of total 24-h energy requirements (calculated from 1.33 × REE using indirect calorimetry) with 35% at lunch, and either 50% at breakfast, 15% at dinner (LCD-BR) or 15% at breakfast, 50% at dinner (LCD-D).

[e]1600 kcal/day (30% fat, 50% CHO, 20% protein).

[f]Fasted for 3 weeks.

[g]With diet and exercise BMI fallen from >35 to ≤25 kg/m^2 and weight stable ≥ 3 months.

[h]But no localization reported.

TABLE 2 Demographic data.

Author, year	*N*	Group (s)	Female	Age at baseline (y)	T2DM	White Caucasian
			n (%)	Mean ± SD or median [IQR] (range)	*n* (%)	*n* (%)
DOPAMINE						
^{11}C-raclopride						
Steele, 2010	5	RYGB	5 (100%)	32.2 ± 7.3 (20–38)	0 (0%)	2 (40.0%)
	5	NWC	5 (100%)	21.8	0 (0%)	?
Karlsson, 2016[a]	16 (? RYGB, ? VSG)	RYGB/VSG	16 (100%)	42.8 ± 10.2	6 (37.5%)	?
	14	NOC	14 (100%)	44.9 ± 12.9	0 (0%)	?
^{18}F-fallypride						
Dunn, 2010	5 (4 RYGB, 1 VSG)	RYGB/VSG	5 (100%)	45.8 ± 4.3 (41–50)	0 (0%)	4 (80%)
Dunn, 2017	15	OB-VLCD[m]	15 (100%)	39 ± 8	1 (6.7%)	8 (53.3%)
^{123}I-IBZM						
de Weijer, 2014[b]	19	RYGB	19 (100%)	40.4 ± 8 (26–49)	?	19 (100%)
van der Zwaal, 2016[b]	11 (14 overall)[d]	RYGB	11 (100%), overall 14 (100%)	44.3 ± 6	?	11 (100%)
	11	NOC	11 (100%)	40.5 ± 4	?	11 (100%)
^{123}I-FP-CIT						
Versteeg, 2017[c]	9 (12 overall)[e]	OB-LCD-BR[n]	0 (0%), 0 (0%)	60.7 ± 7.7[j]	0 (0%) but 100% IFG or IR	?
	11	OB-LCD-D[n]	0 (0%)	59.0 ± 8.5	0 (0%) but 100% IFG or IR	?
SEROTONIN						
^{123}I-FP-CIT						
Versteeg, 2017[c]	9 (12 overall)[e]	OB-LCD-BR[n]	0 (0%), overall 0 (0%)	60.7 ± 7.7[e]	0 (0%) but 100% IFG or IR	?
	11	OB-LCD-D[n]	0 (0%)	59.0 ± 8.5	0 (0%) but 100% IFG or IR	?
^{18}F-altanserin and ^{11}C-DASB						
Haahr, 2015	pre-RYGB: 20–21, post-RYGB: 12–13	RYGB	pre-RYGB: 16–17 (80.0–80.9%), post-RYGB: 10–11 (83.3–84.6%)	41.3 ± 8.4[s]	?	?
	10	NWC	7 (70.0%)	45.6 ± 9.7	0 (0%)	?
NORADRENALINE						
^{11}C-MRB						
Vettermann, 2018	10	OB-LCD	4 (40.0%)	34.4 ± 9.0	0 (0%)	10 (100%)
	9 (10 overall)[f]	NOC-NT	? (?%), overall 4 (40.0%)[f]	33.3 ± 10.0[f]	0 (0%)	10 (100%)[l]
OPIOID						
^{11}C-carfentanil						
Karlsson, 2016[a]	16 (? RYGB, ? VSG)	RYGB/VSG	16 (100%)	42.8 ± 10.1	6 (37.5%)	?
	14	NOC	14 (100%)	44.9 ± 12.9	0 (0%)	?
Burghardt, 2015	6 (7 overall)[g]	OB-VLCD[o]	0 (0%), overall 0 (0%)	51.4 ± 11.2[g]	?	?
	7	NWC	0 (0%)	52.4 ± 9.0	?	?

TABLE 2 (Continued)

Author, year	N	Group (s)	Female	Age at baseline (y)	T2DM	White Caucasian
GLUCOSE METABOLISM						
^{18}F-FDG						
Hunt, 2016	9	RYGB	8 (88.9%)	45.1 ± 10.7	? (1 on metformin)	5 (55.6%)
	21	OB	19 (90.5%)	31.1 ± 10.5	? (1 on metformin)	14 (66.7%)
	12	NWC	9 (75%)	32.3 ± 9.3	?	11 (91.7%)
Rebelos, 2019	16–20[h] (11 RYGB, 9 VSG)	RYGB/VSG	16 (100%), overall 19 (95.0%)[h]	46 ± 9[h]	6 (31.6%)[h]	?
	12	NOC	8 (66.7%)	43 ± 11	0 (0%)	?
Marques, 2014	17	RYGB	17 (100%)	40.5 ± 10.1	0 (0%)	?
	16	NWC	16 (100%)	41.4 ± 8.7	0 (0%)	?
Tuulari, 2013	17–22[i] (? RYGB, ? VSG)	RYGB/VSG	17 (100%), 20 (90.9%)	45.4 ± 9.3	4 (23.5%)	?
	7	NOC	5 (71.4%)	47.9 ± 5.6	0 (0%)	?
Guzzardi, 2018	11–14[j]	OW-LCD (low-YFAS)[p]	11 (100%), overall 14 (100%)	33.8 ± 10.8	0 (0%)	?
	12–22[j]	OW-LCD (high-YFAS)[p]	12 (100%), overall 22 (100%)	37.5 ± 8.9	0 (0%)	?
Redies, 1989[a]	4	OB-fast	0 (0%)	37.8 ± 6.2	0 (0%)	?
Almby, 2021	11	RYGB	8 (72.7%)	35 ± 8	0 (0%)	?
CEREBRAL BLOOD FLOW						
^{15}O-H_2O						
Redies, 1989[a]	4	OB-fast[w]	0 (0%)	38 ± 6.2	0 (0%)	?
Delparigi, 2004[b]	11	post-OB-LCD[q]	8 (72.72%)	40 ± 6	0 (0%)	?
	23	OB	12 (52.2%)	29 ± 6	0 (0%)	?
	21	NWC	10 (47.6%)	33 ± 9	0 (0%)	?
Delparigi, 2007[b]	9	post-OB-LCD[q]	9 (100%)	38.0 ± 6.5	0 (0%)	?
	20	OB	20 (100%)	31.3 ± 8.6	0 (0%)	?
Le, 2007[b]	8	post-OB-LCD[q]	8 (100%)	39 ± 7	0 (0%)	8 (100%)
	9	OB	9 (100%)	31 ± 8	0 (0%)	9 (100%)
	10	NWC	10 (100%)	33 ± 10	0 (0%)	10 (100%)
ASL						
Almby, 2021	11	RYGB	8 (72.7%)	35 ± 8	0 (0%)	?

(Continues)

TABLE 2 (Continued)

Author, year	N	Group (s)	Female	Age at baseline (y)	T2DM	White Caucasian
FATTY ACID METABOLISM						
^{18}F-FTHA and ^{11}C-palmitate						
Karmi, 2010	16 (overall 23)[k]	MS-VLCD[r]	11 (68.8%), overall 15 (65.2%)[k]	43 ± 7[k]	? but 100% MS	?
	7	NOC	0 (0%)	42 ± 11	0 (0%)	?
Rebelos, 2020	21 (overall 24)[l] (? RYGB, ? VSG)	RYGB/VSG	21 (100%), overall 24 (100%)	43 ± 10	9 (37.5%) T2DM, 4 (16.7%) IGT, 1 (4.2%) IFG	?
	14	NOC	14 (100%)	45 ± 12	0 (0%)	?

Abbreviations: ?, unknown; →, no change; ↑, increase; ↓, decrease; ^{11}C-DASB, ^{11}C-3-amino-4-(2-dimethylaminomethyl-phenylsulfanyl)-benzonitrile; ^{11}C-MRB, ^{11}C-methylreboxetine; ^{123}I-FP-CIT, ^{123}I-N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl) nortropane; ^{123}I-IBZM, ^{123}I-iodobenzamide; ^{15}O-H_2O, ^{15}O-water; ^{18}F-FDG, ^{18}F-fluorodeoxyglucose; ^{18}F-FTHA, ^{18}F-fluoro-6-thia-heptadecanoic acid; ASL, arterial spin labeling; BMI, body mass index; BR, breakfast; CHO, carbohydrate; D, dinner; DAT, dopamine transporter; FPG, fasting plasma glucose (to convert mmol/L to mg/dL multiply by 18); HbA1c, glycated hemoglobin; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IQR, interquartile range; IR, insulin resistance; LCD, low-calorie diet; MS, metabolic syndrome; n/a, not applicable; NOC, non-obese control; NT, no treatment; NWC, normal weight control (lean); OB, obesity; OW, overweight; PG, plasma glucose; REE, resting energy expenditure; RYGB, Roux-en-Y gastric bypass; SD, standard deviation; SERT, serotonin transporter; SPECT, single-photon emission computerized tomography; T2DM, type 2 diabetes mellitus; VLCD, very low-calorie diet; VSG, vertical sleeve gastrectomy; YFAS, Yale Food Addiction Scale.

[a]Same datasets.
[b]Overlapping dataset.
[c]Same dataset and tracer (SERT binding at 2 h, DAT binding at 3 h.
[d]For $n = 14$ overall (includes $n = 3$ without SPECT scan).
[e]For $n = 12$ overall (includes $n = 3$ without SPECT scan).
[f]For $n = 10$ overall (includes $n = 1$ excluded from analysis as lost >10% weight).
[g]For $n = 7$ overall (includes $n = 1$ with only baseline but no post-VLCD PET scan).
[h]$n = 20$ baseline, $n = 16$ at 6 months, $n = 17$ at 2 years, $n = 13$ at 3 years.
[i]For $n = 22$ overall (includes $n = 5$ with only baseline but no post-RYGB PET scan).
[j]Higher number at baseline only, lower number post-LCD.
[k]For $n = 23$ overall (including $n = 7$ with only baseline and without post-VLCD PET scan).
[l]For $n = 24$ overall (including $n = 3$ with only baseline and without post-RYGB/VSG PET scan).
[m]800 kcal per day.
[n]50% of total energy requirements (calculated from 1.33 × REE using indirect calorimetry) with 35% at lunch, and either 50% at breakfast, 15% at dinner (LCD-BR) or 15% at breakfast, 50% at dinner (LCD-D).
[o]800 kcal per day as total meal replacement.
[p]1600 kcal/day (30% fat, 50% CHO, 20% protein).
[q]With diet and exercise BMI fallen from >35 to ≤ 25 kg/m^2 and weight stable ≥ 3 months.
[r]550 kcal per day meal replacement (7% fat, 51% CHO, 42% protein).
[s]For $n = 21$ at baseline, $n = 14$ post-intervention.
[t]Estimated from change in average BMI.
[u]Estimated from change in average weight.
[v]For $n = 18$ at baseline.
[w]Fasted for 3 weeks.

TABLE 2 (Continued)

Author, year	Control intervention	Time scan pre-intervention (months)	Time between scans (months)	Time scan post-intervention (months)	Baseline BMI	Current/post-BMI (kg/m2)	Weight loss	Change in glycaemia
				Mean ± SD or median [IQR] (range)	Mean ± SD or median [IQR] (range)	Mean ± SD or median [IQR] (range) kg/m^2	Mean ± SD (range) % or kg	Mean ± SD
DOPAMINE								
^{11}C-raclopride								
Steele, 2010	n/a	?	?	(0.9–1.4)	45.2 ± 5.9 (40–53)	38.0 ± 6.9	12.9 ± 6.5% (6.5–23.0)[t]	?
	None	n/a	n/a	n/a	21.3	n/a	n/a	n/a
Karlsson, 2016[a]	n/a	pre-VLCD	?	6	40.3 ± 3.9 (36.1–49.3)	31.0 ± 3.7	∼23.3%[u]	HbA1c (%): ↓ pre-RYGB: 5.9 ± 0.8, post-RYGB: 5.4 ± 0.5
	None	n/a	n/a	n/a	22.7 ± 2.9	n/a	n/a	

TABLE 2 (Continued)

Author, year	Control intervention	Time scan pre-intervention (months)	Time between scans (months)	Time scan post-intervention (months)	Baseline BMI	Current/post-BMI (kg/m2)	Weight loss	Change in glycaemia
^{18}F-fallypride								
Dunn, 2010	n/a	?	median 2.1 (1.8–5.3)	median 1.6 (1.4–2.5)	43.2 ± 6.3 (38–54)	38 ± 7	11.6 ± 2.0% (8.5–13.4)[u]	?
Dunn, 2017	n/a	0	(0.26–0.32)	(0.26–0.32)	39 ± 6	38 ± 6	∼2.9%[u]	FPG (mmol/L): ↓
^{123}I-IBZM								
de Weijer, 2014[b]	n/a	?	?	1.4	45.7 ± 6.3 (38.7–1.3)	40.9 ± 6.3 (34.1–57.6)	14 ± 4.6 kg (8–24)	?
van der Zwaal, 2016[b]	n/a	?	?	37.2 (25.2–43.2)[g]	45.2 ± 6.7 (38.7–61.3)[g]	31.2 ± 5.7 (24.1–43.7)[g]	∼30.9%[t,g]	FPG (mmol/L): ↓ pre-RYGB: 5.6 ± 0.8, post-RYGB: 4.6 ± 0.2 g
	None	n/a	n/a	n/a	21.9 ± 2.0	n/a	n/a	
^{123}I-FP-CIT								
Versteeg, 2017[c]	n/a	0	0.9	0.9	34.2 ± 4.2[j]	?	6.5 ± 1.5%[u]	?
	n/a	0	0.9	0.9	34.3 ± 3.7	?	6.2 ± 1.9%[u]	?
SEROTONIN								
^{123}I-FP-CIT								
Versteeg, 2017[c]	n/a	0	0.9	0.9	34.2 ± 4.2[e]	?	6.5 ± 1.5%[u]	?
	n/a	0	0.9	0.9	34.3 ± 3.7	?	6.2 ± 1.9%[u]	?
^{18}F-altanserin and ^{11}C-DASB								
Haahr, 2015	n/a	3.1 [1.8–6.0]	?	8.2 [7.5–8.5]	40.1 ± 4.1	28.9 ± 4.1	25.80%	?
	None	n/a	n/a	n/a	24.6 ± 1.5	n/a	n/a	n/a
NORADRENALINE								
^{11}C-MRB								
Vettermann, 2018	n/a	?	6.7 ± 1.5	6	42.4 ± 3.7	41.0 ± 3.8	3.7%[u]	?
	None	n/a	6.7 ± 1.6	6	23.9 ± 2.5[f]	23.8 ± 2.5[f]	∼0.5%[u]	n/a
OPIOID								
^{11}C-carfentanil								
Karlsson, 2016[a]	n/a	pre-VLCD	?	6	40.3 ± 3.9 (36.1–49.3)	31.0 ± 3.7	∼23.3%[u]	HbA1c (%):↓ pre-RYGB: 5.9 ± 0.8, post-RYGB: 5.4 ± 0.5
	None	n/a	n/a	n/a	22.7 ± 2.9	n/a	n/a	
Burghardt, 2015	n/a	?	?	3.6 ± 0.7 (2.9–4.5)	38.0 ± 3.4[g]	31.8 ± 1.8	∼16.2%[u]	?
	None	n/a	n/a	n/a	24.0 ± 1.7	n/a	n/a	
GLUCOSE METABOLISM								
^{18}F-FDG								
Hunt, 2016	n/a	n/a	n/a	18 ± 12.6	?	34.0 ± 3.3	30.9 ± 8.5%	n/a
	n/a	n/a	n/a	n/a	n/a	34.1 ± 2.6	n/a	
	n/a	n/a	n/a	n/a	n/a	22.3 ± 1.4	n/a	
Rebelos, 2019	n/a	> 1	∼7	6	43.1 [2.5][h]	32.2 [3.1]	∼26.1%[u], ∼25.3%[t]	T2DM: ↓ 30.0% to 6.3%
	None	n/a	n/a	n/a	23.2 [3.0]	n/a	n/a	IGT: ↓ 50.0% to 12.5%
								HbA1c (%): ↓ pre: 5.8 ± 0.5, post: 5.5 ± 0.3

TABLE 2 (Continued)

Author, year	Control intervention	Time scan pre-intervention (months)	Time between scans (months)	Time scan post-intervention (months)	Baseline BMI	Current/post-BMI (kg/m2)	Weight loss	Change in glycaemia
Marques, 2014	n/a	?	?	6	50.1 ± 4.7	37.2 ± 4.1	∼25.7%[t]	FPG (mmol/L): ↓ pre: 5.4 ± 0.7, post: 4.7 ± 0.5
	None	n/a	n/a	n/a	22.3 ± 2.1	n/a	n/a	
Tuulari, 2013	n/a	>1	>7	6	43.1 ± 3.0	33.2 ± 3.8	∼23.3%[u]	HbA1c (%): ↓ pre: 5.8 ± 0.5 post: 5.5 ± 0.3
	None	n/a	n/a	n/a	23.8 ± 2.1	n/a	n/a	FPG (mmol/L): ↓ pre: 6.2 ± 0.9, post: 5.3 ± 0.6
								T2DM: ↓ 23.5% to 17.6%
								IGT: ↓ 23.5% to 17.6%
Guzzardi, 2018	n/a	0	3	3	32.9 ± 3.7	32.0 ± 4.0	4.6 ± 1.1%	HbA1c (%): pre: 5.4 ± 0.3, post: 5.4 ± 0.3
	n/a	0	3	3	32.7 ± 3.3	31.8 ± 3.5	4.1 ± 1.2%	HbA1c (%): pre: 5.4 ± 3.3, post: 5.3 ± 0.4
Redies, 1989[a]	n/a	0	0.6–0.8	0.6–0.8	36.2 ± 4.1	?	11.8 ± 1.9%	FPG (mmol/L): ↓ pre: 5.4 ± 1.1, post: 4.1 ± 0.3
Almby, 2021	n/a	1.3 (0.7–2.5)[v]	∼5.6	4.4 ± 16	40.2 ± 3.6	29.9 ± 4.0	∼26.6%[u]	FPG (mmol/L): ↓ pre: 6.0 ± 0.5, post: 5.3 ± 0.5
								HbA1c: ↓ pre: 5.3 [5.3, 5.4], post: 5.2 [4.9, 5.3]
CEREBRAL BLOOD FLOW								
^{15}O-H_2O								
Redies, 1989[a]	n/a	0	0.6–0.8	0.6–0.8	36.2 ± 4.1	?	11.8 ± 1.9%	FPG (mmol/L): ↓ pre: 5.4 ± 1.1, post: 4.1 ± 0.3
Delparigi, 2004[b]	n/a	n/a	n/a	n/a	> 35	23.6 ± 1.9	?	?
	n/a	n/a	n/a	n/a	n/a	39.6 ± 3.8	n/a	n/a
	n/a	n/a	n/a	n/a	n/a	22.8 ± 2.1	n/a	n/a
Delparigi, 2007[b]	n/a	n/a	n/a	n/a	> 35	∼23.2	?	?
	n/a	n/a	n/a	n/a	n/a	∼32.0	n/a	
Le, 2007[b]	n/a	n/a	n/a	n/a	> 35	? (65 ± 6 kg)	?	?
	n/a	n/a	n/a	n/a	n/a	? (113 ± 16 kg)	n/a	n/a
	n/a	n/a	n/a	n/a	n/a	? (61 ± 7 kg)	n/a	n/a
ASL								
Almby, 2021	n/a	1.3 (0.7–2.5)[v]	∼5.6	4.4 ± 16	40.2 ± 3.6	29.9 ± 4.0	∼26.6%[u]	FPG (mmol/L): ↓ pre: 6.0 ± 0.5, post: 5.3 ± 0.5
								HbA1c: ↓ pre: 5.3 [5.3, 5.4], post: 5.2 [4.9, 5.3]

TABLE 2 (Continued)

Author, year	Control intervention	Time scan pre-intervention (months)	Time between scans (months)	Time scan post-intervention (months)	Baseline BMI	Current/post-BMI (kg/m2)	Weight loss	Change in glycaemia
FATTY ACID METABOLISM								
^{18}F-FTHA and ^{11}C-palmitate								
Karmi, 2010	n/a	?	?	1.4 (plus 1 week isocaloric diet)	34.0 ± 3.9	30.2 ± 3.9	∼11.1%[u]	FPG (mmol/L): ↓ pre-VLCD: 10.0 ± 0.6, post-VLCD: 5.7 ± 0.5
	None	n/a	n/a	n/a	26.8 ± 2.5	n/a	n/a	
Rebelos, 2020	n/a	>1	>7	6	41.1 ± 4.2	31.8 ± 4.2	∼22.6%[t] (26 ± 8 kg)	PG (mmol/L): → pre-RYGB/VSG: 5.7 ± 1.0, post-RYGB/VSG: 5.3 ± 0.8
	None	n/a	n/a	n/a	22.6 ± 2.8	n/a	n/a	HbA1c (%): ↓ pre-RYGB/VSG: 6.0 ± 0.7, post-RYGB/VSG: 5.4 ± 0.4

Abbreviations: ?, unknown; →, no change; ↑, increase; ↓, decrease; ^{11}C-DASB, ^{11}C-3-amino-4-(2-dimethylaminomethyl-phenylsulfanyl)-benzonitrile; ^{11}C-MRB, ^{11}C-methylreboxetine; ^{123}I-FP-CIT, ^{123}I-N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl) nortropane; ^{123}I-IBZM, ^{123}I-iodobenzamide; ^{15}O-H_2O, ^{15}O-water; ^{18}F-FDG, ^{18}F-fluorodeoxyglucose; ^{18}F-FTHA, ^{18}F-fluoro-6-thia-heptadecanoic acid; ASL, arterial spin labeling; BMI, body mass index; BR, breakfast; CHO, carbohydrate; D, dinner; DAT, dopamine transporter; FPG, fasting plasma glucose (to convert mmol/L to mg/dL multiply by 18); HbA1c, glycated hemoglobin; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IQR, interquartile range; IR, insulin resistance; LCD, low-calorie diet; MS, metabolic syndrome; n/a, not applicable; NOC, non-obese control; NT, no treatment; NWC, normal weight control (lean); OB, obesity; OW, overweight; PG, plasma glucose; REE, resting energy expenditure; RYGB, Roux-en-Y gastric bypass; SD, standard deviation; SERT, serotonin transporter; SPECT, single-photon emission computerized tomography; T2DM, type 2 diabetes mellitus; VLCD, very low-calorie diet; VSG, vertical sleeve gastrectomy; YFAS, Yale Food Addiction Scale.

