The impact of gut hormones on the neural circuit of appetite and satiety: A systematic review

Zanchi, Davide; Depoorter, Antoinette; Egloff, Laura; Haller, Sven; Mählmann, Laura; Lang, Undine E; Drewe, Jürgen; Beglinger, Christoph; Schmidt, André; Borgwardt, Stefan

How to cite

ZANCHI, Davide et al. The impact of gut hormones on the neural circuit of appetite and satiety: A systematic review. In: Neuroscience and Biobehavioral Reviews, 2017, vol. 80, p. 457–475. doi: 10.1016/j.neubiorev.2017.06.013

This publication URL: https://archive-ouverte.unige.ch/unige:145429
Publication DOI: 10.1016/j.neubiorev.2017.06.013

Neuroscience and Biobehavioral Reviews 80 (2017) 457–475

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review article

The impact of gut hormones on the neural circuit of appetite and satiety: A systematic review

Davide Zanchi[a], Antoinette Depoorter[b], Laura Egloff[a], Sven Haller[c,d,e,f], Laura Mählmann[a], Undine E. Lang[a], Jürgen Drewe[g], Christoph Beglinger[g], André Schmidt[a,*], Stefan Borgwardt[a,*]

[a] University of Basel, Department of Psychiatry (UPK), CH-4012 Basel, Switzerland
[b] Division of Neuropaediatrics & Developmental Medicine, University Children's Hospital, Basel, Switzerland
[c] Centre de Diagnostic Radiologique de Carouge CDRC, Geneva, Switzerland
[d] Faculty of Medicine of the University of Geneva, Switzerland
[e] Department of Surgical Sciences, Radiology, Uppsala University, Uppsala, Sweden
[f] Department of Neuroradiology, University Hospital Freiburg, Germany
[g] Department of Research, St. Claraspital, Switzerland

ARTICLE INFO

Keywords:
Gut
Brain
Insulin
Ghrelin
Leptin
Glucose
GLP-1
PYY
fMRI

ABSTRACT

The brain–gut-axis is an interdependent system affecting neural functions and controlling our eating behaviour. In recent decades, neuroimaging techniques have facilitated its investigation. We systematically looked into functional and neurochemical brain imaging studies investigating how key molecules such as ghrelin, glucagon-like peptide-1 (GLP-1), peptide tyrosine–tyrosine (PYY), cholecystokinin (CCK), leptin, glucose and insulin influence the function of brain regions regulating appetite and satiety.

Of the 349 studies published before July 2016 identified in the database search, 40 were included (27 on healthy and 13 on obese subjects).

Our systematic review suggests that the plasma level of ghrelin, the gut hormone promoting appetite, is positively correlated with activation in the pre-frontal cortex (PFC), amygdala and insula and negatively correlated with activation in subcortical areas such as the hypothalamus. In contrast, the plasma levels of glucose, insulin, leptin, PYY, GLP-1 affect the same brain regions conversely. Our study integrates previous investigations of the gut-brain matrix during food-intake and homeostatic regulation and may be of use for future meta-analyses of brain-gut interactions.

1. Introduction

The brain–gut axis is an interdependent system that affects neural function and controls our eating behaviour through biochemical signalling between the endocrine and nervous system through hormonal peptides in the gastrointestinal tract (Huda et al., 2006; Steinert et al., 2017; Wren and Bloom, 2007). The two main families of gastrointestinal (GI) hormones are a) Appetite stimulators, such as ghrelin, a 28 amino acid peptide that promotes meal initiation by increasing appetite and hunger feelings (Cummings et al., 2001; Kojima et al., 1999), and b) Satiety stimulators, such as the gut hormones glucagon-like peptide-1 (GLP-1), peptide tyrosine tyrosine (PYY3-36) cleaved from PYY1-36, cholecystokinin (CCK) and leptin that signal the brain to decrease hunger and promote meal cessation (Figlewicz, 2003; Woods et al., 1998). Next to these GI hormones, insulin, a pancreatic hormone, as well as insulin regulated glucose, play a major role in human metabolism and eating behaviour (Figlewicz, 2003; Woods et al., 1998).