[a]Same datasets.

[b]Overlapping dataset.

[c]Same dataset and tracer (SERT binding at 2 h, DAT binding at 3 h.

[d]For $n = 14$ overall (includes $n = 3$ without SPECT scan).

[e]For $n = 12$ overall (includes $n = 3$ without SPECT scan).

[f]For $n = 10$ overall (includes $n = 1$ excluded from analysis as lost >10% weight).

[g]For $n = 7$ overall (includes $n = 1$ with only baseline but no post-VLCD PET scan).

[h]$n = 20$ baseline, $n = 16$ at 6 months, $n = 17$ at 2 years, $n = 13$ at 3 years.

[i]For $n = 22$ overall (includes $n = 5$ with only baseline but no post-RYGB PET scan).

[j]Higher number at baseline only, lower number post-LCD.

[k]For $n = 23$ overall (including $n = 7$ with only baseline and without post-VLCD PET scan).

[l]For $n = 24$ overall (including $n = 3$ with only baseline and without post-RYGB/VSG PET scan).

[m]800 kcal per day.

[n]50% of total energy requirements (calculated from 1.33 × REE using indirect calorimetry) with 35% at lunch, and either 50% at breakfast, 15% at dinner (LCD-BR) or 15% at breakfast, 50% at dinner (LCD-D).

[o]800 kcal per day as total meal replacement.

[p]1600 kcal/day (30% fat, 50% CHO, 20% protein).

[q]With diet and exercise BMI fallen from >35 to ≤ 25 kg/m^2 and weight stable ≥ 3 months.

[r]550 kcal per day meal replacement (7% fat, 51% CHO, 42% protein).

[s]For $n = 21$ at baseline, $n = 14$ post-intervention.

[t]Estimated from change in average BMI.

[u]Estimated from change in average weight.

[v]For $n = 18$ at baseline.

[w]Fasted for 3 weeks.

pharmacological weight loss has revealed the difficulties in drawing definitive conclusions as to their effects on brain function and their potential contributions to or consequence of weight loss and changes in appetite and eating behavior. This results from the following factors:

i. Limited number of studies examining each neurotransmitter or metabolite system or rCBF, and within neurotransmitter studies the use of different tracers, as well as limited number of participants within each study.
ii. Variability in type of bariatric surgery used and often combination of multiple types of surgery in single studies.
iii. Methodological heterogeneity across studies including participant characteristics (age, sex, ethnicity, presence of type 2 diabetes mellitus [T2DM]), timing after intervention, degree of weight loss, nutritional status at scanning session, and statistical analysis.
iv. Lack of inclusion of appropriate dietary control interventions, for example VLCD or even LCD, in the same study to control for weight loss and reduced energy intake after bariatric surgery.
v. Uncommon examination of associations of changes in PET/SPECT outcomes after intervention with clinical outcomes such as weight loss or improvements in glycemic control, changes in measures of eating behavior, or potential mechanistic mediators (e.g., appetitive gut hormones).
vi. Uncommon inclusion in studies of confounds that may affect the interpretation of PET/SPECT findings such as phase of menstrual cycle, use of psychotropic medications, or improvements in mood.

4.1 | Dopamine system

Dopamine plays a major role in motivation, reward, and prediction of reward.[54] Dopamine influences food intake via the mesolimbic circuitry (projections from the ventral tegmental area to regions including the ventral and dorsal striatum) by modulating appetitive motivational processes.[55,56] Dopaminergic neurotransmission is mediated by five distinct receptor subtypes, which are classified into two main classes of receptors termed D1-like (D1 and D5) and D2-like (D2, D3, and D4).[54] The D2-like receptors have been associated with feeding and addictive behaviors in human and animal studies.[57–59]

Although one small study ($n = 5$) found an *increase* in striatal ^{11}C-raclopride binding potential (BP) at 4–6 weeks after RYGB surgery following ~13% weight loss in the majority of women, no formal statistics was performed,[32] while no changes were seen in the striatum (or elsewhere in brain) in a larger study (n = 16) of older women at 6 months after RYGB/VSG surgery despite 23% weight loss.[33] Similarly, no change was observed in striatal ^{123}I-iodobenzamide (^{123}I-IBZM) BP 6 weeks post-RYGB surgery after average 14kg weight loss,[51] suggesting that different results are unrelated to temporary early *increases* after surgery or differences in degree of weight loss. However, another study showed an increase in ^{123}I-IBZM BP in striatum and caudate (with trend in putamen) at average 3.1 years after RYGB surgery after 31% weight loss.[52]

By contrast, another small study ($n = 5$) found a *decrease* in ^{18}F-fallypride BP in caudate at ~7 weeks after RYGB/VSG surgery with average ~12% weight loss.[34] There was a similar trend for a *decrease* in ^{18}F-fallypride BP in caudate, putamen, and nucleus accumbens after 7–10 days of VLCD with average ~3% weight loss in a larger study ($n = 15$),[35] suggesting that these changes may be because of weight loss or reduced energy intake rather than being specific to bariatric surgery.

To interpret these changes in dopamine 2 and 3 receptors (DRD2/3) receptor availability after weight loss needs an understanding of the effects of obesity or higher BMI itself on DRD2/3 receptor availability. In those interventional studies that examined influence of obesity at baseline, there was no difference in striatal ^{11}C-raclopride BP between participants without obesity/normal weight controls and pre-operative group with obesity,[32,33] nor any correlation of striatal ^{123}I-IBZM binding with BMI in pre-operative group with obesity.[51,52]

However, in other studies, correlations between DRD2/3 receptor availability and BMI or obesity have been highly inconsistent, likely related to (i) multiple different tracers with variable characteristics, (ii) neuroanatomical localization of BP differences, (iii) severity of obesity (with some reviews suggesting inverted U-shape relationship), (iv) potential differential effects of tonic and phasic dopamine release, and (v) variable sample sizes.[58,60,61]

Higher BMI has been associated with decreased DRD2/3 receptor availability in the ventromedial striatum using ^{18}F-fallypride,[59] in striatum using ^{11}C-raclopride[62]; in dorsal caudate using 6-^{18}F-fluoro-L-m-tyrosine[63]; and in ventral striatum, putamen and caudate using 6-^{18}F-fluoro-L-3,4-dihydroxyphenylalanine.[64] By contrast, higher BMI has been associated with higher ^{18}F-fallypride BP in the dorsal and lateral striatum[59]; in caudate[65]; in midbrain, putamen, and ventral striatum,[66] and higher N-methyl benperidol BP in caudate.[67] Greater reduction in BMI was positively associated with decrease ^{123}I-N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl) nortropane, (^{123}I-FP-CIT) BP over 24 months in caudate and putamen.[68] No association of BMI has been found with DRD2/3 availability in striatum using N-methyl benperidol tracer.[67]

^{11}C-4-propyl-9-hydroxynaphthoxazine (^{11}C-PHNO) is more highly selective for DRD3 over DRD2 receptors, and results have differed from the other DRD2/3 tracers. In the same study of participants without obesity (BMI 18.6–27.8 kg/m^2), BMI was positively correlated with ^{11}C-PHNO BP in ventral striatum (but not caudate or putamen) but not in any striatal region with ^{11}C-raclopride.[69] Higher BMI (range from 20.8 to 36.5 kg/m2) has also been associated with higher ^{11}C-PHNO BP in the dorsal striatum,[70] and across those with normal weight, overweight, and obesity in substantia nigra/ventral tegmental area, ventral striatum, and pallidum.[71] To our knowledge no studies have examined the effects of bariatric surgery or dietary weight loss on ^{11}C-PHNO BP.

Furthermore, ^{18}F-fallypride is not as easily displaced by endogenous dopamine compared to ^{11}C-raclopride and ^{123}I-IBZM tracer and so is less sensitive to changes in endogenous dopamine release.[72–76] Furthermore, DRD2/3 receptors exist in either high- or low-affinity states with respect to agonists, and while agonist tracers (^{11}C-PHNO, (-)-N-[^{11}C]propyl-norapomorphine (^{11}C-NPA), (R)-2-^{11}CH3O-N-n-

propylnorapomorphine (^{11}C-MNPA)) bind preferentially to the high-affinity state, antagonists (^{11}C-raclopride, ^{11}C-N-methylspiperone, ^{11}C-FLB-457, ^{18}F-fallypride, ^{123}I-IBZM and ^{123}I-epidepride) do not distinguish between the two states.[77]

When looking at voxel-based analysis rather than averaging BP across striatal brain regions, positive correlations of BMI were found with ^{18}F-fallypride BP in the dorsolateral striatum including caudate and putamen, and negative correlations in the ventromedial striatum, in lean/patients with obesity.[59]

Interpreting changes in baseline ^{11}C-raclopride, ^{123}I-IBZM, and ^{18}F-fallypride BP after weight loss interventions is also difficult because it is assessing post-synaptic (and potentially also pre-synaptic auto-receptors) DA receptor availability rather than the flux through the dopaminergic system. A recent review suggested that the relationship between obesity and DRD2/3 availability can be best described by a nonlinear relationship,[75] where tracer BP reflects changes in both receptor density and endogenous dopamine levels. The nonlinear relationship may be the result of an increase in tonic dopamine (sustained) levels, accompanied by a decrease in phasic dopamine (momentary) release in moderate obesity which may induce a transient, compensatory upregulation of striatal DRD2/3, resulting in a higher tracer BP in moderate obesity. However, with further progression of obesity (BMI > 40 kg/m^2), the lower tracer BP may reflect primarily a downregulation of DRD2/3, which can be compensatory to long-term high tonic dopamine exposure.[78]

The obesity intervention studies using DRD2/3 tracers examined alterations in tonic dopamine, measured during the fasting or pre-meal state without any active interventions such as presentation of food stimuli or acute food ingestion. Physiologically, dopamine is released in the striatum from midbrain neurons in response to stimuli in a phasic manner. Indeed, greater post-prandial decreases in striatal ^{11}C-raclopride BP, indicating greater endogenous dopamine release, have been associated with greater pleasantness of the food eaten in adults without obesity.[76] To our knowledge, there are no published studies of the effects of bariatric surgery or weight loss on post-prandial endogenous dopamine release.

No association between BMI and striatal dopamine transporter (DAT) availability was found using ^{123}I-FP-CIT,[79] whereas a negative association was observed in obesity using (−)-2-β-Carbomethoxy-3-β-(4-fluorophenyl)tropane (β-CFT, WIN 35,428) (^{3}H-WIN35,428) tracer[80] and in participants without obesity (BMI 18–30 kg/m^2) using TRODAT-1 tracer.[81]

One study examined the effect of LCD-induced weight loss on striatal DAT using ^{123}I-FP-CIT, but this has not been examined after bariatric surgery. Although there was no overall change in striatal ^{123}I-FP-CIT binding after 1 month LCD following 6–7% weight loss, the timing of the LCD meals over the day (50% of energy intake at breakfast vs. supper) did produce differential effects on striatal ^{123}I-FP-CIT binding, suggesting the effect of meal timing on weight maintenance after hypocaloric diets.[53]

A further limitation of these obesity interventional studies using tracers targeting the dopamine system is the inclusion of only females, limiting generalization of the results to both sexes.[82,83]

4.2 | Serotonin system

Serotonin plays an integral role in maintaining energy homeostasis, controlling eating behavior, suppressing appetite, and promoting energy expenditure.[75,84] Serotonin (5-HT) receptors are classified into seven types, 5-HT$_1$ through 5-HT$_7$ with each type having subtypes (A, B, etc.). The brain distribution of these receptors is not homogeneous nor identical. Brainstem serotonin neurons send ascending projections that terminate in a defined and organized manner in cortical, limbic, midbrain, and hindbrain regions, with brain regions expressing multiple serotonin receptors in a receptor subtype-specific fashion.[75,84]

The serotonin system has provided a viable target for weight control.[85] Serotonin 5-HT$_{1B}$ and 5-HT$_{2C}$ receptors have been specifically recognized as mediators of serotonin-induced reductions in appetite.[85] Systemic serotonin administration decreases food intake in humans,[86] and there is an important role for the anorexigenic hypothalamic serotonin 2C receptor (5-HT$_{2C}$R).[87] A number of serotonergic drugs, including selective serotonin reuptake inhibitors, dexfenfluramine, and 5-HT$_{2C}$R agonists, have been shown to attenuate rodent body weight gain. This effect is strongly associated with marked hypophagia and is probably mediated by the hypothalamic melanocortin system.[88] However, there are inconsistencies in the effect of those drugs on humans.[89–93] Additionally, sibutramine, dexfenfluramine, fluoxetine, and the 5-HT$_{2C}$R agonist chlorophenylpiperazine have all been shown to modify appetite in both lean and patients with obesity, resulting in reduced caloric intake.[85] A new generation of 5-HT$_{2C}$R selective agonists have been developed such as lorcaserin which helped patients with overweight or obesity to lose weight and maintain weight loss.[85] In addition, hypothalamic serotonin 2A receptor (5-HT$_{2A}$R) might have a role in the control of feeding and energy homeostasis. Positive correlations were found between BMI and 5-HT$_{2A}$R binding using ^{18}F-altanserin tracer in different cortical regions.[94,95] Individuals with obesity had significantly higher neocortical 5-HT$_{2A}$R binding relative to lean individuals.[37] On the other hand, serotonin receptor (SERT) binding was negatively correlated to BMI in cortical and subcortical regions using ^{11}C-3-amino-4-(2-dimethylaminomethyl-phenylsulfanyl)-benzonitrile (^{11}C-DASB) PET tracer.[96]

In the only study of RYGB surgery, there was no effect on ^{18}F-altanserin BP (targeting 5-HT$_{2A}$R) despite average 25.8% weight loss.[37] This was despite there being an overall increase in neocortical (averaged across orbitofrontal, medial inferior frontal, superior frontal, medial inferior and superior temporal, sensorimotor, parietal and occipital cortices) ^{18}F-altanserin BP in obesity (both pre- and post-RYGB surgery) than normal weight participants, and a positive correlation with BMI across participants without and with obesity. In agreement with these findings, two other studies found a positive correlation between BMI (across range from participants without and with obesity) and ^{18}F-altanserin binding in the neocortex (averaged across eight cortical anatomical regions of interest (aROIs): orbitofrontal, medial inferior frontal, superior frontal, superior temporal, medial inferior temporal, sensory-motor, parietal, and occipital cortices), and also individually in the above aROIs, as well as insula, hippocampus,

anterior cingulate cortex and posterior cingulate cortex, in one study,[95] and in the other study in the superior temporal, medial inferior temporal, dorsolateral prefontal, and sensory-motor cortical aROIs (but not cerebellum, amygdala/hippocampus, pons, orbitofrontal cortex, ventrolateral frontal cortex, anterior cingulate gyrus, thalamus, caudate, putamen/pallidum, insula, superior medial frontal cortex, occipital cortex, or parietal cortex).[94]

The lack of any reduction in ^{18}F-altanserin BP after weight loss from RYGB surgery suggests persistence of alterations in the serotonin system in obesity, perhaps consistent with lower intra-synaptic serotonin concentrations. However, because there are no reported studies of weight loss induced by a dietary intervention on ^{18}F-altanserin BP, it is unclear if this is a general lack of effect from weight loss or whether RYGB surgery actually increases ^{18}F-altanserin BP.

The ^{11}C-Cimbi PET tracer is also available to target 5-HT$_{2A}$R in humans, but no studies could be found assessing influence of BMI, obesity, or interventions on its binding.[97,98]

In rats with diet-induced obesity from high fat diet, RYGB surgery decreased ^{3}H-MDL100907 binding by autoradiography (targeting 5-HT$_{2A}$R) in the nucleus accumbens (but not cortex, caudate/putamen, hippocampus, or hypothalamus) compared with sham operated rats, but no changes were seen in SERT (using (S)-[*N*-methyl-^{3}H]citalopram) or 5-HT$_4$R (using ^{3}H-SB207145) binding restriction.[99]

Unfortunately, there are no specific tracers for the anorexigenic 5-HT$_{2C}$R. Radioligands for the other serotonin 1A and 1B (5-HT$_{1A/B}$R) and 4 (5-HT$_4$R) receptors have been validated in humans, but there are no reported studies of their use in surgical or dietary weight loss interventions.

One study showed no effect of RYGB surgery on ^{11}C-DASB BP (targeting SERT) averaged across caudate, putamen, and thalamus, despite 25.8% weight loss.[37] In agreement with this, studies have found no difference in ^{11}C-DASB BP between participants with and without obesity,[100] and with other tracers targeting SERT, no correlation between BMI and ^{123}I-labeled 2β-carboxymethoxy-3β-(4-iodophenyl)tropane (^{123}I-nor-β-CIT) BP across participants without and with obesity,[96,101] nor correlation of BMI with midbrain/cerebellum ratio of ^{123}I-(2-((2-([dimethylamino]methyl)phenyl)thio)-5-iodophenylamine (^{123}I-ADAM) BP across participants without obesity and participants with severe obesity,[102] indicating that SERT is unaltered in obesity.

However, although LCD producing 6.5% weight loss had no overall effect on ^{123}I-FP-CIT BP in thalamus and hypothalamus, an increase in tracer BP in thalamus was seen when 50% of energy was consumed in breakfast (vs. supper), suggesting that thalamus SERT may be affected by timing of dietary patterns but not weight loss per se.[53]

4.3 | Opioid system

There are three main families of opioid receptors (μ, κ, and δ) of which μ-opioid receptors (MOR) are most strongly implicated in reward processing. The endogenous opioid system and MOR influence food and energy balance, particularly by modulating consummatory behavior beyond changes in appetite.[103–105] Additionally, the opioid system is involved in the regulation of affective and stress responses and is therefore positioned as a common mediator that underlies the interface of food intake, hedonic response, and emotional regulation.[106–108] Administration of MOR antagonists to animals reduces food intake and body weight in rodent models,[109–112] while MOR agonists increase food intake.[113,114] In humans, pharmacological studies of high affinity but non-selective MOR antagonists such as naloxone, naltrexone and nalmefene found decreases in short-term food intake but no effects on hunger in participants with normal weight.[115–117] Recently, studies using a selective MOR antagonist GSK1521498 showed reductions in hedonic responses to sweetened dairy products and reduced energy intake, particularly of high-fat foods during ad libitum buffet meals in obesity with binge eating disorder,[118,119] and reduced attentional bias for food cues on the visual dot probe task.[120]

Two studies observed an increase in ^{11}C-carfentanil BP after both RYGB/VSG surgical and VLCD dietary weight loss interventions in ventral striatum, thalamus, and orbitofrontal cortex, suggesting this is because of weight loss itself rather than changes in gut-brain axis from surgery.[33,36] After bariatric surgery but not dietary interventions there were also increases in ^{11}C-carfentanil BP in amygdala, dorsal caudate, insula, putamen, and anterior, middle and posterior cingulate cortex,[33] whereas an increase in ^{11}C-carfentanil BP in temporal pole was observed after dietary but not surgical interventions.[36]

The anatomical differences in the increases in ^{11}C-carfentanil BP between surgical and dietary interventions may be a result of the greater weight loss in the former (23.3% vs. 16.1%, respectively) as well as the time since start of intervention (6.0 vs. 3.7 months, respectively). Moreover, the surgical intervention study was much larger than the dietary study (16 vs. 7 participants), and there were differences in participant sex (all female in surgical, all male in dietary study), prevalence of T2DM (38% vs 0%), and nutritional state (fed in surgical, fasted in dietary study) which further impairs the comparison between these two studies.[36]

These results suggest that weight loss by surgical or dietary interventions is normalizing the lower ^{11}C-carfentanil BP seen in obesity (pre-intervention vs. participants without obesity) in ventral striatum, dorsal caudate, putamen, thalamus, amygdala, insula, posterior cingulate cortex and orbitofrontal cortex (average and individual regions of interests [ROIs]),[33] thalamus, amygdala, temporal pole, and prefrontal cortex.[36] These cross-sectional findings in obesity are supported by others that have found lower ^{11}C-carfentanil BP in ventral striatum, dorsal caudate, putamen, insula, amygdala, thalamus, orbitofrontal cortex, and posterior cingulate cortex.[61]

There are no PET studies investigate κ- and δ-opioid receptors in human obesity or interventions. Preliminary data from transgenic knockout models suggest that mice lacking some of these receptors are resistant to high fat diet-induced obesity, suggesting a role of these receptors in controlling energy metabolism.[121,122] Moreover, the κ-specific antagonist norbinaltorphimine showed robust reductions in the intake of palatable diets high in fat or sucrose.[123–126]

4.4 | Noradrenaline system

The main source of noradrenergic neurons is the midbrain locus coeruleus projecting to many areas in the central nervous system, and they influence a broad range of physiological and behavioral functions, including arousal, memory, attention, and mood.[127–129] Noradrenaline also plays an important role in energy balance.[128,129] In rodent studies, exogenous noradrenaline can elicit or reduce feeding, depending on the site of infusion (lateral hypothalamus stimulates feeding; perifornical hypothalamus inhibits feeding; lesions of the ascending ventral noradrenergic bundle increases food intake and produces obesity, whereas interruption of projections of the dorsal noradrenergic bundle lowers body weight) and the relative balance of post-synaptic α2-adrenoceptors (stimulate food intake) and α1-adrenoceptors (inhibit food intake).[130,131] These two adrenoceptor subtypes are localized in the hypothalamic paraventricular nucleus and appear to be organized in an antagonistic fashion.[132]

The noradrenaline transporters (NAT) take up synaptically released noradrenaline and thus serves as a primary mechanism for inactivation of noradrenergic signaling.[133–135]

In the only study, there was no effect of LCD intervention on ^{11}C-methylreboxetine (^{11}C-MRB) BP (targeting NAT) after 3.7% weight loss over 6 months.[47] However, the weight loss was minimal, and the participants still had obesity after the intervention with average BMI 41.0 kg/m^2. However, greater weight loss after LCD was associated with a greater increase in ^{11}C-MRB BP in the insula and hippocampus, but the role of noradrenergic signaling on energy balance in these brain regions is unclear. Furthermore, lower ^{11}C-MRB BP at baseline was associated with greater weight loss after LCD in insula and hippocampus, and also putamen, midbrain, and dorsolateral prefrontal cortex.[47]

A recent study that investigated the effect of RYGB surgery on NAT observed a higher ^{11}C-MRB BP in hypothalamus at baseline was associated with greater weight loss 6 months post-RYGB surgery, a brain region responsible for appetite control and homeostasis. Moreover, reductions in BMI after RYGB surgery was associated with reductions in NAT availability in the dorsolateral prefrontal cortex and a general tendency towards reduced NAT throughout the brain.[136] However, these preliminary findings need confirmation with larger cohorts.

While this direction of change in ^{11}C-MRB BP with weight loss has been supported by cross-sectional studies in obesity, the exact brain regions involved have differed: (i) in lean-to- participants with severe obesity, higher BMI was associated with lower ^{11}C-MRB BP in the hypothalamus,[137] whereas (ii) participants with class I obesity (mean BMI 34.7 kg/m^2) had lower ^{11}C-MRB BP in the thalamus but not hypothalamus compared to lean participants.[138] However, these results have not been replicated in more severe class II and class III obesity (BMI > 35 kg/m^2).[139,140]

It therefore remains uncertain if impaired NAT availability is a definite feature of obesity and if it is playing any pathogenic role in overeating behavior. A number of anti-obesity drugs have targeted the noradrenaline system though rarely used clinically because of adverse effect profiles particularly due to peripheral monoamine release such as increased heart rate and blood pressure. Their mechanisms of action are complex though, because they often affect multiple monoamine neurotransmitter systems, for example, sibutramine reduces reuptake of noradrenaline and also serotonin and dopamine; phentermine and amphetamine stimulate monoamine release from neurons via trace-amine associated receptor 1 (TAAR1) receptor including noradrenaline and, to a lesser extent, serotonin and dopamine.[128] The potential reduced NAT uptake in obesity and its increase with dietary weight loss could therefore represent a counter-regulatory response to obesity rather than a pathogenic cause.

4.5 | Fatty acid uptake

The hypothalamic metabolism of fatty acids can modify feeding behavior and has been proposed to function as a biochemical sensor for nutrient availability that in turn exerts negative feedback on nutrient intake.[87,141,142] The mechanisms by which hypothalamic long-chain fatty acid (acyl-CoAs) concentrations can be increased are enhanced esterification of circulating or central nervous system lipids[143,144] and/or by the local inhibition of lipid oxidation.[145] These interventions also result in marked inhibition of feeding behavior in pre-clinical studies.[146–149] In animal studies, saturated fats disturb melanocortin signaling of hypothalamic neuronal subgroups pivotal to energy balance.[150–152] Moreover, hypothalamic injury can occur in response to increased dietary fat very early (1–3 days) even before the development of obesity in rodents,[153] and the normalization of hypothalamic lipid sensing has been linked to normalization of energy and glucose homeostasis in rats.[154]

In addition, free fatty acids induce insulin and leptin resistance which may cause neuronal damage through inflammation including the hypothalamus and so further affect control of energy balance.[151,155,156] Hypothalamic overexpression of a constitutively active IKKβ isoform (which is activated by saturated fatty acids and oxidative stress) can reduce both insulin and leptin signaling[151]; conversely, intracerebroventricular administration of an IKKβ inhibitor reverses high fat diet-induced hypothalamic insulin resistance,[157] and neuron-specific deletion of IKKβ maintains leptin and insulin sensitivity in high fat diet fed mice.[151] These control processes are difficult to examine in humans in vivo, and so most data in this regard have only been demonstrated in animals.[146,148,158] One key unresolved question regarding the effect of fatty acids in the brain is the nature of the cell types and if there are other brain regions involved in the response.

Both PET studies of dietary and surgical weight loss interventions showed higher brain ^{18}F-fluoro-6-thia-heptadecanoic acid (^{18}F-FTHA) BP (which measures total FA uptake and is found mostly in triglycerides in brain lipids) globally and in cortical regions in obesity (pre-intervention vs. participants without obesity),[46,49] as well in subcortical and hypothalamus in one study.[46] However, only the dietary intervention study observed a reversal with weight loss with a decrease in ^{18}F-FTHA BP globally and regionally in cortical, subcortical, and hypothalamus 1.5 months after VLCD with 11.1% weight

loss.[46] However, ^{18}F-FTHA BP was unchanged 6 months post-RYGB/VSG surgery in cortical regions despite greater 22.6% weight loss to a similar BMI to the post-VLCD study.[49] Unfortunately, this surgical study did not include the hypothalamus as a region of interest. Instead, they measured the ratio of hypothalamic-to-amygdala signal intensity (using fluid-attenuated inversion recovery, FLAIR-MRI) which has been previously shown to reflect hypothalamic inflammation,[153] but this did not differ between participants with obesity and controls at baseline nor change after surgery.[49] The authors mentioned this may be a result of methodological limitations because of slice thickness of 5 mm.

Thus, these differences between the two studies in changes in ^{18}F-FTHA BP in cortical regions are unlikely to be explained by magnitude of weight loss, but there could be adaptation to weight loss over time, or else surgical intervention increases ^{18}F-FTHA BP through uncertain mechanisms. The authors hypothesized that surgical stress may be a factor, but this is unlikely to be important at 6 months post-surgery.[49] Moreover, there were differences between these studies in sex ratio (all female in surgical study, 68.8% female in dietary study) and baseline BMI (average 41 kg/m^2 in surgical study, 34 kg/m^2 in dietary study), which further impairs the direct comparison between the studies if being female or having more severe obesity reduces reversibility with weight loss, though no evidence is yet available for this.[46,49]

^{11}C-palmitate measures non-oxidative fatty acid uptake and is found mostly in phospholipids in brain lipids, with only trace amounts in triglycerides and fatty acids. Interestingly, ^{11}C-palmitate BP did not change after weight loss from VLCD dietary intervention, suggesting that the greater ^{18}F-FTHA BP in obesity, and decrease in ^{18}F-FTHA BP after VLCD, is primarily because of decreases in oxidative fatty acids, which are those associated with inflammation and neuronal damage.[46]

4.6 | Regional cerebral blood flow

Regional cerebral blood flow can be used to assess local neuronal activity at rest and/or in response to interventions because of the neurovascular coupling that results in local vasodilation. rCBF can be measured by PET imaging with ^{15}O-water (^{15}O-H_2O)[12] and by magnetic resonance imaging using arterial spin labeling (ASL).[159]

One small longitudinal study with only males with obesity ($n = 4$) showed no change in rCBF using ^{15}O-H_2O PET averaged across the whole brain after 3 weeks of total fasting.[43] Only one larger study ($n = 11$) assessed the effect of RYGB surgery on rCBF, in this case using ASL.[50] After RYGB, there was increased rCBF in the whole brain, white and gray matter, and individually within caudate, putamen, pallidum, thalamus, amygdala, hippocampus, hypothalamus, frontal, parietal, temporal and occipital lobes, and cerebellum, during normoglycemia and in most of these brain regions during hypoglycemia.[50] This suggests differential global changes in neuronal activity after weight loss from RYGB surgery than extreme dietary restriction. However, interpretation of these findings is complicated by (i) neither study including normal weight participants (unclear what direction of change would be expected to normalize obesity-associated changes in rCBF), (ii) global effects raise the possibility of non-specific effects after RYGB surgery, (iii) prolonged fasting was a dietary intervention that is an unusual treatment, (iv) samples sizes were small, and (v) these two studies used different methods to assess rCBF.

Furthermore, another longitudinal study using ASL found no change in rCBF at 6 months after RYGB surgery versus pre-operatively ($n = 9$) nor any difference in rCBF at baseline compared to controls without obesity ($n = 8$), in any regional brain network defined using resting state functional MRI (dorsal default mode, ventral default mode, auditory, basal ganglia, left or right executive control, language, precuneus, sensorimotor network, primary visual, visuospatial, higher visual, anterior salience, and posterior salience networks).[160]

Three cross-sectional studies used ^{15}O-H_2O PET to compare successful dieters with non-dieters with obesity (and sometimes also those who never had obesity) to measure rCBF responses to taste or intake of a liquid meal (Ensure) but with overlapping datasets.[44,45,48] However, none of these studies just compared rCBF between groups when fasted.

In the insula (a brain region that includes the taste cortex), increase in rCBF after taste (but not after food intake) relative to fasting was higher in both non-dieters with obesity and successful dieters (but similar between groups) than those who have never had obesity, suggesting a persistence of potentially pathogenic abnormality from obesity even after dietary-induced weight loss.[44,45,48]

Few studies have examined the effects of obesity surgery on brain responses to sweet taste using fMRI.[161,162] Interestingly, one study found a reduction in blood oxygen level dependent (BOLD) signal to chocolate milk taste (sweet, high fat) in the insula (which includes gustatory cortex) after RYGB surgery.[161] Furthermore, this was attenuated by acute administration of the glucagon-like peptide-1 (GLP-1) analog Exendin(9–39), indicating a potential role for the increased plasma GLP-1 after RYGB in these changes of sweet/fat taste responsivity.[163,164]

In the hippocampus and parahippocampal gyrus (regions involved in memory and learning), rCBF after food intake decreased more in both non-dieters with obesity and successful dieters (but similar between groups) than those who have never had obesity, again suggesting a persistence of response from obesity even after dietary-induced weight loss,[44] but this was only replicated for non-dieters with obesity in a reanalysis of this study.[48]

By contrast, in the amygdala and posterior cingulate cortex, a greater increase in rCBF after food intake was seen in non-dieters with obesity than both successful dieters and participants who never had obesity, suggesting a reversible consequence of obesity that normalizes after weight loss.[44] However, these findings were not replicated in the other two studies.[45,48]

By contrast, more consistent results were found in the dorsal and dorsolateral pre-frontal cortex (a region involved in top-down inhibitory control[165]), with a greater decrease in rCBF after food intake in non-dieters with obesity than both successful dieters and participants

who never had obesity.[45,48] This is supported by other studies finding lower rCBF in those with compared to without obesity using ^{15}O-H_2O PET during fed state[166,167] and during response to a liquid meal.[168–170] Reduced prefrontal cortex function in obesity when fasted or after food intake may contribute to a lack of inhibition of overeating in obesity,[171] and impaired cessation of a feeding episode, as the dorsal prefrontal cortex has efferent inhibitory projections to the central orexigenic system.[172] Indeed, impairments of prefrontal cortex function have been associated with eating dysregulation and weight gain in many human lesion studies such as dementia.[173–175]

Although not always replicated or regions were not re-examined, rCBF after food intake (vs. fasted) was greater in putamen, and lower in orbitofrontal cortex and occipital lobe in successful dieters (but not those who never had obesity) than non-dieters with obesity,[45,48] whereas rCBF after food intake was greater in cerebellum, and lower in STG and MTG, in successful dieters than those who never had obesity.[45,48]

Several factors may contribute to differences between these ^{15}O-H_2O PET studies that investigate response to food, including sex ratio (both sexes,[44] only females[45,48]), different pre-processing steps,[45,48] and statistical analyses (single-level, fixed-effect analysis[44]; second-level, random-effects re-analysis[48,166]).

4.7 | Brain glucose uptake

The brain uses glucose as a primary fuel for energy generation. Glucose enters the brain by facilitated diffusion across the blood–brain barrier. BGU can be used to assess local neuronal activity by PET imaging with ^{18}F-FDG tracer,[176] though glucose transport might also be altered during changes in non-neuronal glucose uptake (e.g. astrocytes, glia cells)[177] and non-specific changes in cerebral glucose metabolism and/or insulin resistance and plasma glucose concentrations.[178,179] Several studies investigated BGU post-bariatric surgery[38–41,50] or post-dietary intervention,[42,43] but the findings are sometimes difficult to compare because of methodological differences, especially around nutritional and metabolic state.

In one cross-sectional study, BGU was measured in response to food intake post-RYGB surgery compared with adults with and without obesity,[38] whereas in longitudinal studies, one study measured BGU in response to hyperinsulinemic normoglycemic or hypoglycemic clamps post-RYGB surgery,[50] and two studies during hyperinsulinemia normoglycemic clamp post-RYGB/VSG surgery.[39,41] During hyperinsulinemia normoglycemic clamps, there was a decrease in whole brain BGU post-RYGB surgery[50] and post-RYGB/VSG surgery in one of the two studies which included patients with T2DM,[39] but not the other without patients with T2DM, despite similar weight loss.[41] This may be consistent with the reductions in insulin resistance seen after bariatric surgery, though none of these studies correlated changes in BGU with changes in insulin resistance.

A cross-sectional study of response to food intake post-RYGB surgery found greater increase in BGU in the hypothalamus, pituitary, and medial orbitofrontal cortex compared with controls with and without obesity, and greater decrease in BGU in dorsolateral prefrontal cortex and default mode network (posterior cingulate gyrus, precuneus cortex, cuneus, angular gyrus, superior temporal gyrus posterior, middle temporal gyrus posterior, occipital pole, and parietal lobule) compared with controls with and without obesity.[38] Surprisingly, these changes post-RYGB surgery appeared to be largely independent of gut hormone release as they persisted after administration of the somatostatin analog Octreotide that suppresses satiety gut hormones such as peptide YY (PYY) and GLP-1.

One longitudinal study of RYGB surgery examined BGU without a hyperinsulinemic clamp but did not report the nutritional state of participants.[40] The two dietary intervention studies only measured BGU during the fasting state[42,43]; however, one was after 3 weeks of total fasting without any task,[43] whereas the other was while viewing high-energy, palatable food pictures.[42]

No studies were found investigating the effect of VSG alone (always combined with RYGB surgery as one group), gastric banding, or biliopancreatic diversion for obesity on neurotransmitter systems or brain metabolism, nor the effects of any obesity surgery on the noradrenaline system.

4.8 | Correlations of PET/SPECT findings with clinical outcomes

Results from the studies examining associations of PET/SPECT findings (at baseline or their change post-intervention) with clinical outcomes did not offer reproducible evidence that their changes predict weight loss or improvements in glucose metabolism because of the paucity of studies with each intervention, tracer and neurotransmitter system, and lack of consistency between the overall effects of intervention on neuroimaging outcomes and correlations.[35–37,39,42,47,49,52]

For example, looking at *baseline* PET results correlating with weight loss, (i) higher BP in neocortex for $5HT_{2A}R$ but not serotonin transporter was correlated with greater weight loss post-RYGB surgery[37]; (ii) a greater post-prandial increase in MOR availability in temporal pole was correlated with less weight loss after VLCD intervention[36]; (iii) no correlation was observed between baseline BGU and weight loss post-RYGB/VSG surgery[39]; while (iv) higher BP for NAT in putamen, hippocampus, midbrain, insula, and dorsolateral prefrontal cortex was correlated with less weight loss post-LCD intervention.[47]

When looking at correlation of *changes* in PET/SPECT findings with weight loss: (i) despite no overall changes in BP after the intervention, a smaller increase in neocortex $5HT_{2A}R$ availability, and in caudate, putamen, and thalamus for serotonin transporter, was correlated with greater weight loss post-RYGB[37]; (ii) no correlations between loss of weight nor fat mass and change in DRD2/3 receptor availability were seen post-RYGB despite changes in BP being seen after surgery[52]; (iii) a greater increase in NAT in hippocampus and insula was associated with greater weight loss post-LCD, despite no overall change in transporter post-dietary intervention[47]; while (iv) changes in BGU did not correlate with loss of weight or fat post-LCD.[42]

When looking at correlation of *baseline* PET/SPECT findings with changes in glycemic control, two studies of RYGB/VSG surgery for obesity (with 32–38% having T2DM) found that: (i) higher whole brain BGU (during insulin stimulation) was correlated with less improvement in fasting plasma glucose (FPG) at 3 years, perhaps indicative of better insulin sensitivity at baseline with a floor effect[39]; and similarly (ii) higher whole brain free fatty acid (FFA) uptake was correlated with less improvement in FPG at 2 years.[49]

When looking at correlation of *changes* in PET/SPECT findings with changes in glycemic control, (i) there was no correlation between increase in DRD2/3 availability (^{123}I-IBZM BP) in striatum with decrease in FPG at 3 years post-RYGB surgery for obesity (with unknown number having T2DM at baseline)[52]; while (ii) greater reduction in DRD2/3 availability (^{18}F-fallypride BP) in caudate, putamen, and substantial nigra correlated with greater decrease in FPG 10 days post-VLCD for obesity (only 7% with T2DM).[35]

4.9 | Correlations of PET/SPECT findings with mechanistic measures

Bariatric surgery involves a profound anatomical change to the gastrointestinal tract, which causes a more rapid delivery of nutrients to the distal small bowel.[3,180] As a result, after RYGB and VSG surgery, gut adaptation facilitates an exaggerated, early post-prandial rise in peripheral anorexigenic gut hormones including PYY and GLP-1, and a reduced post-weight loss rise in fasting and/or post-prandial plasma concentrations of the potentially orexigenic stomach-derived hormone ghrelin, likely as a result of the exclusion of food from the stomach (though the majority of studies have examined total rather than acyl ghrelin), that occurs within days after surgery and persists long term.[3,181] These appetitive gut hormones have receptors in the peripheral and central nervous systems forming a gut-brain hormonal axis. Therefore, these obesity surgeries promote weight loss by reducing appetite, partly mediated by changes in appetitive gastrointestinal hormone secretion.[3,5]

Furthermore, the effects of RYGB and VSG surgery on gut hormones are different from the effects of dietary intervention.[181] Fasting plasma total ghrelin decreased more after RYGB surgery than matched weight loss from VLCD, whereas post-oral glucose plasma total ghrelin was unchanged after RYGB surgery, but increased after matched weight loss from diet alone.[182,183] Post-oral glucose plasma GLP-1 increased after RYGB surgery for obesity with T2DM, but not after matched weight loss from LCD.[184] In addition, despite similar weight loss, fasting and post-prandial acyl ghrelin may decrease more after VSG than RYGB surgery, while post-prandial plasma $PYY_{3\text{-}36}$ and active GLP-1 may increase more after RYGB than VSG surgery.[185]

Observations of differences in PET/SPECT outcomes between surgical and dietary interventions implicate some of these mechanistic changes in gut anatomy–physiology after surgery compared with dietary intervention,[46,49] as opposed to similar effects for surgical and non-surgical interventions that implicate mechanisms related to weight loss itself or perhaps psychological changes attempting to inhibit excess energy intake.[33,36]

However, when looking at roles for specific mechanisms, a limited number of studies have assessed correlations between PET/SPECT findings and potential mediators, again meaning that definitive conclusions cannot be made. No correlations were seen among the following: (i) changes in fasting total ghrelin (overall no change) or decrease in serum insulin and increase in striatum DRD2/3 availability (^{123}I-IBZM BP) post-RYGB surgery;[52] (ii) changes in fasting acyl ghrelin (overall no change) or decrease in fasting serum insulin and decreases in DRD2/3 availability (^{18}F-fallypride) in ventral striatum, caudate, and putamen post-VLCD;[35] and (iii) increase in post-prandial plasma GLP-1 (400 kcal) and changes in SERT (average caudate, putamen, and thalamus) or 5-HT_{2A}R (neocortex) availability (^{11}C-DASB or ^{18}F-altanserin BP) post-RYGB surgery.[37]

Acute administration of the somatostatin analog Octreotide to patients after RYGB surgery to suppress anorexigenic gut hormones GLP-1 and PYY (with co-administration of insulin to avoid hyperglycemia) had no effect on BGU (fed vs. fasted) in sub-callosal gyrus, hypothalamus, insula, precuneus, cuneus, posterior cingulate cortex, dorsolateral prefrontal cortex, orbitofrontal cortex, frontal operculum, angular gurus, parietal lobule, superior temporal gyrus, middle temporal gyrus, occipital lobe, and lingual gyrus.[38] This was despite these regions being those showing differences in post-prandial BGU in patients post-RYGB surgery compared to participants with obesity or normal weight controls, suggesting that the exaggerated post-prandial GLP-1 and PYY responses after RYGB surgery were not responsible for changes in regional BGU, though sample size was small for the post-RYGB group ($n = 9$). This is in contrast to an fMRI study of food cue reactivity, where acute suppression of post-prandial plasma GLP-1 and PYY with Octreotide increased food picture appeal and cue reactivity across nucleus accumbens, anterior insula, amygdala, and caudate post-RYGB surgery (but not gastric banding), while the greater the suppression of plasma PYY and GLP-1, the greater the increase in food cue reactivity across both post-surgical groups.[186]

4.10 | Correlations of PET/SPECT findings with behavioral measures

Similarly, very few studies have assessed correlations between PET/SPECT findings and changes in eating behavior precluding any definitive conclusions of brain changes with behaviors leading to weight loss: (i) the decrease in state (but not trait) food craving was positively correlated to the increase in striatal DRD2/3 availability (^{123}I-IBZM BP) 3 years post-RYGB[52]; (ii) changes in post-prandial 5-HT_{2A}R and SERT availability did not correlate with increased post-prandial satiety post-RYGB surgery, though this is unsurprising as overall there was no change in the PET outcomes.[37]

None of the studies included in this systematic review correlated change in PET measures with change in food liking or wanting score,

changing in taste function, nausea, dumping syndrome, or food aversion.