Neuroimaging techniques have greatly facilitated the investigation of human brain–gut interactions in recent decades. Pioneering studies (Liu et al., 2000) combining functional magnetic resonance imaging (fMRI) with hormonal blood analyses have demonstrated a direct link between changes in plasma concentrations in hormones and modifications in brain regions that are part of the neural circuit of appetite, as identified by Woods et al. (1998). In particular, increased insulin plasma levels are linked to changes in brain activity in the anterior cingulate cortex (ACC), in the orbitofrontal cortex (OFC), in the sensorimotor cortex and in the hypothalamus. On the other hand, it is well established that ghrelin (Malik et al., 2008) acts through the

Abbreviations: ACC, Anterior Cingulate Cortex; ASL, Arterial Spin Labelling; BOLD, Blood Oxygen Level Dependent; CBF, Cerebral Blood Flow; CNS, Central Nervous System; CSF, Cerebrospinal Fluid; dACC, Dorsal Anterior Cingulate Cortex; fMRI, Functional Magnetic Resonance Imaging; OFC, Orbitofrontal Cortex; OGTT, Oral Glucose Tolerance Test; PET, Positron Emission Tomography; PFC, Pre-frontal cortex; rsfMRI, Resting State fMRI; vmPFC, Ventromedial Prefrontal Cortex; vmPFC, Ventromedial Prefrontal Cortex

* Corresponding authors.
E-mail addresses: andre.schmidt@unibas.ch (A. Schmidt), stefan.borgwardt@upkbs.ch (S. Borgwardt).

http://dx.doi.org/10.1016/j.neubiorev.2017.06.013
Received 11 February 2017; Received in revised form 8 June 2017; Accepted 27 June 2017
Available online 29 June 2017