4.11 | Correlations of PET/SPECT measures with mood

Most longitudinal studies did not measure changes in mood,[35,38–46,48–53] and some found no change in mood post-RYGB or VSG surgery[33,34,37] or LCD[47] or VLCD,[36] whereas one study showed lower depression post-RYGB surgery that was associated with a reduction in DRD2/3 availability (^{11}C-raclopride BP) across ventral striatum, caudate, and putamen, though no direct correlation was performed.[32] Improvements in mood are often seen after bariatric surgery,[187,188] and so may be a cofounding factor when interpreting PET findings. For example, depression is associated with higher DRD2/3 availability (^{11}C-raclopride BP) in putamen region.[189]

4.12 | Interactions between neurotransmitter systems

Furthermore, published studies have generally examined neurotransmitter systems and brain regions in isolation and have not examined how the neurotransmitter systems interact with each other and how they work on a systemic level such as in the brain reward system. Only two longitudinal studies included multiple tracers looking at neurotransmitter systems in the same participants, but none looked at correlations between changes in the different tracer BPs as a result of the intervention. There were increases in ^{11}C-carfentanil BP (MOR) in ventral and dorsal striatum, but no changes in ^{11}C-raclopride BP (DRD2/3) in these regions, in a longitudinal study of RYGB/VSG surgery,[33] that normalized the reductions in ^{11}C-carfentanil BP seen in obesity (vs. without obesity), with no effect of obesity for ^{11}C-raclopride BP.[33,61] Examining dopamine and serotonin transporter (both FP-CIT) in a longitudinal study of 4 weeks LCD found no changes in former and changes in serotonin transporter BP in thalamus, the direction of which depended on distribution of energy intake over the day.[53]

Interaction of dopaminergic/noradrenergic systems with opioid and serotonin systems is demonstrated from PET studies of effects of oral administration of amphetamine, which increases dopaminergic and noradrenergic systems (via dopamine and noradrenaline transporter inhibition, vesicular monoamine transporter 2 [VMAT-2] inhibition, and monoamine oxidase activity inhibition).[97,190,191] Amphetamine administration released endogenous beta-endorphin and serotonin as measured by reductions in BP for ^{11}C-carfentanil (MOR agonist) in putamen, caudate, nucleus accumbens, frontal cortex, anterior cingulate cortex, insula, and thalamus,[190,191] and by reductions in ^{11}C-CIMBI-36 (5HT-2A receptor agonist) in frontal, parietal, temporal, and occipital cortex.[97] However, while blunting of these effects of amphetamine have been reported in gambling disorder and abstinent alcohol dependence,[192,193] and depression,[194] to our knowledge they have not been studied in obesity or following its treatment.

Positive correlations between DRD2 and MOR availability using ^{11}C-raclopride and ^{11}C-carfentanil BP were reported in the ventral striatum and caudate but not in the putamen in lean participants, and in severe obesity the correlation in the ventral striatum was attenuated, suggesting aberrant mesolimbic dopamine–opiate interaction in obesity.[195] However, it has not yet been reported whether surgical or dietary interventions for obesity normalize this correlation in the ventral striatum.

The poor temporal resolution of PET/SPECT imaging precludes examination of temporal interactions of dynamic changes in neurotransmitter systems between brain regions that is better explored using resting state or task-related functional connectivity, a topic outside the scope of this review, that has been examined in several fMRI studies.[16,196–203]

4.13 | Limitations

Although it was hoped to conduct a meta-analysis, this was not possible because of several limitations from the available studies: (i) combined groups composed of patients who underwent different surgeries which have differing effects on gut anatomy and physiology, (ii) different times since surgery or start of dietary intervention, (iii) small number of included manuscripts for each brain neurotransmitters system or metabolite, let alone the specific PET/SPECT tracer used, (iv) different nutritional and metabolic states used between studies, (v) different ROIs used in particular studies further decreasing the number of studies that could be included in a meta-analysis, and (vi) very few studies reported spatial co-ordinates from whole brain analysis precluding combination of results using an ALE analysis (using GingerALE software, http://brainmap.org). In addition, this systematic review did not focus on the different analytical models used in quantification in PET/SPECT data.

4.14 | Recommendations

There are notable gaps in the literature. We offer the following recommendations to further accelerate the field's understanding of the effect of obesity surgery on neurotransmitter systems and brain metabolism and to determine the potential of these surgeries for the clinical treatment of obesity:

i. Enrolment of larger sample sizes with greater representation across age and sex, particularly studies involving young adults and males.
ii. Subgrouping according to the type of the surgery and classification of participants according to BMI.
iii. Including a control group for effects of weight loss or dietary/psychological advice.
iv. Examine the effect of VSG surgery, because 20% of the bariatric surgery studies included in this systematic review had mixed groups post-RYGB/VSG, and no studies examined VSG alone,

nor included gastric banding or biliopancreatic diversion surgery.

v. Careful consideration regarding the control groups used (e.g., controlling for BMI, T2DM, age, mood, and medication).
vi. Simultaneous assessment of multiple biomarkers (e.g., mechanistic outcome) to determine the additive value of each marker in the clinical assessment of brain function.
vii. Address mediators of the effect of the intervention on brain function (e.g., hormonal change and behavior change).
viii. Correlate change in PET/SPECT measures with change in food liking or wanting score, change in taste function, nausea, dumping syndrome or food aversion.
ix. Although it would be best to have a double-blind, randomized control study design in studies involving surgical procedures, this is difficult because of logistical and ethical issues.
x. Some of the reviewed studies only included one sampling time point (if any) for gastrointestinal hormones, usually in the fasted state. It is of interest to determine how these appetitive hormones are affected in the postprandial state. Therefore, future studies should sample before and after a meal to capture the gastrointestinal hormone response profile.
xi. Reporting data using whole brain analysis or/and standardization of ROIs so meta-analysis can be easily performed.
xii. Assessment of interactions between neurotransmitter systems and their association with changes in functional MRI measures, for example, food cue reactivity or resting state functional connectivity, aided by dual PET/MRI scanners now being available.

4.15 | Conclusions

There is an increase in MOR BP post-RYGB/VSG surgery and VLCD intervention, suggesting changes in the opioid system may be secondary to weight loss or reduced energy intake rather than changes in gut-brain axis from surgery. It also suggests that weight loss normalizes the lower ^{11}C-carfentanil BP seen in obesity. BGU both globally and regionally usually decreased after bariatric surgery, and was also seen with LCD and prolonged fasting, again suggesting the effects are because of weight loss itself or reduced energy intake. The findings are sometimes difficult to compare because of methodological differences, especially around nutritional and metabolic state.

Results from the studies examining associations of PET/SPECT findings with clinical outcomes did not offer reproducible evidence that their changes predict weight loss or improvements in glucose metabolism because of the paucity of studies with each intervention, tracer, and neurotransmitter system, and lack of consistency between overall effects of intervention on neuroimaging outcomes and correlations. A limited number of studies have assessed correlations between PET/SPECT findings and potential mediators or behavioral outcomes, again meaning that definitive conclusions cannot be made. Most longitudinal studies did not measure changes in mood which may be a cofounding factor when interpreting PET/SPECT findings. None of the studies included in this systematic review correlated changes in PET/SPECT measures with changes in food liking or wanting score, taste function, nausea, dumping syndrome or food aversion.

The small number of studies with each tracer and lack of control groups made definitive conclusions challenging. Variability in methodology used, duration since intervention, amount of weight loss, nutritional status, methods of statistical analysis, small sample size, predominantly females included, and the use of combined surgical groups also limit conclusions. These limitations need to be addressed in future studies examining the effects of different bariatric surgeries in order to fully understand the role for changes in neurotransmitter systems or brain metabolism involved in changing eating behavior. This will help us understand the mechanisms that cause weight loss after surgical interventions and in return help tailor treatments for the patient and identify potential therapeutic targets for non-surgical weight loss in obesity.

AUTHOR CONTRIBUTIONS

Conceptualization: Alhanouf S. Al-Alsheikh, Alexander D. Miras, Anthony P. Goldstone; methodology: Alhanouf S. Al-Alsheikh, Anthony P. Goldstone; validation: Alhanouf S. Al-Alsheikh, Shahd Alabdulkader, Anthony P. Goldstone; investigation: Alhanouf S. Al-Alsheikh; resources: Alhanouf S. Al-Alsheikh, Shahd Alabdulkader, Anthony P. Goldstone; data curation: Anthony P. Goldstone; writing—original draft preparation: Alhanouf S. Al-Alsheikh, Anthony P. Goldstone; writing: Alhanouf S. Al-Alsheikh, Anthony P. Goldstone; review and editing: Alhanouf S. Al-Alsheikh, Shahd Alabdulkader, Alexander D. Miras, Anthony P. Goldstone; visualization: Alhanouf S. Al-Alsheikh, Anthony P. Goldstone; supervision: Alexander D. Miras, Anthony P. Goldstone; project administration: Anthony P. Goldstone. All authors have read and agreed to the published version of the manuscript.

ACKNOWLEDGMENTS

The PsychoNeuroEndocrinology Research Group, Division of Psychiatry, Department of Brain Sciences, and Department of Metabolism, Digestion and Reproduction, Imperial College London are, or have been, funded by grants from the UK Medical Research Council (MRC), BBSRC, National Institute for Health and Care Research (NIHR) and Wellcome Trust. Infrastructure support was provided by the NIHR Biomedical Research Centre and the NIHR Imperial Clinical Research Facility. A.S.A. was funded by the Department of Community Health Sciences, College of Applied Medical Sciences, King Saud University, Riyadh, Saudi Arabia. S.A. was funded by the Deanship of Scientific Research at Princess Nourah Bint Abdulrahman University, Saudi Arabia through the Fast-Track Research Funding Program. A.D.M. has received research funding from the MRC, NIHR, Jon Moulton Charity Trust, Fractyl, and Novo Nordisk. A.P.G. has received research funding from the MRC and Wellcome Trust. The views expressed in this manuscript are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

CONFLICT OF INTEREST STATEMENT

No conflict of interest statement.

ORCID

Alhanouf S. Al-Alsheikh https://orcid.org/0000-0002-2294-2221

Anthony P. Goldstone https://orcid.org/0000-0001-8179-7071

REFERENCES

1. WHO. *Obesity and Overweight*. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight
2. NHS Digital. *Statistics on Obesity, Physical Activity and Diet, England*. http://digitalnhsuk/data-and-information/publications/statistical/statistics-on-obesity-physical-activity-and-diet. 2019.
3. Miras AD, le Roux CW. Mechanisms underlying weight loss after bariatric surgery. *Nat Rev Gastroenterol Hepatol*. 2013;10(10):575-584.
4. Gloy VL, Briel M, Bhatt DL, et al. Bariatric surgery versus non-surgical treatment for obesity: a systematic review and meta-analysis of randomised controlled trials. *BMJ*. 2013;347:f5934.
5. Al-Najim W, Docherty NG, le Roux CW. Food intake and eating behavior after bariatric surgery. *Physiol Rev*. 2018;98(3):1113-1141.
6. Angrisani L, Santonicola A, Iovino P, Formisano G, Buchwald H, Scopinaro N. Bariatric surgery worldwide 2013. *Obes Surg*. 2015;25(10):1822-1832.
7. Kalinowski P, Paluszkiewicz R, Wroblewski T, et al. Ghrelin, leptin, and glycemic control after sleeve gastrectomy versus Roux-en-Y gastric bypass-results of a randomized clinical trial. *Surg Obes Relat Dis*. 2017;13(2):181-188.
8. Sjostrom L. Review of the key results from the Swedish obese subjects (SOS) trial—a prospective controlled intervention study of bariatric surgery. *J Intern Med*. 2013;273(3):219-234.
9. Al-Alsheikh AS, Alabdulkader S, Johnson B, Goldstone AP, Miras AD. Effect of obesity surgery on taste. *Nutrients*. 2022;14(4):866.
10. Scholtz S, Miras AD, Chhina N, et al. Obese patients after gastric bypass surgery have lower brain hedonic responses to food than after gastric banding. *Gut*. 2014;63:891-902.
11. Ochner CN, Stice E, Hutchins E, et al. Relation between changes in neural responsivity and reductions in desire to eat high-calorie foods following gastric bypass surgery. *Neuroscience*. 2012;209:128-135.
12. Zoon HFA, de Bruijn SEM, Smeets PAM, et al. Altered neural responsivity to food cues in relation to food preferences, but not appetite-related hormone concentrations after RYGB-surgery. *Behav Brain Res*. 2018;353:194-202.
13. Li G, Ji G, Hu Y, et al. Reduced plasma ghrelin concentrations are associated with decreased brain reactivity to food cues after laparoscopic sleeve gastrectomy. *Psychoneuroendocrinology*. 2019;100:229-236.
14. Faulconbridge LF, Ruparel K, Loughead J, et al. Changes in neural responsivity to highly palatable foods following Roux-en-Y gastric bypass, sleeve gastrectomy, or weight stability: an fMRI study. *Obesity*. 2016;24(5):1054-1060.
15. Hu Y, Ji G, Li G, et al. Laparoscopic sleeve gastrectomy improves brain connectivity in obese patients. *J Neurol*. 2020;267(7):1931-1940.
16. Baboumian S, Pantazatos SP, Kothari S, McGinty J, Holst J, Geliebter A. Functional magnetic resonance imaging (fMRI) of neural responses to visual and auditory food stimuli pre and post Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG). *Neuroscience*. 2019;409:290-298.
17. Miras AD, Jackson RN, Jackson SN, et al. Gastric bypass surgery for obesity decreases the reward value of a sweet-fat stimulus as assessed in a progressive ratio task. *Am J Clin Nutr*. 2012;96(3):467-473.
18. Kapoor N, Al Najim W, Menezes C, et al. A comparison of total food intake at a personalised buffet in people with obesity, before and 24 months after Roux-en-Y-gastric bypass surgery. *Nutrients*. 2021;13(11):3873.
19. Nielsen MS, Christensen BJ, Ritz C, et al. Factors associated with favorable changes in food preferences after bariatric surgery. *Obes Surg*. 2021;31(8):3514-3524.
20. Sondergaard Nielsen M, Rasmussen S, Just Christensen B, et al. Bariatric surgery does not affect food preferences, but individual changes in food preferences may predict weight loss. *Obesity*. 2018;26(12):1879-1887.
21. Blum K, Braverman ER, Holder JM, et al. Reward deficiency syndrome: a biogenetic model for the diagnosis and treatment of impulsive, addictive, and compulsive behaviors. *J Psychoactive Drugs*. 2000;32(Suppl i-iv):1-112.
22. Morys F, Garcia-Garcia I, Dagher A. Is obesity related to enhanced neural reactivity to visual food cues? A review and meta-analysis. *Soc Cogn Affect Neurosci*. 2020;18(1):nsaa113.
23. Yang Y, Wu Q, Morys F. Brain responses to high-calorie visual food cues in individuals with normal-weight or obesity: an activation likelihood estimation meta-analysis. *Brain Sci*. 2021;11(12):1587.
24. Qiao YS, Tang X, Chai YH, et al. Cerebral blood flow alterations and obesity: a systematic review and meta-analysis. *J Alzheimers Dis*. 2022;90(1):15-31.
25. MacLean PS, Higgins JA, Jackman MR, et al. Peripheral metabolic responses to prolonged weight reduction that promote rapid, efficient regain in obesity-prone rats. *Am J Physiol Regul Integr Comp Physiol*. 2006;290(6):R1577-R1588.
26. Tataranni PA, Delparigi A. Functional neuroimaging: a new generation of human brain studies in obesity research. *Obes Rev*. 2003;4(4):229-238.
27. Letra L, Pereira D, Castelo-Branco M. Functional neuroimaging in obesity research. *Adv Neurobiol*. 2017;19:239-248.
28. Terbeck S, Savulescu J, Chesterman LP, Cowen PJ. Noradrenaline effects on social behaviour, intergroup relations, and moral decisions. *Neurosci Biobehav Rev*. 2016;66:54-60.
29. Schlögl H, Horstmann A, Villringer A, Stumvoll M. Functional neuroimaging in obesity and the potential for development of novel treatments. *Lancet Diabetes Endocrinol*. 2016;4(8):695-705.
30. Tonelli H, Sartori FM, Marchesini JCD, Marchesini JB, Tonelli DG. Effects of bariatric surgery on the central nervous system and eating behavior in humans: a systematic review on the neuroimaging studies. *J Bras Psiquiatr*. 2013;62(4):297-305.
31. Maass SW, Roorda C, Berendsen AJ, Verhaak PF, de Bock GH. The prevalence of long-term symptoms of depression and anxiety after breast cancer treatment: a systematic review. *Maturitas*. 2015;82(1):100-108.
32. Steele KE, Prokopowicz GP, Schweitzer MA, et al. Alterations of central dopamine receptors before and after gastric bypass surgery. *Obes Surg*. 2010;20:369-374.
33. Karlsson HK, Tuulari JJ, Tuominen L, et al. Weight loss after bariatric surgery normalizes brain opioid receptors in morbid obesity. *Mol Psychiatry*. 2016;21(8):1057-1062.
34. Dunn JP, Cowan RL, Volkow ND, et al. Decreased dopamine type 2 receptor availability after bariatric surgery: preliminary findings. *Brain Res*. 2010;1350:123-130.
35. Dunn JP, Abumrad NN, Kessler RM, et al. Caloric restriction-induced decreases in dopamine receptor availability are associated with leptin concentration. *Obesity*. 2017;25(11):1910-1915.
36. Burghardt PR, Rothberg AE, Dykhuis KE, Burant CF, Zubieta JK. Endogenous opioid mechanisms are implicated in obesity and weight loss in humans. *J Clin Endocrinol Metab*. 2015;100(8):3193-3201.
37. Haahr ME, Hansen DL, Fisher PM, et al. Central 5-HT neurotransmission modulates weight loss following gastric bypass surgery in obese individuals. *J Neurosci*. 2015;35(14):5884-5889.

38. Hunt KF, Dunn JT, le Roux CW, et al. Differences in regional brain responses to food ingestion after Roux-en-Y gastric bypass and the role of gut peptides: a neuroimaging study. *Diabetes Care*. 2016; 39(10):1787-1795.
39. Rebelos E, Immonen H, Bucci M, et al. Brain glucose uptake is associated with endogenous glucose production in obese patients before and after bariatric surgery and predicts metabolic outcome at follow-up. *Diabetes Obes Metab*. 2019;21(2):218-226.
40. Marques EL, Halpern A, Corrêa Mancini M, et al. Changes in neuropsychological tests and brain metabolism after bariatric surgery. *J Clin Endocrinol Metab*. 2014;99(11):E2347-E2352.
41. Tuulari JJ, Karlsson HK, Hirvonen J, et al. Weight loss after bariatric surgery reverses insulin-induced increases in brain glucose metabolism of the morbidly obese. *Diabetes*. 2013;62(8):2747-2751.
42. Guzzardi MA, Garelli S, Agostini A, et al. Food addiction distinguishes an overweight phenotype that can be reversed by low calorie diet. *Eur Eat Disord Rev*. 2018;26(6):657-670.
43. Redies C, Hoffer LJ, Beil C, et al. Generalized decrease in brain glucose metabolism during fasting in humans studied by PET. *Am J Physiol*. 1989;256(6 Pt 1):E805-E810.
44. Delparigi A, Chen K, Salbe AD, et al. Persistence of abnormal neural responses to a meal in postobese individuals. *Int J Obes Relat Metab Disord*. 2004;28(3):370-377.
45. DelParigi A, Chen K, Salbe AD, et al. Successful dieters have increased neural activity in cortical areas involved in the control of behavior. *Int J Obes (Lond)*. 2007;31(3):440-448.
46. Karmi A, Iozzo P, Viljanen A, et al. Increased brain fatty acid uptake in metabolic syndrome. *Diabetes*. 2010;59(9):2171-2177.
47. Vettermann FJ, Rullmann M, Becker GA, et al. Noradrenaline transporter availability on [(11)C]MRB PET predicts weight loss success in highly obese adults. *Eur J Nucl Med Mol Imaging*. 2018;45(9):1618-1625.
48. Le DS, Pannacciulli N, Chen K, et al. Less activation in the left dorsolateral prefrontal cortex in the reanalysis of the response to a meal in obese than in lean women and its association with successful weight loss. *Am J Clin Nutr*. 2007;86(3):573-579.
49. Rebelos E, Hirvonen J, Bucci M, et al. Brain free fatty acid uptake is elevated in morbid obesity, and is irreversible 6 months after bariatric surgery: a positron emission tomography study. *Diabetes Obes Metab*. 2020;22(7):1074-1082.
50. Almby KE, Lundqvist MH, Abrahamsson N, et al. Effects of gastric bypass surgery on the brain; simultaneous assessment of glucose uptake, blood flow, neural activity and cognitive function during normo- and hypoglycemia. *Diabetes*. 2021;70(6):1265-1277.
51. de Weijer BA, van de Giessen E, Janssen I, et al. Striatal dopamine receptor binding in morbidly obese women before and after gastric bypass surgery and its relationship with insulin sensitivity. *Diabetologia*. 2014;57(5):1078-1080.
52. van der Zwaal EM, de Weijer BA, van de Giessen EM, et al. Striatal dopamine D2/3 receptor availability increases after long-term bariatric surgery-induced weight loss. *Eur Neuropsychopharmacol*. 2016; 26(7):1190-1200.
53. Versteeg RI, Schrantee A, Adriaanse SM, et al. Timing of caloric intake during weight loss differentially affects striatal dopamine transporter and thalamic serotonin transporter binding. *FASEB J*. 2017;31(10):4545-4554.
54. Wang GJ, Volkow ND, Telang F, et al. Evidence of gender differences in the ability to inhibit brain activation elicited by food stimulation. *PNAS*. 2009;106(4):1249-1254.
55. Avena NM, Rada P, Hoebel BG. Underweight rats have enhanced dopamine release and blunted acetylcholine response in the nucleus accumbens while bingeing on sucrose. *Neuroscience*. 2008;156(4): 865-871.
56. Baldo BA, Kelley AE. Discrete neurochemical coding of distinguishable motivational processes: insights from nucleus accumbens control of feeding. *Psychopharmacology (Berl)*. 2007;191(3):439-459.
57. Wise RA. Role of brain dopamine in food reward and reinforcement. *Philos Trans R Soc Lond B Biol Sci*. 2006;361(1471):1149-1158.
58. van de Giessen E, Celik F, Schweitzer DH, van den Brink W, Booij J. Dopamine D2/3 receptor availability and amphetamine-induced dopamine release in obesity. *J Psychopharmacol*. 2014;28(9): 866-873.
59. Guo J, Simmons WK, Herscovitch P, Martin A, Hall KD. Striatal dopamine D2-like receptor correlation patterns with human obesity and opportunistic eating behavior. *Mol Psychiatry*. 2014;19(10): 1078-1084.
60. Eisenstein SA, Bischoff AN, Gredysa DM, et al. Emotional eating phenotype is associated with central dopamine D2 receptor binding independent of body mass index. *Sci Rep*. 2015;5:11283.
61. Karlsson HK, Tuominen L, Tuulari JJ, et al. Obesity is associated with decreased mu-opioid but unaltered dopamine D2 receptor availability in the brain. *J Neurosci*. 2015;35(9):3959-3965.
62. Haltia LT, Rinne JO, Merisaari H, et al. Effects of intravenous glucose on dopaminergic function in the human brain in vivo. *Synapse*. 2007; 61(9):748-756.
63. Wilcox CE, Braskie MN, Kluth JT, Jagust WJ. Overeating behavior and striatal dopamine with 6-[F]-fluoro-L-m-tyrosine PET. *J Obes*. 2010;2010:909348.
64. Lee Y, Kroemer NB, Oehme L, Beuthien-Baumann B, Goschke T, Smolka MN. Lower dopamine tone in the striatum is associated with higher body mass index. *Eur Neuropsychopharmacol*. 2018;28(6): 719-731.
65. Dunn JP, Kessler RM, Feurer ID, et al. Relationship of dopamine type 2 receptor binding potential with fasting neuroendocrine hormones and insulin sensitivity in human obesity. *Diabetes Care*. 2012;35(5): 1105-1111.
66. Dang LC, Samanez-Larkin GR, Castrellon JJ, Perkins SF, Cowan RL, Zald DH. Associations between dopamine D2 receptor availability and BMI depend on age. *Neuroimage*. 2016;138:176-183.
67. Eisenstein SA, Antenor-Dorsey JA, Gredysa DM, et al. A comparison of D2 receptor specific binding in obese and normal-weight individuals using PET with (N-[(11)C]methyl)benperidol. *Synapse*. 2013; 67(11):748-756.
68. Pak K, Shin HK, Kim EJ, et al. Weight loss is associated with rapid striatal dopaminergic degeneration in Parkinson's disease. *Parkinsonism Relat Disord*. 2018;51:67-72.
69. Caravaggio F, Raitsin S, Gerretsen P, Nakajima S, Wilson A, Graff-Guerrero A. Ventral striatum binding of a dopamine D2/3 receptor agonist but not antagonist predicts normal body mass index. *Biol Psychiatry*. 2015;77(2):196-202.
70. Cosgrove KP, Veldhuizen MG, Sandiego CM, Morris ED, Small DM. Opposing relationships of BMI with BOLD and dopamine D2/3 receptor binding potential in the dorsal striatum. *Synapse*. 2015; 69(4):195-202.
71. Gaiser EC, Gallezot JD, Worhunsky PD, et al. Elevated dopamine D2/3 receptor availability in obese individuals: a PET imaging study with [(11)C](+)PHNO. *Neuropsychopharmacology*. 2016;41(13): 3042-3050.
72. Mann T, Zilles K, Dikow H, et al. Dopamine, noradrenaline and serotonin receptor densities in the striatum of Hemiparkinsonian rats following botulinum neurotoxin-a injection. *Neuroscience*. 2018; 374:187-204.
73. Cropley VL, Innis RB, Nathan PJ, et al. Small effect of dopamine release and no effect of dopamine depletion on [18F]fallypride binding in healthy humans. *Synapse*. 2008;62(6):399-408.
74. Badgaiyan RD, Sinha S, Sajjad M, Wack DS. Attenuated tonic and enhanced phasic release of dopamine in attention deficit hyperactivity disorder. *PLoS ONE*. 2015;10(9):e0137326.

75. van Galen KA, Ter Horst KW, Booij J, la Fleur SE, Serlie MJ. The role of central dopamine and serotonin in human obesity: lessons learned from molecular neuroimaging studies. *Metabolism*. 2018;85: 325-339.
76. Small DM, Jones-Gotman M, Dagher A. Feeding-induced dopamine release in dorsal striatum correlates with meal pleasantness ratings in healthy human volunteers. *Neuroimage*. 2003;19(4): 1709-1715.
77. Graff-Guerrero A, Willeit M, Ginovart N, et al. Brain region binding of the D2/3 agonist [11C]-(+)-PHNO and the D2/3 antagonist [11C]raclopride in healthy humans. *Hum Brain Mapp*. 2008;29(4): 400-410.
78. Horstmann A, Fenske WK, Hankir MK. Argument for a non-linear relationship between severity of human obesity and dopaminergic tone. *Obes Rev*. 2015;16(10):821-830.
79. van de Giessen E, Hesse S, Caan MW, et al. No association between striatal dopamine transporter binding and body mass index: a multi-center European study in healthy volunteers. *Neuroimage*. 2013;64:61-67.
80. Wu C, Garamszegi SP, Xie X, Mash DC. Altered dopamine synaptic markers in postmortem brain of obese subjects. *Front Hum Neurosci*. 2017;11:386.
81. Chen PS, Yang YK, Yeh TL, et al. Correlation between body mass index and striatal dopamine transporter availability in healthy volunteers—a SPECT study. *Neuroimage*. 2008;40(1):275-279.
82. Munro CA, McCaul ME, Wong DF, et al. Sex differences in striatal dopamine release in healthy adults. *Biol Psychiatry*. 2006;59(10): 966-974.
83. Honkanen EA, Noponen T, Hirvilammi R, et al. Sex correction improves the accuracy of clinical dopamine transporter imaging. *EJNMMI Res*. 2021;11(1):82.
84. Yabut JM, Crane JD, Green AE, Keating DJ, Khan WI, Steinberg GR. Emerging roles for serotonin in regulating metabolism: new implications for an ancient molecule. *Endocr Rev*. 2019; 40(4):1092-1107.
85. Halford JC, Harrold JA, Boyland EJ, Lawton CL, Blundell JE. Serotonergic drugs: effects on appetite expression and use for the treatment of obesity. *Drugs*. 2007;67(1):27-55.
86. Fletcher PJ, Burton MJ. Microstructural analysis of the anorectic action of peripherally administered 5-HT. *Pharmacol Biochem Behav*. 1986;24(4):1133-1136.
87. Georgescu T, Lyons D, Heisler LK. Role of serotonin in body weight, insulin secretion and glycaemic control. *J Neuroendocrinol*. 2021; 33(4):e12960.
88. Aggarwal A, Jethani SL, Rohatgi RK, Kalra J. Selective serotonin reuptake inhibitors (SSRIs) induced weight changes: a dose and duration dependent study on albino rats. *J Clin Diagn Res*. 2016;10(3): AF01-03.
89. Harvey BH, Bouwer CD. Neuropharmacology of paradoxic weight gain with selective serotonin reuptake inhibitors. *Clin Neuropharmacol*. 2000;23(2):90-97.
90. Fava M. Weight gain and antidepressants. *J Clin Psychiatry*. 2000;61-(Suppl 11):37-41.
91. Proietto J, Fam BC, Ainslie DA, Thorburn AW. Novel anti-obesity drugs. *Expert Opin Investig Drugs*. 2000;9(6):1317-1326.
92. McTavish D, Heel RC. Dexfenfluramine. A review of its pharmacological properties and therapeutic potential in obesity. *Drugs*. 1992; 43(5):713-733.
93. Hainer V, Kabrnova K, Aldhoon B, Kunesova M, Wagenknecht M. Serotonin and norepinephrine reuptake inhibition and eating behavior. *Ann N Y Acad Sci*. 2006;1083:252-269.
94. Adams KH, Pinborg LH, Svarer C, et al. A database of [(18) F]-altanserin binding to 5-HT(2A) receptors in normal volunteers: normative data and relationship to physiological and demographic variables. *Neuroimage*. 2004;21(3):1105-1113.
95. Erritzoe D, Frokjaer VG, Haugbol S, et al. Brain serotonin 2A receptor binding: relations to body mass index, tobacco and alcohol use. *Neuroimage*. 2009;46(1):23-30.
96. Erritzoe D, Frokjaer VG, Haahr MT, et al. Cerebral serotonin transporter binding is inversely related to body mass index. *Neuroimage*. 2010;52(1):284-289.
97. Erritzoe D, Ashok AH, Searle GE, et al. Serotonin release measured in the human brain: a PET study with [(11)C]CIMBI-36 and d-amphetamine challenge. *Neuropsychopharmacology*. 2020;45(5): 804-810.
98. Ettrup A, da Cunha-Bang S, McMahon B, et al. Serotonin 2A receptor agonist binding in the human brain with [(1)(1)C]Cimbi-36. *J Cereb Blood Flow Metab*. 2014;34(7):1188-1196.
99. Ratner C, Ettrup A, Bueter M, et al. Cerebral markers of the serotonergic system in rat models of obesity and after Roux-en-Y gastric bypass. *Obesity*. 2012;20(10):2133-2141.
100. Hesse S, Rullmann M, Luthardt J, et al. Central serotonin transporter availability in highly obese individuals compared with non-obese controls: a [(11)C] DASB positron emission tomography study. *Eur J Nucl Med Mol Imaging*. 2016;43(6):1096-1104.
101. Koskela AK, Kaurijoki S, Pietilainen KH, et al. Serotonin transporter binding and acquired obesity—an imaging study of monozygotic twin pairs. *Physiol Behav*. 2008;93(4–5):724-732.
102. Wu CH, Chang CS, Yang YK, Shen LH, Yao WJ. Comparison of brain serotonin transporter using [I-123]-ADAM between obese and non-obese young adults without an eating disorder. *PLoS ONE*. 2017; 12(2):e0170886.
103. Berthoud H. Multiple neural systems controlling food intake and body weight. *Neurosci Biobehav Rev*. 2002;26(4):393-428.
104. Berthoud HR, Morrison C. The brain, appetite, and obesity. *Annu Rev Psychol*. 2008;59:55-92.
105. Glass MJ, O'Hare E, Cleary JP, Billington CJ, Levine AS. The effect of naloxone on food-motivated behavior in the obese Zucker rat. *Psychopharmacology (Berl)*. 1999;141(4):378-384.
106. Gosnell BA, Levine AS. Reward systems and food intake: role of opioids. *Int J Obes (Lond)*. 2009;33(Suppl 2):S54-S58.
107. Kelley AE, Baldo BA, Pratt WE, Will MJ. Corticostriatal-hypothalamic circuitry and food motivation: integration of energy, action and reward. *Physiol Behav*. 2005;86(5):773-795.
108. Smith KS, Berridge KC. Opioid limbic circuit for reward: interaction between hedonic hotspots of nucleus accumbens and ventral pallidum. *J Neurosci*. 2007;27(7):1594-1605.
109. Cole JL, Leventhal L, Pasternak GW, Bowen WD, Bodnar RJ. Reductions in body weight following chronic central opioid receptor subtype antagonists during development of dietary obesity in rats. *Brain Res*. 1995;678(1–2):168-176.
110. Levine AS, Grace M, Billington CJ. Beta-funaltrexamine (beta-FNA) decreases deprivation and opioid-induced feeding. *Brain Res*. 1991; 562(2):281-284.
111. Statnick MA, Tinsley FC, Eastwood BJ, Suter TM, Mitch CH, Heiman ML. Peptides that regulate food intake: antagonism of opioid receptors reduces body fat in obese rats by decreasing food intake and stimulating lipid utilization. *Am J Physiol Regul Integr Comp Physiol*. 2003;284(6):R1399-R1408.
112. Sahr AE, Sindelar DK, Alexander-Chacko JT, Eastwood BJ, Mitch CH, Statnick MA. Activation of mesolimbic dopamine neurons during novel and daily limited access to palatable food is blocked by the opioid antagonist LY255582. *Am J Physiol Regul Integr Comp Physiol*. 2008;295(2):R463-R471.
113. Gosnell BA, Levine AS, Morley JE. The stimulation of food intake by selective agonists of mu, kappa and delta opioid receptors. *Life Sci*. 1986;38(12):1081-1088.
114. Noel MB, Wise RA. Ventral tegmental injections of a selective mu or delta opioid enhance feeding in food-deprived rats. *Brain Res*. 1995; 673(2):304-312.

115. Trenchard E, Silverstone T. Naloxone reduces the food intake of normal human volunteers. *Appetite*. 1983;4(1):43-50.
116. Yeomans MR, Wright P, Macleod HA, Critchley JA. Effects of nalmefene on feeding in humans. Dissociation of hunger and palatability. *Psychopharmacology (Berl)*. 1990;100(3):426-432.
117. Bertino M, Beauchamp GK, Engelman K. Naltrexone, an opioid blocker, alters taste perception and nutrient intake in humans. *Am J Physiol*. 1991;261(1 Pt 2):R59-R63.
118. Ziauddeen H, Chamberlain SR, Nathan PJ, et al. Effects of the mu-opioid receptor antagonist GSK1521498 on hedonic and consummatory eating behaviour: a proof of mechanism study in binge-eating obese subjects. *Mol Psychiatry*. 2013;18(12):1287-1293.
119. Nathan PJ, O'Neill BV, Bush MA, et al. Opioid receptor modulation of hedonic taste preference and food intake: a single-dose safety, pharmacokinetic, and pharmacodynamic investigation with GSK1521498, a novel mu-opioid receptor inverse agonist. *J Clin Pharmacol*. 2012;52(4):464-474.
120. Chamberlain SR, Mogg K, Bradley BP, et al. Effects of mu opioid receptor antagonism on cognition in obese binge-eating individuals. *Psychopharmacology (Berl)*. 2012;224(4):501-509.
121. Czyzyk TA, Nogueiras R, Lockwood JF, et al. Kappa-opioid receptors control the metabolic response to a high-energy diet in mice. *FASEB j*. 2010;24(4):1151-1159.
122. Czyzyk TA, Romero-Pico A, Pintar J, et al. Mice lacking delta-opioid receptors resist the development of diet-induced obesity. *FASEB j*. 2012;26(8):3483-3492.
123. Morley JE, Levine AS. Involvement of dynorphin and the kappa opioid receptor in feeding. *Peptides*. 1983;4(6):797-800.
124. Morley JE, Levine AS, Kneip J, Grace M, Zeugner H, Shearman GT. The kappa opioid receptor and food intake. *Eur J Pharmacol*. 1985;112(1):17-25.
125. Koch JE, Glass MJ, Cooper ML, Bodnar RJ. Alterations in deprivation, glucoprivic and sucrose intake following general, mu and kappa opioid antagonists in the hypothalamic paraventricular nucleus of rats. *Neuroscience*. 1995;66(4):951-957.
126. Brugman S, Clegg DJ, Woods SC, Seeley RJ. Combined blockade of both micro - and kappa-opioid receptors prevents the acute orexigenic action of Agouti-related protein. *Endocrinology*. 2002;143(11):4265-4270.
127. Robertson IH. A noradrenergic theory of cognitive reserve: implications for Alzheimer's disease. *Neurobiol Aging*. 2013;34(1):298-308.
128. Wellman PJ. Norepinephrine and the control of food intake. *Nutrition*. 2000;16(10):837-842.
129. Pruccoli J, Parmeggiani A, Cordelli DM, Lanari M. The role of the noradrenergic system in eating disorders: a systematic review. *Int J Mol Sci*. 2021;22(20):11086.
130. Ahlskog JE, Hoebel BG. Overeating and obesity from damage to a noradrenergic system in the brain. *Science*. 1973;182(4108):166-169.
131. Hoebel BG, Hernandez L, Schwartz DH, Mark GP, Hunter GA. Microdialysis studies of brain norepinephrine, serotonin, and dopamine release during ingestive behavior. Theoretical and clinical implications. *Ann N Y Acad Sci*. 1989;575:171-191.
132. Waterhouse BD, Navarra RL. The locus coeruleus-norepinephrine system and sensory signal processing: a historical review and current perspectives. *Brain Res*. 2019;1709:1-15.
133. Tellioglu T, Robertson D. Genetic or acquired deficits in the norepinephrine transporter: current understanding of clinical implications. *Expert Rev Mol Med*. 2001;2001:1-10.
134. Blakely RD, Bauman AL. Biogenic amine transporters: regulation in flux. *Curr Opin Neurobiol*. 2000;10(3):328-336.
135. Zavosh A, Schaefer J, Ferrel A, Figlewicz DP. Desipramine treatment decreases 3H-nisoxetine binding and norepinephrine transporter mRNA in SK-N-SHSY5Y cells. *Brain Res Bull*. 1999;49(4):291-295.
136. Soeder JM, Luthardt J, Rullmann M, et al. Central noradrenergic neurotransmission and weight loss 6 months after gastric bypass surgery in patients with severe obesity. *Obes Surg*. 2021;31(11):4868-4876.
137. Melasch J, Rullmann M, Hilbert A, et al. The central nervous norepinephrine network links a diminished sense of emotional well-being to an increased body weight. *Int J Obes (Lond)*. 2016;40(5):779-787.
138. Li CS, Potenza MN, Lee DE, et al. Decreased norepinephrine transporter availability in obesity: positron emission tomography imaging with (S,S)-[(11)C]O-methylreboxetine. *Neuroimage*. 2014;86:306-310.
139. Hesse S, Becker GA, Rullmann M, et al. Central noradrenaline transporter availability in highly obese, non-depressed individuals. *Eur J Nucl Med Mol Imaging*. 2017;44(6):1056-1064.
140. Bresch A, Rullmann M, Luthardt J, et al. Hunger and disinhibition but not cognitive restraint are associated with central norepinephrine transporter availability. *Appetite*. 2017;117:270-274.
141. Loftus TM, Jaworsky DE, Frehywot GL, et al. Reduced food intake and body weight in mice treated with fatty acid synthase inhibitors. *Science*. 2000;288(5475):2379-2381.
142. Minokoshi Y, Alquier T, Furukawa N, et al. AMP-kinase regulates food intake by responding to hormonal and nutrient signals in the hypothalamus. *Nature*. 2004;428(6982):569-574.
143. Kimes AS, Sweeney D, Rapoport SI. Brain palmitate incorporation in awake and anesthetized rats. *Brain Res*. 1985;341(1):164-170.
144. DeGrado TR, Coenen HH, Stocklin G. 14(R,S)-[18F]fluoro-6-thia-heptadecanoic acid (FTHA): evaluation in mouse of a new probe of myocardial utilization of long chain fatty acids. *J Nucl Med*. 1991;32(10):1888-1896.
145. Guiducci L, Gronroos T, Jarvisalo MJ, et al. Biodistribution of the fatty acid analogue 18F-FTHA: plasma and tissue partitioning between lipid pools during fasting and hyperinsulinemia. *J Nucl Med*. 2007;48(3):455-462.
146. Obici S, Feng Z, Morgan K, Stein D, Karkanias G, Rossetti L. Central administration of oleic acid inhibits glucose production and food intake. *Diabetes*. 2002;51(2):271-275.
147. Pocai A, Obici S, Schwartz GJ, Rossetti L. A brain-liver circuit regulates glucose homeostasis. *Cell Metab*. 2005;1(1):53-61.
148. Lam TK, Pocai A, Gutierrez-Juarez R, et al. Hypothalamic sensing of circulating fatty acids is required for glucose homeostasis. *Nat Med*. 2005;11(3):320-327.
149. Obici S, Feng Z, Arduini A, Conti R, Rossetti L. Inhibition of hypothalamic carnitine palmitoyltransferase-1 decreases food intake and glucose production. *Nat Med*. 2003;9(6):756-761.
150. Velloso LA, Schwartz MW. Altered hypothalamic function in diet-induced obesity. *Int J Obes (Lond)*. 2011;35(12):1455-1465.
151. Zhang X, Zhang G, Zhang H, Karin M, Bai H, Cai D. Hypothalamic IKKbeta/NF-kappaB and ER stress link overnutrition to energy imbalance and obesity. *Cell*. 2008;135(1):61-73.
152. Posey KA, Clegg DJ, Printz RL, et al. Hypothalamic proinflammatory lipid accumulation, inflammation, and insulin resistance in rats fed a high-fat diet. *Am J Physiol Endocrinol Metab*. 2009;296(5):E1003-E1012.
153. Thaler JP, Yi CX, Schur EA, et al. Obesity is associated with hypothalamic injury in rodents and humans. *J Clin Invest*. 2012;122(1):153-162.
154. Pocai A, Lam TK, Obici S, et al. Restoration of hypothalamic lipid sensing normalizes energy and glucose homeostasis in overfed rats. *J Clin Invest*. 2006;116(4):1081-1091.
155. Benoit SC, Kemp CJ, Elias CF, et al. Palmitic acid mediates hypothalamic insulin resistance by altering PKC-theta subcellular localization in rodents. *J Clin Invest*. 2009;119(9):2577-2589.
156. Yue JT, Lam TK. Lipid sensing and insulin resistance in the brain. *Cell Metab*. 2012;15(5):646-655.
157. De Souza CT, Araujo EP, Prada PO, Saad MJ, Boschero AC, Velloso LA. Short-term inhibition of peroxisome proliferator-activated receptor-gamma coactivator-1alpha expression reverses