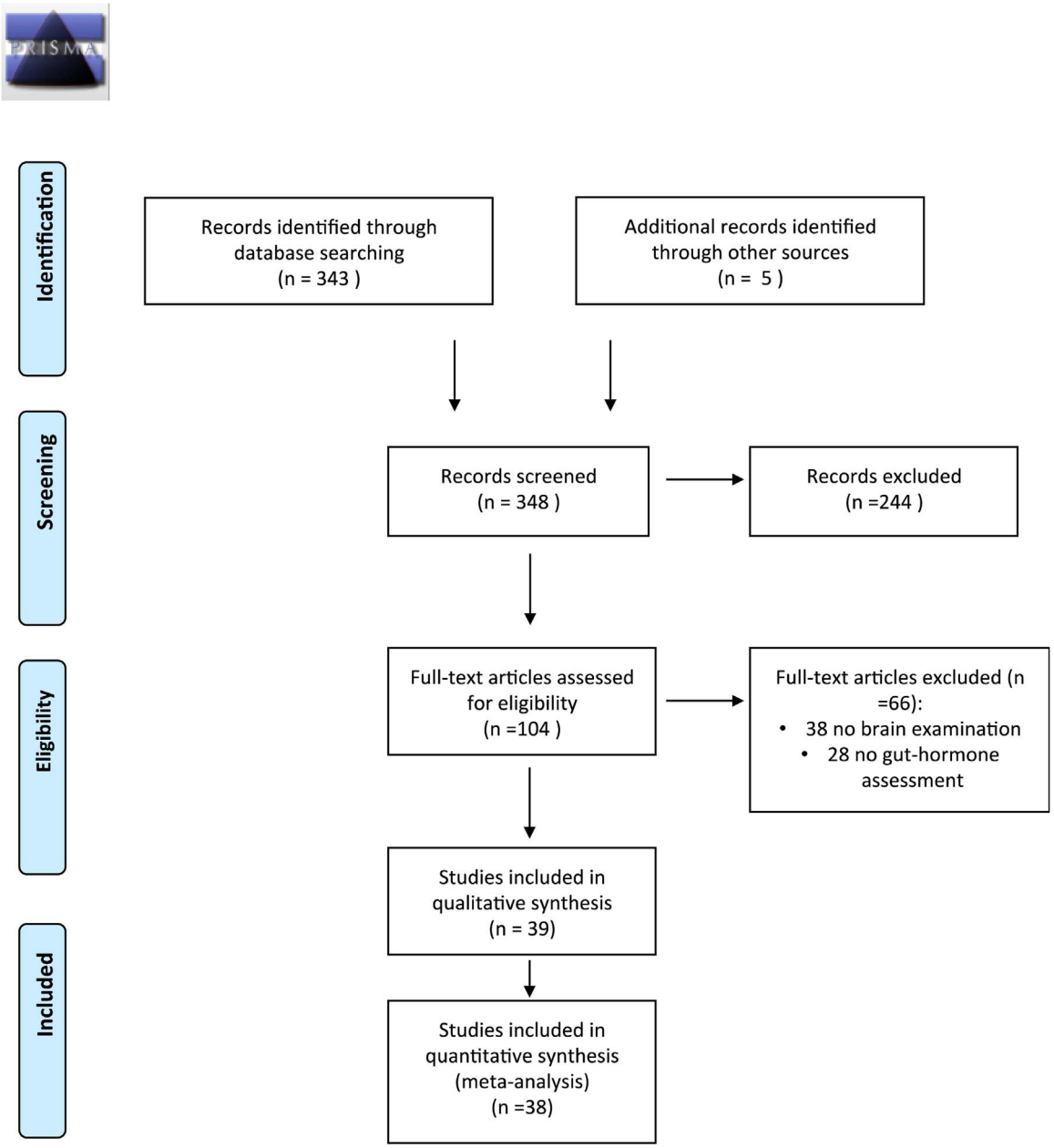

Fig. 1. Flowchart of the selection procedure.

hypothalamus to influence several brain regions involved in the food-reward pathway, including the ventral tegmental area (VTA), nucleus accumbens, amygdala, and hippocampus (Abizaid et al., 2006; Diano et al., 2006; Nakazato et al., 2001). These findings suggest that different gut peptides divergently modulate brain activation in the neural circuit controlling appetite and thereby regulate our prospective eating behaviour.

However, studies often report inconsistent findings making a general interpretation difficult. There are different reasons for the discrepancies: study designs have been variable with different nutrients ingested (stimulating different gut peptides) and different paradigms have been used during fMRI examination.

A general overview of the different studies and of the methodologies used in the field is therefore necessary.

In the present study, we systematically reviewed functional and neurochemical brain imaging studies investigating how the main gut peptides (ghrelin, PYY3-36, leptin, GLP-1 and CCK), insulin and glucose influence activation in brain regions regulating appetite and satiety in healthy and obese subjects. On the basis of the findings of these studies, we hypothesised that the brain areas involved in the food-reward circuit, such as the anterior cingulate cortex (ACC), the insula and the hypothalamus, are activated in opposite directions, by gut peptides linked to satiety or to appetite stimulation.

2. Methods

To ensure high quality reporting, PRISMA guidelines for systematic reviews were followed (Moher et al., 2015).

2.1. Search strategy

An electronic search was performed using the PubMed database. The following search terms were used: ((ghrelin OR glucose OR insulin OR peptide YY OR leptin OR GLP-1 OR cholecystokinin) AND (appetite OR satiety)) AND (mri OR fmri OR pet OR spect OR imaging OR neuroimaging). All studies published before July 2016 were included,

without any language restriction. Additionally, the reference lists of all included studies identified in the database search were manually screened for relevant studies.

2.2. Selection criteria and study selection

The review included original publications in peer reviewed journals, observational or interventional study designs and applications of functional or neurochemical neuroimaging techniques. All the included articles used a randomised double-blinded placebo-controlled design. Based on previous studies and on the existing literature (Huda et al., 2006; Jenkins et al., 1987; Wren and Bloom, 2007), one gut peptide regulating appetite (ghrelin) and four regulating satiety (peptide YY, leptin, GLP-1, CCK), as well as insulin and glucose, were investigated. The current review focuses on how changes in plasma concentration of gut hormones result in modifications of brain functions regulating appetite and satiety.

After inspection for duplicates, the titles and abstracts of all records were reviewed. Publications that clearly did not meet inclusion criteria were excluded. The decision for inclusion or exclusion of the remaining publications was made on the basis of a review of the full texts. The whole process was independently conducted by two reviewers (DZ, SB). In case of disagreement, reviewers discussed their reasons for initial inclusion and exclusion. If consensus was not reached, a third reviewer (AS) was included.

2.3. Recorded variables, data extraction and analysis

The recorded variables for each article included in the review were: authors and year of publication, study design, assessed peptides, administered substance, amount of nutrient received, modality of administration, imaging method, number of healthy subjects, number of obese subjects, gender distribution, age, Body max index (BMI), brain region investigated, analysed brain regions, statistical thresholds and main findings. If overlaps between subjects were suspected but the original publications did not contain information on that topic, we contacted the authors and included the obtained data in the review.

3. Results

3.1. Identified studies

Of 343 publications found in the PubMed database and 6 articles identified in the reference lists, 40 articles were included in this review.