diet-induced diabetes mellitus and hepatic steatosis in mice. *Diabetologia*. 2005;48(9):1860-1871.
158. Morgan K, Obici S, Rossetti L. Hypothalamic responses to long-chain fatty acids are nutritionally regulated. *J Biol Chem*. 2004;279(30):31139-31148.
159. Thamm T, Guo J, Rosenberg J, et al. Contralateral hemispheric cerebral blood flow measured with arterial spin labeling can predict outcome in acute stroke. *Stroke*. 2019;50(12):3408-3415.
160. Saindane AM, Drane DL, Singh A, Wu J, Qiu D. Neuroimaging correlates of cognitive changes after bariatric surgery. *Surg Obes Relat Dis*. 2020;16(1):119-127.
161. Ten Kulve JS, Veltman DJ, Gerdes VEA, et al. Elevated postoperative endogenous GLP-1 levels mediate effects of Roux-en-Y gastric bypass on neural responsivity to food cues. *Diabetes Care*. 2017;40(11):1522-1529.
162. Wang JL, Yang Q, Hajnal A, Rogers AM. A pilot functional MRI study in Roux-en-Y gastric bypass patients to study alteration in taste functions after surgery. *Surg Endosc*. 2016;30(3):892-898.
163. Connolly L, Coveleskie K, Kilpatrick LA, et al. Differences in brain responses between lean and obese women to a sweetened drink. *Neurogastroenterol Motil*. 2013;25(7):579-e460.
164. Szalay C, Aradi M, Schwarcz A, et al. Gustatory perception alterations in obesity: an fMRI study. *Brain Res*. 2012;1473:131-140.
165. Lavagnino L, Arnone D, Cao B, Soares JC, Selvaraj S. Inhibitory control in obesity and binge eating disorder: a systematic review and meta-analysis of neurocognitive and neuroimaging studies. *Neurosci Biobehav Rev*. 2016;68:714-726.
166. Le DS, Pannacciulli N, Chen K, et al. Less activation of the left dorsolateral prefrontal cortex in response to a meal: a feature of obesity. *Am J Clin Nutr*. 2006;84(4):725-731.
167. Volkow ND, Wang GJ, Telang F, et al. Inverse association between BMI and prefrontal metabolic activity in healthy adults. *Obesity*. 2009;17(1):60-65.
168. Delparigi A, Chen K, Salbe AD, Reiman EM, Tataranni PA. Sensory experience of food and obesity: a positron emission tomography study of the brain regions affected by tasting a liquid meal after a prolonged fast. *Neuroimage*. 2005;24(2):436-443.
169. Gautier JF, Chen K, Salbe AD, et al. Differential brain responses to satiation in obese and lean men. *Diabetes*. 2000;49(5):838-846.
170. Gautier JF, Del Parigi A, Chen K, et al. Effect of satiation on brain activity in obese and lean women. *Obes Res*. 2001;9(11):676-684.
171. Appelhans BM, Woolf K, Pagoto SL, Schneider KL, Whited MC, Liebman R. Inhibiting food reward: delay discounting, food reward sensitivity, and palatable food intake in overweight and obese women. *Obesity*. 2011;19(11):2175-2182.
172. Farr OM, Li CR, Mantzoros CS. Central nervous system regulation of eating: insights from human brain imaging. *Metabolism*. 2016;65(5):699-713.
173. Ikeda M, Brown J, Holland AJ, Fukuhara R, Hodges JR. Changes in appetite, food preference, and eating habits in frontotemporal dementia and Alzheimer's disease. *J Neurol Neurosurg Psychiatry*. 2002;73(4):371-376.
174. Landtblom AM, Dige N, Schwerdt K, Safstrom P, Granerus G. A case of Kleine-Levin syndrome examined with SPECT and neuropsychological testing. *Acta Neurol Scand*. 2002;105(4):318-321.
175. Whitwell JL, Przybelski SA, Weigand SD, et al. 3D maps from multiple MRI illustrate changing atrophy patterns as subjects progress from mild cognitive impairment to Alzheimer's disease. *Brain*. 2007;130(Pt 7):1777-1786.
176. Joseph-Mathurin N, Su Y, Blazey TM, et al. Utility of perfusion PET measures to assess neuronal injury in Alzheimer's disease. *Alzheimers Dement (Amst)*. 2018;10:669-677.
177. Zimmer ER, Parent MJ, Souza DG, et al. [(18)F]FDG PET signal is driven by astroglial glutamate transport. *Nat Neurosci*. 2017;20(3):393-395.
178. Sprinz C, Zanon M, Altmayer S, et al. Effects of blood glucose level on 18F fluorodeoxyglucose (18F-FDG) uptake for PET/CT in normal organs: an analysis on 5623 patients. *Sci Rep*. 2018;8(1):2126.
179. Busing KA, Schonberg SO, Brade J, Wasser K. Impact of blood glucose, diabetes, insulin, and obesity on standardized uptake values in tumors and healthy organs on 18F-FDG PET/CT. *Nucl Med Biol*. 2013;40(2):206-213.
180. Melissas J, Daskalakis M, Koukouraki S, et al. Sleeve gastrectomy—a "food limiting" operation. *Obes Surg*. 2008;18(10):1251-1256.
181. Beckman LM, Beckman TR, Earthman CP. Changes in gastrointestinal hormones and leptin after Roux-en-Y gastric bypass procedure: a review. *J am Diet Assoc*. 2010;110(4):571-584.
182. Halliday TM, Polsky S, Schoen JA, et al. Comparison of surgical versus diet-induced weight loss on appetite regulation and metabolic health outcomes. *Physiol Rep*. 2019;7(7):e14048.
183. Olivan B, Teixeira J, Bose M, et al. Effect of weight loss by diet or gastric bypass surgery on peptide YY3-36 levels. *Ann Surg*. 2009;249(6):948-953.
184. Laferrere B, Teixeira J, McGinty J, et al. Effect of weight loss by gastric bypass surgery versus hypocaloric diet on glucose and incretin levels in patients with type 2 diabetes. *J Clin Endocrinol Metab*. 2008;93(7):2479-2485.
185. Yousseif A, Emmanuel J, Karra E, et al. Differential effects of laparoscopic sleeve gastrectomy and laparoscopic gastric bypass on appetite, circulating acyl-ghrelin, peptide YY3-36 and active GLP-1 levels in non-diabetic humans. *Obes Surg*. 2014;24(2):241-252.
186. Goldstone AP, Miras AD, Scholtz S, et al. Link between increased satiety gut hormones and reduced food reward following gastric bypass surgery for obesity. *J Clin Endocrinol Metab*. 2016;101(2):599-609.
187. Loh HH, Francis B, Lim LL, Lim QH, Yee A, Loh HS. Improvement in mood symptoms after post-bariatric surgery among people with obesity: a systematic review and meta-analysis. *Diabetes Metab Res Rev*. 2021;37(8):e3458.
188. Gill H, Kang S, Lee Y, et al. The long-term effect of bariatric surgery on depression and anxiety. *J Affect Disord*. 2019;246:886-894.
189. Meyer JH, McNeely HE, Sagrati S, et al. Elevated putamen D(2) receptor binding potential in major depression with motor retardation: an [11C]raclopride positron emission tomography study. *Am J Psychiatry*. 2006;163(9):1594-1602.
190. Mick I, Myers J, Stokes PR, et al. Amphetamine induced endogenous opioid release in the human brain detected with [(1)(1)C]carfentanil PET: replication in an independent cohort. *Int J Neuropsychopharmacol*. 2014;17(12):2069-2074.
191. Colasanti A, Searle GE, Long CJ, et al. Endogenous opioid release in the human brain reward system induced by acute amphetamine administration. *Biol Psychiatry*. 2012;72(5):371-377.
192. Mick I, Myers J, Ramos AC, et al. Blunted endogenous opioid release following an oral amphetamine challenge in pathological gamblers. *Neuropsychopharmacology*. 2016;41(7):1742-1750.
193. Turton S, Myers JF, Mick I, et al. Blunted endogenous opioid release following an oral dexamphetamine challenge in abstinent alcohol-dependent individuals. *Mol Psychiatry*. 2020;25(8):1749-1758.
194. Erritzoe D, Godlewska BR, Rizzo G, et al. Brain serotonin release is reduced in patients with depression: a [(11)C]Cimbi-36 positron emission tomography study with a d-amphetamine challenge. *Biol Psychiatry*. 2022;93(12):1089-1098.
195. Tuominen L, Tuulari J, Karlsson H, et al. Aberrant mesolimbic dopamine-opiate interaction in obesity. *Neuroimage*. 2015;122:80-86.
196. Frank S, Wilms B, Veit R, et al. Altered brain activity in severely obese women may recover after Roux-en Y gastric bypass surgery. *Int J Obes (Lond)*. 2014;38(3):341-348.
197. Cerit H, Davidson P, Hye T, et al. Resting-state brain connectivity predicts weight loss and cognitive control of eating behavior

after vertical sleeve gastrectomy. *Obesity*. 2019;27(11):1846-1855.
198. Li P, Shan H, Nie B, et al. Sleeve gastrectomy rescuing the altered functional connectivity of lateral but not medial hypothalamus in subjects with obesity. *Obes Surg*. 2019;29(7):2191-2199.
199. van de Sande-Lee S, Pereira FR, Cintra DE, et al. Partial reversibility of hypothalamic dysfunction and changes in brain activity after body mass reduction in obese subjects. *Diabetes*. 2011;60(6):1699-1704.
200. Lepping RJ, Bruce AS, Francisco A, et al. Resting-state brain connectivity after surgical and behavioral weight loss. *Obesity*. 2015;23(7):1422-1428.
201. Wiemerslage L, Zhou W, Olivo G, et al. A resting-state fMRI study of obese females between pre- and postprandial states before and after bariatric surgery. *Eur J Neurosci*. 2017;45(3):333-341.
202. Olivo G, Zhou W, Sundbom M, et al. Resting-state brain connectivity changes in obese women after Roux-en-Y gastric bypass surgery: a longitudinal study. *Sci Rep*. 2017;7(1):6616.
203. Zhang Y, Ji G, Li G, et al. Ghrelin reductions following bariatric surgery were associated with decreased resting state activity in the hippocampus. *Int J Obes (Lond)*. 2019;43(4):842-851.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Al-Alsheikh AS, Alabdulkader S, Miras AD, Goldstone AP. Effects of bariatric surgery and dietary interventions for obesity on brain neurotransmitter systems and metabolism: A systematic review of positron emission tomography (PET) and single-photon emission computed tomography (SPECT) studies. *Obesity Reviews*. 2023;e13620. doi:10.1111/obr.13620

SUPPLEMENTARY INFORMATION

Effects of Bariatric Surgery and Dietary Interventions for Overweight and Obesity on the Brain: a Systematic Review of Positron Emission Tomography (PET) and Single-Photon Emission Computed Tomography (SPECT) Studies

Alhanouf S. Al-Alsheikh [a, b], Shahd Alabdulkader [c], Alexander D. Miras [a,d], Anthony P. Goldstone [e]

[a] Department of Metabolism, Digestion and Reproduction, Imperial College London, Hammersmith Hospital, London W12 0NN, UK

[b] Department of Community Health Sciences, College of Applied Medical Sciences, King Saud University, Riyadh 11451, Saudi Arabia

[c] Department of Health Sciences, College of Health and Rehabilitation Sciences, Princess Nourah Bint Abdulrahman University, Riyadh 84428, Saudi Arabia

[d] Ulster University, School of Medicine, Faculty of Life & Health Sciences, Londonderry, Northern Ireland, BT48 7JL, UK

[e] PsychoNeuroEndocrinology Research Group, Division of Psychiatry, Department of Brain Sciences, Imperial College London, Hammersmith Hospital, London W12 0NN, UK

Email: tony.goldstone@imperial.ac.uk

CONTENTS

SUPPLEMENTARY METHODS

2.2. Database Search

2.2.1. Keywords/terms used

The keywords used in the database searches were: (obesity OR overweight OR diabetes) AND (brain) AND [(surgery) OR (weight loss) OR (fat loss) OR (weight reduction) OR (weight maintenance) OR (gastric bypass) OR (RYGB) OR (sleeve gastrectomy) OR (VSG) OR (LVSG) OR (gastric sleeve) OR (gastric band) OR (gastric banding) OR (gastroplasty) OR (stomach balloon) OR (gastric balloon) OR (biliary pancreatic diversion) OR (diet) OR (lifestyle modification) OR (behavioural therapy) OR (psychological therapy)] AND [(PET) OR (positron emission tomography) OR (SPECT) OR (single photon emission computed tomography) OR (fluorodeoxyglucose) OR (FDG) OR (H2O) OR (raclopride) OR (fallypride) OR (PHNO) OR (DAT) OR (dopamine transporter) OR (carfentanil) OR (serotonin) OR (5HT) OR (5-HT) OR (opioid) OR (noradrenaline) OR (dopamine) OR (fatty acid) OR (cerebral blood flow)]. Once the database searches were accomplished, the papers listed were analysed based on the exclusion and inclusion criteria by examination of the titles, abstracts, and methods used.

2.3. Data Extraction

The core data generated from each article were:

(i) Study summary (authors name, publication year, journal, country, tracer used, target system in the brain, study design, if including bariatric surgery or non-surgical dietary intervention or control group, type of intervention, task, paradigm nutritional state (fed vs. fasted) or other state intervention (e.g. acute drug vs. placebo), inclusion of clinical, mechanistic or behaviour outcomes and correlation with PET/SPECT findings, exclusion criteria: use of psychotropic medication).

(ii) Demographic characteristics and clinical outcomes (sample size, sex ratio, age, T2DM, ethnicity, control intervention, time scan pre- and post-intervention, time between scans, BMI at baseline and post-intervention, weight loss, improvements in glycaemic control).

(iii) Study protocol (state manipulation, nutritional state, whether controlled for feeding/manipulation order effects, type of meal and macronutrient composition; time since last meal (defined as fasted ≥ 8h, pre-meal >2 to <8 h, fed ≤ 2h); whether controlled for menstrual cycle or mood).

(iv) PET/SPECT protocol (radioligand name, PET or SPECT, task during PET/SPECT scan (if any), task paradigm, duration of scan, reference region).

(v) PET/SPECT analysis (software, analysis methodology, statistical threshold; correction for multiple comparison, covariates).

(vi) PET/SPECT results (relevant contrasts (e.g. post- vs. pre-intervention, post-surgery vs. unoperated, fasted vs. fed etc.), analysis method (whole brain, small volume correction, anatomical or functional ROIs), reported by brain region.

(vii) Eating behaviour and other psychological measures (appetite ratings, food wanting/liking, food intake, eating behaviour questionnaires, other cognitive outcomes, mood).

(viii) Mechanistic measures (appetitive gut hormones (e.g. ghrelin, GLP-1, PYY), leptin, insulin, insulin resistance, nausea ratings, symptoms of dumping syndrome).

SUPPLEMENTARY RESULTS

3.2. Study Summaries

3.2.1. PET/SPECT tracers

Radioactive tracers used to investigate neurotransmitter systems illustrated in Figure 2 in the main paper. One or more tracers were used for each neurotransmitter system: (i) for dopamine system, three different tracers were used for D2RD2/3 (11-raclopride, ^{123}I-IBZM and 18F-fallypride) and one tracer was used for DAT (^{123}I-FP-CIT); (ii) for serotonin system, one tracer was used for 5-HT_{2A}R (18F-altanserin), and two tracers were used for serotonin transporter (^{11}C-DASB, ^{123}I-FP-CIT); (iii) only one tracer was used for noradrenaline (^{11}C-MRB) and (iv) one tracer for MOR (11C-carfentanil).

Radioactive tracers used to investigate brain metabolism illustrated in Figure 3 in the main paper. For assessment of brain metabolism: (i) Fluorodeoxyglucose (^{18}FDG) tracer was used for measuring brain glucose uptake (BGU); (ii) ^{18}F- FTHA was used to measure total fatty acid uptake and 11C-palmitate to measure non-oxidised fatty acid uptake; (iii) ^{15}O-H_2O labelled water was used for rCBF. In addition, although it is a not a PET tracer technique, one ^{18}FDG study also used the MRI technique of ASL which also measures rCBF.

3.2.2. Country

Seven of the 22 studies were carried out in the USA (31.8%) (Delparigi et al. 2004; DelParigi et al. 2007; Le et al. 2007; Dunn et al. 2010; Steele et al. 2010; Burghardt et al. 2015; Dunn et al. 2017), five in Finland (22.7%) (Karmi et al. 2010; Tuulari et al. 2013; Karlsson et al. 2016; Rebelos et al. 2019; Rebelos et al. 2020), three in the Netherlands (13.6%) (de Weijer et al. 2014; van der Zwaal et al. 2016; Versteeg et al. 2017) and one study (4.5%) was conducted in each of the following countries: Denmark (Haahr et al. 2015), United Kingdom (Hunt et al. 2016), Brazil (Marques et al. 2014), Italy (Guzzardi et al. 2018), Canada (Redies et al. 1989), Sweden (Almby et al. 2021) and Germany (Vettermann et al. 2018). Five publications (22.7%) contained overlapping datasets from two protocols (de Weijer et al. 2014; van der Zwaal et al. 2016) and (Delparigi et al. 2004; DelParigi et al. 2007; Le et al. 2007), while two publications (9.1%) (Redies et al. 1989; Karlsson et al. 2016) contained the same dataset, leaving 13 completely independent datasets.

3.3. Demographic Data

Demographic data for individual studies is given in Table 2 in the main paper.

3.3.1. Participant characteristics

With regard to PET sample size in the intervention group, nine studies (40.9%) included less than or equal to 10 participants (Redies et al. 1989; DelParigi et al. 2007; Le et al. 2007; Dunn et al. 2010; Steele et al. 2010; Burghardt et al. 2015; Hunt et al. 2016; Versteeg et al. 2017; Vettermann et al. 2018); eight studies (36.4%) included between 11 and 20 participants (Delparigi et al. 2004; de Weijer et al. 2014; Marques et al. 2014; Karlsson et al. 2016; van der Zwaal et al. 2016; Dunn et al. 2017; Guzzardi et al. 2018; Almby et al. 2021); and six studies (27.3%) included over 20 participants (Karmi et al. 2010; Tuulari et al. 2013; Haahr et al. 2015; Guzzardi et al. 2018; Rebelos et al. 2019; Rebelos et al. 2020). Note that the total number of studies here is more than the number of publications as some studies had more than one intervention group.

The total number of baseline participants across all studies was 558, 440 of whom were female (78.9%), with eleven studies including only females (DelParigi et al. 2007; Le et al. 2007; Dunn et al. 2010; Steele et al. 2010; de Weijer et al. 2014; Marques et al. 2014; Karlsson et al. 2016; van der Zwaal et al. 2016; Dunn et al. 2017; Guzzardi et al. 2018; Rebelos et al. 2020), seven with ≥50% females (Delparigi et al. 2004; Karmi et al. 2010; Tuulari et al. 2013; Haahr et al. 2015; Hunt et al. 2016; Rebelos et al. 2019; Almby et al. 2021), one study included 40% female (Vettermann et al. 2018) and three studies including only males (Redies et al. 1989; Burghardt et al. 2015; Versteeg et al. 2017).

Only eight out of 22 studies (36.4%) reported participants' ethnicity (Le et al. 2007; Dunn et al. 2010; Steele et al. 2010; de Weijer et al. 2014; Hunt et al. 2016; van der Zwaal et al. 2016; Dunn et al. 2017; Vettermann et al. 2018) and out of these 163 participants, 132 (81.0%) were white Caucasian.

Eleven studies (50%) were conducted exclusively on patients without type 2 diabetes mellitus (T2DM) (Redies et al. 1989; Delparigi et al. 2004; DelParigi et al. 2007; Le et al. 2007; Dunn et al. 2010; Steele et al. 2010; Marques et al. 2014; Versteeg et al. 2017; Guzzardi et al. 2018; Vettermann et al. 2018; Almby et al. 2021), while five studies (22.7%) included some participants with T2DM (Tuulari et al. 2013; Karlsson et al. 2016; Dunn et al. 2017; Rebelos et al. 2019; Rebelos et al. 2020), and six studies (27.3%) did not report the prevalence of T2DM (Karmi et al. 2010; de Weijer et al. 2014; Burghardt et al. 2015; Haahr et al. 2015; Hunt et al. 2016; van der Zwaal et al. 2016), although one of these only included participants with metabolic syndrome (Karmi et al. 2010).

3.3.2. Time since intervention

In longitudinal studies, the time of PET/SPECT scanning post-intervention varied greatly from as early as 8 or 10 days (Dunn et al. 2017) to 3.1 years (van der Zwaal et al. 2016). Seven studies conducted PET/SPECT scans from 3 weeks to 3 months post-intervention (Redies et al. 1989; Dunn et al. 2010; Karmi et al. 2010; Steele et al. 2010; de Weijer et al. 2014; Versteeg et al. 2017; Guzzardi et al. 2018), two studies from 3 to 6 months after intervention (Burghardt et al. 2015; Almby et al. 2021), six studies at 6 months after intervention (Delparigi et al. 2004; Tuulari et al. 2013; Marques et al. 2014; Karlsson et al. 2016; Rebelos et al. 2019; Rebelos et al. 2020), and one study 8 months post-intervention (Haahr et al. 2015).

In cross-sectional studies, one study carried out PET scanning 1.5 years after surgery (Hunt et al. 2016), while the other three studies did not clearly report the time after intervention (Delparigi et al. 2004; DelParigi et al. 2007; Le et al. 2007).

3.3.3. Weight loss ranges

The mean percentage weight loss in surgery intervention studies was variable in part related to variable duration of follow-up, with average of 11-20% (Dunn et al. 2010; Steele et al. 2010), over 20% (Tuulari et al. 2013; Marques et al. 2014; Haahr et al. 2015; Hunt et al. 2016; Karlsson et al. 2016; van der Zwaal et al. 2016; Rebelos et al. 2019; Rebelos et al. 2020; Almby et al. 2021), and up to 31% (Hunt et al. 2016; van der Zwaal et al. 2016). Meanwhile in dietary intervention group studies, the average weight loss was generally lower being less than 5% (Dunn et al. 2017; Guzzardi et al. 2018; Vettermann et al. 2018), 6-10% (Versteeg et al. 2017), or 11-20% (Redies et al. 1989; Karmi et al. 2010; Burghardt et al. 2015). The individual results are summarised in Table 2 in the main paper.

3.3.4. Control groups

Fifteen of the studies included a non-interventional control group, either normal weight participants (BMI <25 kg/m^2) (Delparigi et al. 2004; Le et al. 2007; Steele et al. 2010; Marques et al. 2014; Burghardt et al. 2015; Haahr et al. 2015; Hunt et al. 2016) or participants without obesity (BMI <30 kg/m^2) (Karmi et al. 2010; Tuulari et al. 2013; Karlsson et al. 2016; van der Zwaal et al. 2016; Vettermann et al. 2018; Rebelos et al. 2019; Rebelos et al. 2020) or with obesity without an intervention (Delparigi et al. 2004; DelParigi et al. 2007; Le et al. 2007). However, none of the studies compared findings between two different interventions (surgery vs. dietary, or between different

surgeries).

3.4. Study Protocols and Analysis

Study protocols are summarised in Supplementary Table S1

3.4.1. Nutritional status

In eleven studies (50.0%) participants were scanned when fasted: five after "overnight" fasting (de Weijer et al. 2014; van der Zwaal et al. 2016; Versteeg et al. 2017; Rebelos et al. 2019; Almby et al. 2021); two studies, after fasting for 8 hours (Dunn et al. 2010; Dunn et al. 2017); and four after 10-14 hours fasting (Redies et al. 1989; Karmi et al. 2010; Tuulari et al. 2013; Rebelos et al. 2020). One study (4.5%) assessed participants pre-meal (6 hours since last meal) (Guzzardi et al. 2018). In two studies (9.1%), participants were fed (2 hours after meal) (Karlsson et al. 2016) (did not report the time since last meal) (Haahr et al. 2015) and five studies (22.7%) included two nutritional states, fasted (>10 hours) and fed (30 minutes since meal) (Burghardt et al. 2015), fasted (>9 hours) and fed (1 hour since meal) (Hunt et al. 2016), fasted (36 hours) and fed (30 minutes since meal) (Delparigi et al. 2004; DelParigi et al. 2007; Le et al. 2007). Three studies (13.6%) did not report nutritional status (Steele et al. 2010; Marques et al. 2014; Vettermann et al. 2018).

3.4.2. Menstrual cycle

Only five studies (22.7%) including pre-menopausal women controlled for stage of the menstrual cycle, with four conducted during the follicular phase (Delparigi et al. 2004; DelParigi et al. 2007; Le et al. 2007; Guzzardi et al. 2018), while one study scanned in the first ten days of menstrual cycle (Hunt et al. 2016).

3.4.3. Mood assessment

Only six studies (27.3%) assessed mood and psychological factors as a potential confound for differences in PET/SPECT findings using Beck Depression Inventory-II questionnaire (BDI-II) (Dunn et al. 2010; Steele et al. 2010; Karlsson et al. 2016), state-trait anxiety inventory questionnaire (STAI) (Karlsson et al. 2016), adult temperament questionnaire (ATQ) (Vettermann et al. 2018), positive and negative affect schedule questionnaire (PANAS) (Burghardt et al. 2015), symptom checklist-90-R (SCL-90-R) questionnaire, major depression index and Cohen's perceived stress (Haahr et al. 2015).

However, only one of these studies observed an improvement in mood 4-6 months post-RYGB surgery (Steele et al. 2010), while no change in mood was observed 1.6 months post-RYGB/VSG (Dunn et al. 2010), 8.2 months post-RYGB (Haahr et al. 2015), 6 months post-LCD (Vettermann et al. 2018), 3.6 months post-VLCD (Burghardt et al. 2015) or 6 months post-VLCD (Karlsson et al. 2016).

3.4.4. PET paradigm and stimulus type

Summary of PET/SPECT protocols methodology is given in Supplementary Table S2. Three dietary intervention studies used sensory stimulation inside the PET scanner. One study used ^{18}F-FDG to study the effect of LCD used three sensory stimuli involving visual, olfactory and taste during neutral (e.g., landscape) or palatable food cues (e.g., chocolate cake) (Guzzardi et al. 2018). Two studies used rCBF (^{15}O-H_2-O) to investigate the effect of LCD used a gustatory stimulus (after tasting and after consuming a satiating liquid meal) (Delparigi et al. 2004; DelParigi et al. 2007).

3.4.5. PET/SPECT analysis methodology

Summary of PET/SPECT analysis methodology is given in Supplementary Table S3. Only one (4.5%) study used whole brain analysis only (Marques et al. 2014); nine studies (40.9%) used a predefined ROIs from previous study (Redies et al. 1989; Dunn et al. 2010; Steele et al. 2010; de Weijer et al. 2014; Haahr et al. 2015; van der Zwaal et al. 2016; Dunn et al. 2017; Guzzardi et al. 2018; Almby et al. 2021); ten studies (45.5%) used both whole brain and ROIs analyses (including on occasion for secondary correlational analyses) (Delparigi et al. 2004; DelParigi et al. 2007; Karmi et al. 2010; Tuulari et al. 2013; Burghardt et al. 2015; Hunt et al. 2016; Karlsson et al. 2016; Vettermann et al. 2018; Rebelos et al. 2019; Rebelos et al. 2020); while one study (4.5%) used whole brain and small volume correction analyses (Le et al. 2007); and one study (4.5%) used both ROIs and small volume correction (for striatum only) analyses (Versteeg et al. 2017).

Only fourteen studies (63.6%) corrected for multiple comparisons in their PET/SPECT analysis of main effects of the intervention (rather than secondary correlations): (i) in whole brain analysis studies (Delparigi et al. 2004; Karmi et al. 2010; Tuulari et al. 2013; Marques et al. 2014; Burghardt et al. 2015; Hunt et al. 2016; Karlsson et al. 2016; Rebelos et al. 2019; Rebelos et al. 2020); (ii) in ROIs studies (Redies et al. 1989; Dunn et al. 2010; Karmi et al. 2010; Karlsson et al. 2016; Guzzardi et al. 2018); and (iii) in small volume correction studies (Delparigi et al. 2004; Le et al. 2007; Versteeg et al. 2017).

Only five studies (22.7%) reported power calculations (de Weijer et al. 2014; Karlsson et al. 2016; Dunn et al. 2017; Versteeg et al. 2017; Rebelos et al. 2019).

Seven studies (31.8%) included covariates in the analysis, adjusting for smoking and medication (antidiabetic, antihypertensive and cholesterol-lowering drugs) with ^{11}C-raclopride tracer in RYGB/VSG patients (Karlsson et al. 2016), age and whole brain blood flow with ^{15}O-H_2O tracer after low calorie diet intervention (DelParigi et al. 2007), whole brain blood flow with ^{15}O-H_2O tracer after low calorie diet intervention (Delparigi et al. 2004), age with ^{18}F-FDG tracer in RYGB patients (Marques et al. 2014; Hunt et al. 2016), education level with ^{18}F-FDG tracer in RYGB patients (Marques et al. 2014), and physical activity with ^{18}F-FDG tracer in RYGB/VSG patients (Tuulari et al. 2013), scanner with ^{18}F-FTHA and ^{11}C-palmitate tracers in VLCD (different PET-scanners were used in this study) (Karmi et al. 2010).

3.4.6. Quality of data

It is important to realise that none of the papers identified in this systematic review came from randomised clinical trials but only from observational cross-sectional and longitudinal observational studies. The average score on the NIH Quality Assessment Scale was 69.7% (range 60-80%). Sixteen studies had good quality, six studies had fair quality and no studies had poor quality (Supplementary Table S4).

3.5. PET/SPECT Study Findings

3.5.1. Dopamine neurotransmitter system

11C-raclopride: Two longitudinal studies examined effects of RYGB and/or VSG surgery and comparing with normal-weight participants (BMI 18-25 kg/m^2) (Steele et al. 2010) or participants without obesity (BMI 18-30 kg/m^2) (Karlsson et al. 2016). There was an increase in dopamine receptor D2 (DRD2) binding-potential (BP) in the average anatomical region of interests (aROIs) (ventral striatum, anterior/posterior putamen and caudate) 4-6 weeks after RYGB surgery in unknown nutritional state (n=5) (Steele et al. 2010), but no change was observed six months after RYGB/VSG in individual aROIs (ventral striatum, caudate, putamen) when fed (n=16) (Karlsson et al. 2016). However, neither study showed differences in DRD2 BP comparing the pre-operative group with obesity and the control group without obesity (Steele et al. 2010; Karlsson et al. 2016)

18F-fallypride: Two longitudinal studies examined effects at seven weeks after RYGB/VSG surgery

(n=5) (Dunn et al. 2010), and ten days after a VLCD intervention (n=5) (Dunn et al. 2017), both done when fasted using aROIs. Both these studies showed a reduction in DRD2/3 BP in the substantia nigra, however a decrease in caudate, medial thalamus, amygdala and hypothalamus was only seen after RYGB/VSG surgery (Dunn et al. 2010), though there as a trend for a decrease after VLCD in the ventral striatum, putamen, caudate and hypothalamus (Dunn et al. 2017).

^{123}I-IBZM: Two longitudinal studies examined effects after RYGB surgery when fasted using aROIs. One showed no changes in DRD2/3 BP in caudate, putamen and whole dorsal/ventral striatum at six weeks after RYGB surgery (n=19) (de Weijer et al. 2014), while the other demonstrated an increase in DRD2/3 BP in caudate and whole striatum with a similar trend towards in putamen 3 years after RYGB surgery (n=11) (van der Zwaal et al. 2016). In the latter study, D2/3 BP in the whole striatum post-RYGB was lower than in a group without obesity (van der Zwaal et al. 2016).

^{123}I-FP-CIT: One longitudinal, dietary intervention study using aROI (striatum) showed no change in DAT BP four weeks after a low-calorie diet (LCD) in combined subgroups (where 50% of energy requirement was consumed at breakfast (n=9) or dinner (n=11) (Versteeg et al. 2017). However, DAT BP in the striatum increased more after LCD in the breakfast group compared to the dinner group. Using small volume correction analysis DAT BP increased in the ventral striatum in the breakfast group and decreased in the dorsal striatum in the dinner group.

3.5.2. Serotonin neurotransmitter system

^{123}I FP-CIT: One longitudinal study showed no differences in extra-striatal aROIs (thalamus, hypothalamus) serotonin transporter BP four weeks LCD in the fasting state in combined subgroups (50% of kCal given at breakfast or dinner) (n=20) (Versteeg et al. 2017). However, when comparing the two groups, serotonin transporter BP increased in the thalamus after LCD in the breakfast group with a decrease in the dinner group.

^{18}F-altanserin: One longitudinal study showed no change in 5-HT_{2A}R BP in the neocortex (volume-weighted average of eight cortical regions: OFC, medial inferior frontal, superior frontal, superior temporal, medial inferior temporal, sensory-motor, parietal and occipital cortices) 8 months after RYGB surgery (n=12) in the fed state using aROIs (Haahr et al. 2015). However, a higher neocortical 5-HT_{2A}R BP was observed in both pre- and post-RYGB surgery compared with normal weight participants.

^{11}C-DASB: The same longitudinal study also used an ^{11}C-DASB tracer to examine changes in serotonin transporter BP averaged across caudate, putamen and thalamus aROIs 8 months after RYGB surgery in the fed state (n=13) (Haahr et al. 2015). No changes were observed in BP after surgery, nor where there any differences between pre- or post-RYGB surgery compared with normal weight participants.

3.5.3. Opioid neurotransmitter system

11C-carfentanil: In one longitudinal study of bariatric surgery in the fed state, there was an increase in MOR 11C-carfentanil BP six months after RYGB/VSG surgery in the following individual aROIs (and averaged across all aROIs) (n=16): ventral striatum, dorsal caudate, putamen, thalamus, amygdala, insula, ACC, medial cingulate cortex, PCC and OFC (Karlsson et al. 2016). Similar increases were seen in these regions using whole brain analysis except for putamen, medial cingulate cortex and PCC. Interestingly, 11C-carfentanil BP was lower pre-RYGB/VSG surgery than a control group without obesity on average across all aROIs and in individual aROIs except ACC and medial cingulate cortex, but no difference when comparing post-RYGB/VSG with controls without obesity. No effect of T2DM diagnosis was seen on 11C-carfentanil BP in any aROIs pre-surgery.

In a second longitudinal study of VLCD in the fasted study, there was an increase in 11C-carfentanil BP in the ventral striatum, thalamus, medial OFC cortex and temporal pole in whole brain analysis, about four months after VLCD (Burghardt et al. 2015). A lower 11C-carfentanil BP in thalamus, amygdala, temporal pole and PFC was observed in before VLCD compared with a group with normal weight, while a lower 11C-carfentanil BP was observed in the frontal pole and temporal pole after VLCD compared with group with normal weight. There was also an increase in 11C-carfentanil BP in a fasted compared with fed state in the ventral striatum and frontal pole in pre-VLCD group; in the ventral striatum, thalamus, amygdala and temporal pole in post-VLCD group; and in the ventral striatum, thalamus, amygdala, frontal pole, medial OFC and temporal pole in group with normal weight.

3.5.4. Noradrenaline neurotransmitter system

^{11}C-MRB: One longitudinal study in demonstrated no change in NAT ^{11}C-MRB BP after six months of LCD in unknown nutritional state (n=10) in individual aROIs: ventral striatum, caudate head, putamen, thalamus, amygdala, hippocampus, hypothalamus, locus coeruleus, insula, medial

prefrontal cortex, ACC, dlPFC, OFC and midbrain (Vettermann et al. 2018).

3.5.5. Regional cerebral blood flow

^{15}O-H_2O: One longitudinal study found no change in rCBF averaged across the whole brain after 3 weeks complete fasting except water and electrolyte supplements (only n=4) (Redies et al. 1989).

One cross-sectional study, comparing rCBF between successful dieters (after LCD) (n=11), group with obesity who were not dieting (n=23), and group with normal weight (n=21 (Delparigi et al. 2004) when fasted (36 hours), immediately after consuming a small (2 ml) quantity of liquid HE food (taste) and 30 mins after food intake (fed). Using fROIs analysis (for those regions showing a significant interaction between group and state), there was greater insula rCBF after tasting (vs. fasted) in both the post-LCD and obesity groups compared to the group with normal weight, and a lower PCC rCBF in the group with obesity compared to the normal weight but not post-LCD group. When fed (vs. fasted) there was greater increase in rCBF in amygdala and PCC in both the successful dieters and group with normal weight compared to group with obesity, with no difference between the former groups. When fed (vs. fasted), both successful dieters and group with obesity showed show a greater decrease in hippocampus rCBF than normal-weight participants, with no difference between the former groups.

Another cross-sectional study by the same group demonstrated using whole brain analysis a greater reduction in rCBF in the hippocampus, parahippocampal gyrus and occipital lobe after a 2mL taste of liquid meal following a 36 h fast in successful dieters (n=9) compared with group with obesity who are not dieting (n=20) (DelParigi et al. 2007). However, there was greater increase in rCBF in the putamen, dorsal frontal pole, dorsal prefrontal cortex, and anterior cerebellum, and less increase in rCBF in OFC, after consuming a meal (fed vs. fasted), in successful dieters compared with group with obesity who are not dieting.

In another cross-sectional study comparing fed with fasted states, women with obesity had lower rCBF in left dlPFC and IFG than both women of normal weight and those participants who were formerly had obesity (post-LCD), with no differences between the latter two groups (Le et al. 2007). In addition, rCBF in OFC and occipital lobe when fed (vs. fasted) was lower in group post-LCD compared with group with obesity, while rCBF in superior and left middle temporal gyri was lower post-LCD than in normal weight groups (Le et al. 2007). Furthermore, when fed (vs. fasted), rCBF in

dlPFC, IFG, hippocampus and parahippocampal gyrus was lower, and rCBF in ACC, dlPFC and MFG was higher in group with obesity compared to group of normal weight.

Arterial spin labelling (ASL): Only one study assessed CBF post-RYGB surgery but using ASL (a functional MRI technique rather than PET imaging using radiolabelled water) (Almby et al. 2021). At average 4 months post-RYGB, rCBF in the fasted state had increased in all brain regions during normoglycemia and in most brain regions during hypoglycaemia (but no regional coordinates given) using hyperinsulinaemic clamps, but no effects of hypoglycaemia itself were seen.

3.5.6. Brain glucose uptake

In a longitudinal RYGB study in unknown nutritional state, there was a decrease in BGU using ^{18}F-FDG in the uncus, parahippocampal gyrus, PCC, middle temporal lobe, anterior cerebellum, and IFG six months after RYGB in whole brain analysis (n=17) (Marques et al. 2014). Furthermore, compared with normal weight participants, a higher BGU was observed pre-RYGB surgery in PCC and posterior cerebellum, while no differences were observed post-RYGB surgery in any brain regions (Marques et al. 2014).

In another longitudinal RYGB study in fasted state, there was also a decrease in grey matter BGU after RYGB surgery during a hyperinsulinaemic normoglycemic clamp using both whole brain and aROIs analyses (though results for individual brain regions were not reported) (n=11) (Almby et al. 2021). Hyperinsulinaemic hypoglycaemia increased grey matter BGU to a similar degree post-RYGB as pre-RYGB surgery, but there was a greater decrease in BGU in the hypothalamus post-RYGB than pre-RYGB surgery with hypoglycaemia.