244 publications did not meet the inclusion criteria (e.g. animal models, case reports, review articles, pathological conditions) and were thus excluded. 66 studies were excluded since they investigated appetite without including any brain examination or hormone administration.

A flowchart of the selection procedure, with the included and excluded studies, is shown in Fig. 1.

3.2. Study characteristics

Of the 40 included articles, 17 studies used fMRI with a “food-cue paradigm” (van Bloemendaal et al., 2014; De Silva et al., 2011; Douglas et al., 2015; Goldstone et al., 2014; Grosshans et al., 2012 Heni et al., 2014, 2015, p. 201; Hinkle et al., 2013; Karra et al., 2013; Kroemer et al., 2013a,b, 2015; Leidy et al., 2013; Malik et al., 2008; Page et al., 2011; Rosenbaum et al., 2008; Wallner-Liebmann et al., 2010), eleven an “on-off treatment related block design” (Batterham et al., 2007; Eldeghaidy et al., 2016; Jones et al., 2012; Lassman et al., 2010; Li et al., 2012; Little et al., 2014; Liu et al., 2000; Purnell et al., 2011; Spetter et al., 2014; Sun et al., 2014), five a resting state fMRI (rsfMRI) paradigm (Jastreboff et al., 2016; Page et al., 2013; Wölnerhanssen et al., 2015; Wright et al., 2016; Zhang et al., 2015) and five studies an fMRI-ASL (arterial spin labelling) sequence (two studies used both rsfMRI and ASL) (Jastreboff et al., 2016; Lennerz et al., 2013; Page et al., 2009, 2013; Schilling et al., 2014). Four were neurochemical imaging studies using positron emission tomography (PET) (Gautier et al., 2000; Pannacciulli et al., 2007; Savage et al., 2014; Tataranni et al., 1999).

All included studies were published between 2007 and 2016. 13 studies investigated the effect of the appetite-stimulating hormone ghrelin (Batterham et al., 2007; Goldstone et al., 2014; Jastreboff et al., 2016; Jones et al., 2012; Kroemer et al., 2013a,b, 2015; Leidy et al., 2013; Li et al., 2012; Malik et al., 2008; Savage et al., 2014; Sun et al., 2014, 2015), while 30 studies investigated the impact of satiety-inducing hormones and glucose (Batterham et al., 2007; van Bloemendaal et al., 2014; De Silva et al., 2011; Douglas et al., 2015; Eldeghaidy et al., 2016; Gautier et al., 2000; Grosshans et al., 2012; Heni et al., 2014, 2015; Hinkle et al., 2013; Jastreboff et al., 2016; Kroemer et al., 2013b, 2015; Leidy et al., 2013; Lennerz et al., 2013; Li et al., 2012; Liu et al., 2000; Page et al., 2009, 2011, 2013; Pannacciulli et al., 2007; Purnell et al., 2011; Rosenbaum et al., 2008; Schilling et al., 2014; Spetter et al., 2014; Tataranni et al., 1999; Wallner-Liebmann et al., 2010; Wölnerhanssen et al., 2015; Wright et al., 2016; Zhang et al., 2015). Eight studies focused on glucose (Gautier et al., 2000; Heni et al., 2014; Lennerz et al., 2013; 2009, Page et al., 2011; Purnell et al., 2011; Wallner-Liebmann et al., 2010; Wright et al., 2016), 15 on insulin (van Bloemendaal et al., 2014; Gautier et al., 2000; Heni et al., 2014; Jastreboff et al., 2016; Kroemer et al., 2013a; Lennerz et al., 2013; Li et al., 2012; Liu et al., 2000; Page et al., 2009, 2013; Schilling et al., 2014; Tataranni et al., 1999; Wallner-Liebmann et al., 2010; Wölnerhanssen et al., 2015; Zhang et al., 2015), four on peptide YY (Batterham et al., 2007; De Silva et al., 2011; Douglas et al., 2015; Leidy et al., 2013), five on leptin (Grosshans et al., 2012; Hinkle et al., 2013; Jastreboff et al., 2016; Kroemer et al., 2015; Rosenbaum et al., 2008), five on GLP-1 (van Bloemendaal et al., 2014; Douglas et al., 2015; Heni et al., 2015, p. 2; Li et al., 2012; Pannacciulli et al., 2007) and four on CCK (Eldeghaidy et al., 2016; Lassman et al., 2010; Li et al., 2012; Little et al., 2014).