Another smaller cross-sectional RYGB study, compared participants on average 18 months post-RYGB (n=9) with unoperated patients with obesity (n=21), and normal-weight (n=12) participants in different nutritional state (fed 400 kcal - vanilla ice cream vs. fasted) in whole brain analysis (Hunt et al. 2016). Participants post-RYGB showed: (i) higher BGU after eating (fed vs. fasted) than participants with obesity or normal weight in ventral cingulate subcallosal gyrus, hypothalamus, pituitary and medial OFC; (ii) lower BGU after eating in cuneus, parietal lobule, superior and middle temporal gyrus, occipital pole, precuneus, PCC, and angular gyrus than the two other groups; (iii) lower BGU in insula, dlPFC, lateral OFC, frontal operculum cortex and anterior medial frontal cortex than participants with obesity (but not normal-weight participants); and (iv) a lower BGU in lingual

gyrus than group with normal weight (but not obesity). Acute administration of somatostatin (and insulin) to suppress the heightened post-prandial satiety gut hormones (including plasma PYY and GLP-1) in the post-RYGB surgery group had no effect on post-prandial BGU in any of the fROIs (determined from regions showing an interaction between group and nutritional state from the results above), except for an attenuated post-prandial increase in BGU in the medial OFC (but no correction was done for multiple comparisons)

Two longitudinal studies with mixed RYGB/VSG surgery groups examined the effects of hyeprinsulinaemic euglycaemic clamps (vs. fasting). RYGB/VSG surgery had no effect on insulin-stimulated BGU at six months (vs. pre-surgery) in whole brain analysis (n=17) (Tuulari et al. 2013). However, in aROIs analysis, insulin-stimulated BGU in midbrain, cerebellum, and iambic, frontal, parietal, temporal and occipital lobes pre-RYGB/VSG but not post-RYGB/VSG surgery (though no direct comparison between visits was reported). By contrast, in the other study, insulin-stimulated whole brain BGU decreased six months after RYGB/VSG surgery, but results for individual brain regions were not reported (n=16) (Rebelos et al. 2019). However, whole brain insulin-stimulated BGU remained higher both pre- and post-RYGB/VSG surgery compared with participants without obesity.

A longitudinal study of LCD on BGU in the fasted state, examined the influence of low or high 'food addiction' using the Yale Food Addiction Scale (YFAS) using aROIs analysis (n=11-12) (Guzzardi et al. 2018). In the high-YFAS group after 3 months of LCD, BGU in response to visual, taste and odour food stimuli decreased in caudate, thalamus, hippocampus, hypothalamus, midbrain, posterior central gyrus, temporal lobe, occipital lobe, with a trend for decrease in putamen, but no change in PFC, dlPFC or OFC. In the low-YFAS group there was no change in BGU in any aROIs (though no direct statistical comparison of effect of LCD intervention was made between groups).

In a very small, longitudinal study of three weeks in men with obesity, total fasting, BGU decreased in all aROIs (white matter, basal and cortical grey matter, caudate/putamen, thalamus/hypothalamus, frontal lobe, temporal lobe, occipital lobe) (n=4) (Redies et al. 1989).

3.5.7. Brain fatty acid uptake

^{18}F-FTHA: One longitudinal study found no change in total FFA uptake six months post-RYGB/VSG surgery when fasted, in whole brain analysis nor ROIs analysis (frontal, parietal, temporal, occipital

or limbic lobes, midbrain, or cerebellum) (n=21) (Rebelos et al. 2020). However, there was higher FFA uptake in all ROIs in obesity pre-surgery compared with controls without obesity.

By contrast, one longitudinal study found a significant reduction in total FFA uptake after six weeks of VLCD followed by 1 week of isocaloric diet, in metabolic syndrome with overweight/obesity (BMI= 33.6 $\pm$ 4 kg/m^2) when fasted in whole brain analysis in the prefrontal cortex and parietal, temporal and occipital lobes, in grey matter, and in average of all aROIs (white matter, striatum, amygdala, hippocampus, hypothalamus, anterior cingulate cortex, prefrontal cortex, parietal and temporal lobes) (n=16) (Karmi et al. 2010). There was a higher total FFA uptake at baseline pre-VLCD compared with controls without metabolic syndrome/overweight (BMI 26.8 $\pm$ 2.5 kg/m^2) in grey matter and average of all aROIs (Karmi et al. 2010).

11C-palmitate: The same study also used 11C-palmitate to examine changes in the non-oxidised fraction of FFA uptake (Karmi et al. 2010). However, no change in fractional FFA uptake rate was seen after VLCD in grey matter, or in average of all or any individual aROIs (white matter, striatum, amygdala, hippocampus, hypothalamus, anterior cingulate cortex, prefrontal cortex, parietal and temporal lobes). Conversely, as with ^{18}F-FTHA uptake, there was a higher fractional FFA uptake at baseline pre-VLCD compared with participants without obesity controls without metabolic syndrome in grey matter, and in average of all and any individual aROIs (Karmi et al. 2010).

3.6. Correlations

3.6.1. Clinical outcomes

The results of the correlations with clinical outcomes from individual studies are summarised in Supplementary Table S6

Correlations of baseline PET/SPECT measures with clinical outcomes

Serotonin system (pre-RYGB): Higher baseline 5-HT$_{2A}$R ^{18}F-altanserin BP in the neocortex was associated with weight loss at ~8 months after RYGB surgery in aROIs analysis, but no correlation was seen for baseline 5-HTT ^{11}C-DASB BP (n=13-21) (Haahr et al. 2015).

Noradrenaline system (pre-LCD): Higher baseline NAT ^{11}C-MRB BP in the putamen, hippocampus, midbrain, insula and dlPFC in whole brain analysis (uncorrected for multiple comparisons) was associated with less weight loss at 6 months after LCD (n=10) (Vettermann et al. 2018).

BGU (pre-RYGB/VSG): Higher baseline insulin-stimulated BGU in whole brain analysis (coordinates not given) was associated with a greater decrease in fasting plasma glucose at two years (n=17) and three years (n=13) after RYGB/VSG surgery, which persisted after correcting for baseline BMI for the two year data (Rebelos et al. 2019). By contrast, baseline BGU was unrelated to changes in BMI or HbA1c at two years after RYGB/VSG surgery (Rebelos et al. 2019).

FFA (pre-RYGB/VSG): Moreover, higher baseline total brain FFA uptake was associated with a lower decrease in fasting plasma glucose at two years after RYGB/LVSG surgery, and this remained significant after adjusting for baseline plasma glucose (n=21) (Rebelos et al. 2020).

Correlations of change in PET/SPECT outcomes with change in clinical outcomes

Dopamine system (post-RYGB): No correlation was seen between the increase in DRD2/3 ^{123}I-IBZM BP in a striatum aROIs and the decrease in BMI, fat percent or fasting plasma glucose at 3.1 years post-RYGB surgery (n=11) (van der Zwaal et al. 2016).

Dopamine system (post-VLCD): A greater reduction in DRD2/3R ^{18}F-fallypride BP in the substantia nigra, with a similar trend for caudate and putamen (but not hypothalamus nor ventral striatum), was associated with a greater reduction in fasting plasma glucose at 8-10 after VLCD (n=15) (Dunn et al. 2017).

Serotonin system (post-RYGB): A greater increase in 5-HT$_{2A}$R ^{18}F-altanserin BP in whole neocortex and in 5-HTT ^{11}C-DASB averaged across all aROIs (caudate, putamen, thalamus) was associated with smaller weight loss at ~8 months after RYGB surgery (n=13-21), although there was no overall change in ^{18}F-altanserin nor ^{11}C-DASB BP (Haahr et al. 2015). Not CORRECTED

Noradrenaline system (post-LCD): A greater increase in NAT ^{11}C-MRB BP in the insula and hippocampus (but not ventral striatum, caudate, putamen, thalamus, amygdala, hypothalamus, midbrain, locus coeruleus, ACC, mid prefrontal cortex, dlPFC, OFC) was associated with less weight loss at 6 months post-LCD (n=10) (though this analysis was not fully corrected for multiple corrections), although there was no overall change in ^{11}C-MRB BP after LCD in any region (Vettermann et al. 2018).

Brain glucose uptake (post-LCD): The change in BGU upon HE food presentation in any aROIs (caudate putamen, thalamus, hippocampus, hypothalamus, midbrain, prefrontal cortex, dlPFC, OFC, post-central gyrus, temporal and occipital lobes) did not correlate with weight loss, body fat percentage, subcutaneous and visceral adipose tissue volumes at three months after LCD (1600kcal per day) in either groups with high or low YFAS questionnaire score (n=11-12) (Guzzardi et al. 2018).

3.6.2. Behavioural outcomes

Behavioural measures and the association with PET/SPECT findings are summarised in Supplementary Tables S7 and S8

Correlations of changes in PET/SPECT measures with changes in behavioural outcomes

Dopamine system

Post-RYGB: A smaller increase in DRD2/3 BP using ^{123}I-IBZM in the striatum aROIs tended to be associated with a greater decrease in general food craving trait (but not state) questionnaire at 3.1 years post-RYGB surgery, despite on average the DRD2/3 BP increasing and the food craving decreasing after RYGB surgery (van der Zwaal et al. 2016).

Serotonin system

Post-RYGB: Neither the change in 5-HT_{2A}R BP using 18F-altanserin tracer in neocortex, nor change in SERT BP using ^{11}C-DASB tracer in average caudate, putamen and thalamus aROIs, correlated with the increase in post-prandial fullness using visual analogue scales at 8 months post-RYGB surgery (Haahr et al. 2015).

Brain glucose uptake

Post-LCD: In one longitudinal study, many correlations (uncorrected for multiple comparisons) were made between BGU using ^{15}O-H_2O PET and YFAS score, hunger ratings, pleasantness of visual, olfactory and gustatory food cues, and dietary recall of oligosaccharide, lipid and cholesterol intake, at either baseline or post-LCD in participants with overweight and either low or high baseline YFAS scores (Guzzardi et al. 2018). However, no predictive correlations were done to examine whether baseline BGU predicted changes in eating behaviour, nor whether changes in BGU correlated with changes in eating behaviour, after the LCD intervention.

Post-RYGB surgery: A cross-sectional study examined correlations between changes in glucose

uptake using ^{18}F-FDG after food intake (fed-fasted) with *ad libitum* energy intake when fasted separately in individual groups: post-RYGB, participants with obesity or normal weight (Hunt et al. 2016). In the normal weight group, the post-prandial change in BGU in the right dlPFC positively correlated with energy intake when fasted, with greater decrease in BGU associated with lower *ad libitum* consumption; while post-prandial changes in BGU in subcallosal gyrus and hypothalamus negatively correlated with energy intake with greater increase in BGU associated with lower *ad libitum* consumption. These positive and negative correlations were also seen in the group post-RYGB surgery, but not the unoperated group with obesity. In both the groups post-RYGB surgery and with unoperated obesity, the post-prandial change in BGU in the right angular gyrus, left parietal lobule, occipital pole and posterior right STG and MTG were also positively correlated with energy intake when fasted. In the group post-RYGB surgery, but not the groups with normal weight or obesity, the post-prandial change in BGU in right medial OFC, posterior cingulate cortex, precuneus and cuneus were positively correlated with energy intake when fasted. However, direct comparison of correlations between the groups was not performed.

Correlations of post-prandial changes in visual analogue scale ratings of fullness and sickness with post-prandial changes in BGU were only reported across all three groups combined, and so the individual effects of RYGB surgery were not assessed (Hunt et al. 2016).

Regional cerebral blood flow

Post-LCD: No cross-sectional correlations were seen between the effect of food intake or tasting of HE food on CBF using ^{15}O-H_2O PET in any fROIs (amygdala, posterior hippocampus, mid insula, PCC) and fed state hunger or fullness ratings in post-LCD, participants with obesity or normal weight groups (Delparigi et al. 2004).

In a combined analysis of participants post-LCD and participants with obesity without intervention, the effects of food intake (fed-fasted) on ^{15}O-H_2O PET in cerebellum and dorsal PFC fROIs were positively correlated, and in OFC negatively correlated (but not putamen, and without correction for multiple comparisons) with TFEQ-dietary restraint, but not disinhibition or hunger-related eating (DelParigi et al. 2007).

3.6.3. Mood assessment

Mood assessment and the association with PET/SPECT findings are summarised in Supplementary

Table S7 and S8.

Correlations of PET/SPECT measures with mood

Opioid system: Burghardt et al. (2015) carried out a study in lean vs. participants with obesity participants. Increment in MOR BP in temporal pole from fasted to fed state negatively correlated with larger decrease in negative affect in lean participants, while no correlation was observed in participants with obesity pre- or post-VLCD.

3.6.4. Mechanistic outcomes

Blood mechanistic measures and the association with PET/SPECT findings are summarised in Supplementary Table S9 and S10

Correlations of changes in PET/SPECT measures with changes in mechanistic outcomes

Dopamine system:

Post-RYGB: The increase in DRD2/3 BP using ^{123}I-IBZM in the striatum aROIs at 3.1 years post-RYGB did not correlate with the decrease in fasting plasma/serum leptin, total ghrelin, insulin, or QUICKI measure of insulin resistance (van der Zwaal et al. 2016).

Post-VLCD: A greater decrease in DRD2/3 BP using ^{18}F-fallypride in the ventral striatum, putamen, caudate, hypothalamus and substantia nigra in aROI analysis was associated with a greater decrease in fasting plasma leptin at 8-10 days post-VLCD, but no correlation was seen with percentage change in fasting insulin, insulin disposition index or plasma acyl ghrelin (Dunn et al. 2017).

Serotonin system:

Post-RYGB: The change in 5-HT_{2A}R BP in neocortex using ^{18}F-altanserin, or SERT BP averaged across caudate, putamen and thalamus aROIs using ^{11}C-DASB, did not correlate with the increase in post-prandial (400 kcal) area under curve (AUC) total GLP-1 at 8 months post-RYGB (Haahr et al. 2015).

Cross-sectional correlations of PET/SPECT measures with mechanistic outcomes

Some cross-sectional studies examined correlations between the effects of food intake on plasma metabolites, insulin and gut hormones, and effects of food intake on rCBF using ^{15}O-H_2O PET across groups (post-VLCD, participants with obesity or normal weight) (DelParigi et al. 2007), or glucose uptake using ^{18}F-FDG across groups (post-RYGB, participants with obesity or normal weight) (Hunt

et al. 2016), but this was not helpful in examining the role for these mechanistic factors on differences in PET measures between intervention groups.

SUPPLEMENTARY REFERENCES

Almby K.E., Lundqvist M.H., Abrahamsson N., Kvernby S., Fahlstrom M., Pereira M.J., Gingnell M., Karlsson F.A., Fanni G., Sundbom M., Wiklund U., Haller S., Lubberink M., Wikstrom J., Eriksson J.W., 2021. Effects of gastric bypass surgery on the brain; simultaneous assessment of glucose uptake, blood flow, neural activity and cognitive function during normo- and hypoglycemia. Diabetes. 70, 1265-1277.

Burghardt P.R., Rothberg A.E., Dykhuis K.E., Burant C.F., Zubieta J.K., 2015. Endogenous Opioid Mechanisms Are Implicated in Obesity and Weight Loss in Humans. J Clin Endocrinol Metab. 100, 3193-3201.

de Weijer B.A., van de Giessen E., Janssen I., Berends F.J., van de Laar A., Ackermans M.T., Fliers E., la Fleur S.E., Booij J., Serlie M.J., 2014. Striatal dopamine receptor binding in morbidly obese women before and after gastric bypass surgery and its relationship with insulin sensitivity. Diabetologia. 57, 1078-1080.

Delparigi A., Chen K., Salbe A.D., Hill J.O., Wing R.R., Reiman E.M., Tataranni P.A., 2004. Persistence of abnormal neural responses to a meal in postobese individuals. Int J Obes Relat Metab Disord. 28, 370-377.

DelParigi A., Chen K., Salbe A.D., Hill J.O., Wing R.R., Reiman E.M., Tataranni P.A., 2007. Successful dieters have increased neural activity in cortical areas involved in the control of behavior. Int J Obes (Lond). 31, 440-448.

Dunn J.P., Abumrad N.N., Kessler R.M., Patterson B.W., Li R., Marks-Shulman P., Tamboli R.A., 2017. Caloric Restriction-Induced Decreases in Dopamine Receptor Availability are Associated with Leptin Concentration. Obesity. 25, 1910-1915.

Dunn J.P., Cowan R.L., Volkow N.D., Feurer I.D., Li R., Williams D.B., Kessler R.M., Abumrad N.N., 2010. Decreased dopamine type 2 receptor availability after bariatric surgery: preliminary findings. Brain Res. 1350, 123-130.

Guzzardi M.A., Garelli S., Agostini A., Filidei E., Fanelli F., Giorgetti A., Mezzullo M., Fucci S., Mazza R., Vicennati V., Iozzo P., Pagotto U., 2018. Food addiction distinguishes an overweight phenotype that can be reversed by low calorie diet. Eur Eat Disord Rev. 26, 657-670.

Haahr M.E., Hansen D.L., Fisher P.M., Svarer C., Stenbaek D.S., Madsen K., Madsen J., Holst J.J., Baare W.F., Hojgaard L., Almdal T., Knudsen G.M., 2015. Central 5-HT neurotransmission modulates weight loss following gastric bypass surgery in obese individuals. J Neurosci. 35, 5884-5889.

Hunt K.F., Dunn J.T., le Roux C.W., Reed L.J., Marsden P.K., Patel A.G., Amiel S.A., 2016. Differences in regional brain responses to food ingestion after Roux-en-Y gastric bypass and the role of gut peptides: a neuroimaging study. Diabetes Care. 39: 1787-1795.

Karlsson H.K., Tuulari J.J., Tuominen L., Hirvonen J., Honka H., Parkkola R., Helin S., Salminen P., Nuutila P., Nummenmaa L., 2016. Weight loss after bariatric surgery normalizes brain opioid receptors in morbid obesity. Mol Psychiatry. 21, 1057-1062.

Karmi A., Iozzo P., Viljanen A., Hirvonen J., Fielding B.A., Virtanen K., Oikonen V., Kemppainen J., Viljanen T., Guiducci L., Haaparanta-Solin M., Nagren K., Solin O., Nuutila P., 2010. Increased brain fatty acid uptake in metabolic syndrome. Diabetes. 59, 2171-2177.

Le D.S., Pannacciulli N., Chen K., Salbe A.D., Del P.A., Hill J.O., Wing R.R., Reiman E.M., Krakoff J., 2007. Less activation in the left dorsolateral prefrontal cortex in the reanalysis of the response to a meal in obese than in lean women and its association with successful weight loss. Am J Clin Nutr. 86, 573-579.

Marques E.L., Halpern A., Corrêa Mancini M., de Melo M.E., Horie N.C., Buchpiguel C.A., Martins Novaes Coutinho A., Ono C.R., Prando S., Santo M.A., Cunha-Neto E., Fuentes D., Cercato C., 2014. Changes in neuropsychological tests and brain metabolism after bariatric surgery. J Clin Endocrinol Metab. 99, E2347-2352.

Rebelos E., Hirvonen J., Bucci M., Pekkarinen L., Nyman M., Hannukainen J.C., Iozzo P., Salminen P., Nummenmaa L., Ferrannini E., Nuutila P., 2020. Brain free fatty acid uptake is elevated in morbid obesity, and is irreversible 6 months after bariatric surgery: A positron emission tomography study. Diabetes Obes Metab. 22, 1074-1082.

Rebelos E., Immonen H., Bucci M., Hannukainen J.C., Nummenmaa L., Honka M.J., Soinio M., Salminen P., Ferrannini E., Iozzo P., Nuutila P., 2019. Brain glucose uptake is associated with endogenous glucose production in obese patients before and after bariatric surgery and predicts metabolic outcome at follow-up. Diabetes Obes Metab. 21, 218-226.

Redies C., Hoffer L.J., Beil C., Marliss E.B., Evans A.C., Lariviere F., Marrett S., Meyer E., Diksic M., Gjedde A., et al., 1989. Generalized decrease in brain glucose metabolism during fasting in humans studied by PET. Am J Physiol. 256, E805-810.

Steele K.E., Prokopowicz G.P., Schweitzer M.A., Magunsuon T.H., Lidor A.O., Kuwabawa H., Kumar A., Brasic J., Wong D.F., 2010. Alterations of central dopamine receptors before and after gastric bypass surgery. Obes Surg. 20, 369-374.

Tuulari J.J., Karlsson H.K., Hirvonen J., Hannukainen J.C., Bucci M., Helmio M., Ovaska J., Soinio M., Salminen P., Savisto N., Nummenmaa L., Nuutila P., 2013. Weight loss after bariatric surgery

reverses insulin-induced increases in brain glucose metabolism of the morbidly obese. Diabetes. 62, 2747-2751.

van der Zwaal E.M., de Weijer B.A., van de Giessen E.M., Janssen I., Berends F.J., van de Laar A., Ackermans M.T., Fliers E., la Fleur S.E., Booij J., Serlie M.J., 2016. Striatal dopamine D2/3 receptor availability increases after long-term bariatric surgery-induced weight loss. Eur Neuropsychopharmacol. 26, 1190-1200.

Versteeg R.I., Schrantee A., Adriaanse S.M., Unmehopa U.A., Booij J., Reneman L., Fliers E., la Fleur S.E., Serlie M.J., 2017. Timing of caloric intake during weight loss differentially affects striatal dopamine transporter and thalamic serotonin transporter binding. FASEB Journal. 31, 4545-4554.

Vettermann F.J., Rullmann M., Becker G.A., Luthardt J., Zientek F., Patt M., Meyer P.M., McLeod A., Brendel M., Blüher M., Stumvoll M., Hilbert A., Ding Y.S., Sabri O., Hesse S., 2018. Noradrenaline transporter availability on [(11)C]MRB PET predicts weight loss success in highly obese adults. Eur J Nucl Med Mol Imaging. 45, 1618-1625.