To assess brain changes associated with these gut peptides, a broad variety of nutrients with extensive differences in protein load were administered. In 16 studies, subjects directly received the target nutrient (such as glucose) (Batterham et al., 2007; De Silva et al., 2011; Eldeghaidy et al., 2016; Heni et al., 2014, 2015; Hinkle et al., 2013; Jones et al., 2012; Kroemer et al., 2013a,b; Little et al., 2014; Malik et al., 2008; Page et al., 2009, 2011, 2013; Rosenbaum et al., 2008; Schilling et al., 2014), while in 24 studies subjects consumed standardised meals (containing for instance: fibres, soy or chocolate milkshake) with different amounts of protein (van Bloemendaal et al., 2014; Douglas et al., 2015; Gautier et al., 2000; Goldstone et al., 2014; Grosshans et al., 2012; Jastreboff et al., 2016; Karra et al., 2013; Kroemer et al., 2015; Lassman et al., 2010; Leidy et al., 2013; Lennerz et al., 2013; Li et al., 2012; Liu et al., 2000; Pannacciulli et al., 2007; Purnell et al., 2011; Savage et al., 2014; Schilling et al., 2014; Spetter et al., 2014; Sun et al., 2014, 2015; Tataranni et al., 1999; Wallner-Liebmann et al., 2010; Wright et al., 2016; Zhang et al., 2015).

As regards the modality of administration, 12 studies used an intravenous canula (Figlewicz, 2003; Goldstone et al., 2014; Grosshans et al., 2012; Heni et al., 2014; Hinkle et al., 2013; Karra et al., 2013; Kojima et al., 1999; Liu et al., 2000; Nakazato et al., 2001; Spetter et al., 2014; Sun et al., 2015), in 22 studies the substances were ingested orally (Douglas et al., 2015; Eldeghaidy et al., 2016; Gautier et al., 2000; Heni et al., 2014, 2015; Jastreboff et al., 2016; Karra et al., 2013; Kroemer et al., 2013a, 2015; Leidy et al., 2013; Lennerz et al., 2013; Li et al., 2012; Little et al., 2014; Liu et al., 2000; Page et al., 2013; Pannacciulli et al., 2007; Schilling et al., 2014; Spetter et al., 2014; Sun et al., 2014, 2015; Tataranni et al., 1999; Wright et al., 2016; Zhang et al., 2015), in three studies a nasogastric tube was used (Lassman et al., 2010; Spetter et al., 2014; Wölnerhanssen et al., 2015), while in

three studies no administration was performed (Grosshans et al., 2012; Savage et al., 2014; Wallner-Liebmann et al., 2010). The time between nutrient administration and brain imaging examination varied as well: in 14 studies, the neuroimaging examination started immediately after nutrient administration (Batterham et al., 2007; van Bloemendaal et al., 2014; Douglas et al., 2015; Gautier et al., 2000; Jastreboff et al., 2016; Jones et al., 2012; Lassman et al., 2010; Li et al., 2012; Malik et al., 2008; Page et al., 2013, 2011; Purnell et al., 2011; Spetter et al., 2014; Zhang et al., 2015), while in the other 20 brain signals were recorded 5–120 min after nutrient administration (De Silva et al., 2011; Eldeghaidy et al., 2016; Gautier et al., 2000; Goldstone et al., 2014; Heni et al., 2014, 2015; Karra et al., 2013; Kroemer et al., 2013a,b; Lennerz et al., 2013; Little et al., 2014; Page et al., 2009; Pannacciulli et al., 2007; Schilling et al., 2014; Sun et al., 2014, 2015; Tataranni et al., 1999; Wölnerhanssen et al., 2015; Wright et al., 2016). Three studies investigated long-term effects by focusing on an administration period between 6 days and 5 weeks (Hinkle et al., 2013; Leidy et al., 2013; Rosenbaum et al., 2008). As stated above, three studies did not administer any treatment (Grosshans et al., 2012; Savage et al., 2014; Wallner-Liebmann et al., 2010).

13 studies included obese participants beside healthy subjects (van Bloemendaal et al., 2014; Gautier et al., 2000; Grosshans et al., 2012; Heni et al., 2014, 2015; Hinkle et al., 2013; Jastreboff et al., 2016; Lennerz et al., 2013; Rosenbaum et al., 2008; Savage et al., 2014; Sun et al., 2015; Wallner-Liebmann et al., 2010; Zhang et al., 2015), while 27 studies focused only on healthy controls(Batterham et al., 2007; De Silva et al., 2011; Douglas et al., 2015; Eldeghaidy et al., 2016; Goldstone et al., 2014; Jones et al., 2012; Karra et al., 2013; Kroemer et al., 2013a,b, 2015; Lassman et al., 2010; Leidy et al., 2013; Li et al., 2012; Little et al., 2014; Liu et al., 2000; Malik et al., 2008; Page et al., 2009, 2011, 2013; Pannacciulli et al., 2007; Purnell et al., 2011; Schilling et al., 2014; Spetter et al., 2014; Sun et al., 2014; Tataranni et al., 1999; Wölnerhanssen et al., 2015; Wright et al., 2016). Details are shown in Table 1.

3.3. Effects of appetite-inducing hormones on the brain: ghrelin

Of the 10 fMRI studies investigating the effects of ghrelin on healthy subjects, four used a food cue paradigm (Table 2). The ‘food cue paradigm’, also called “food-picture paradigm”, refers to a block design in which high/low-energy-dense food pictures were shown in alternation to non-food pictures in a randomised fashion during the fMRI examination.

This approach was used for the first time by Malik et al. (2008) to investigate the effect of ghrelin on brain areas controlling appetite. After placebo (saline) administration, 0.5 mg/kg of ghrelin were injected with a peripheral venous cannula to 21 male healthy participants over a period of 20 min. In a food-cue paradigm, fMRI was performed during both the placebo and ghrelin conditions. Appetite scores were taken regularly during the blood-fMRI examination. Ghrelin increased the neural response to food pictures in different regions of the brain, including the amygdala, orbitofrontal cortex (OFC), anterior insula, and striatum, which are all implicated in encoding the incentive value of food cues. Moreover, the amygdala and OFC responses to ghrelin were positively correlated with subjects’ self-rated hunger ratings. The relationship between enhanced levels of plasma ghrelin and corticolimbic activity is confirmed by a similar study of Goldstone et al. (2014) on 21 healthy participants receiving ghrelin or saline injection, in which increased OFC and hippocampus activity were observed after acute ghrelin administration.

Furthermore, two overlapping fMRI studies of Kroemer et al. (2013a, 2015) using the same study population (26 healthy controls, 13 women) investigated how glucose and nicotine induced changes in ghrelin plasma levels and in brain responses during the presentation of food-related cues. In the first study (Kroemer et al., 2013a), fMRI in a food-cue paradigm was performed after overnight fasting and after a standardised caloric intake (75 g of glucose). Fasting levels of ghrelin correlated positively with food-cue reactivity in the OFC and in the limbic and paralimbic regions, in which ghrelin receptors are densely concentrated. Moreover, fasting ghrelin levels were associated with an increase in subjective appetite.

In the second study (Kroemer et al., 2015), nicotine (2 mg) was administered to fasting subjects and after meal consumption. During fasting, nicotine administration weakened the correlations between ghrelin levels and brain activity in the mesocorticolimbic system (hypothalamus and nucleus accumbens). In contrast, after meal administration, nicotine increased the correlation between ghrelin plasma levels and activity in the ventromedial prefrontal cortex (vmPFC) and in the amygdala. These results confirm that nicotine affects how ghrelin modulates the neural responses of appetite.

Furthermore, five studies used an ‘on-off treatment related block design’ during fMRI examination to investigate the effects of ghrelin on brain areas controlling appetite and satiation. Nutrients are administered during the fMRI examination and the timing of ghrelin plasma absorption is used to investigate the brain response. This approach was used for the first time by Batterham et al. (2007) to investigate the effects of ghrelin on brain activity after placebo and PYY administration (Batterham et al., 2007) on eight healthy males. Ghrelin levels were negatively correlated with activation in the hypothalamus, ventral tegmental areas and brainstem after PYY administration. Furthermore, a negative correlation was shown between activity in these areas and satiety levels. These findings are confirmed by the study of Jones et al. (2012) using the same paradigm, in which an intravenous infusion of ghrelin (1.25 pmol/kg/min) was injected before and after intragastric administration of lipids (dodecanoate, C_{12}) to 20 healthy subjects. During digestion, a decrease in appetite was negatively correlated with activity in the midbrain, thalamus, hypothalamus, insula, amygdala and hippocampus.

Two studies using the same sample size (Sun et al., 2014, 2015) investigated effects of ghrelin on 32 healthy individuals before and after meal ingestion using the same paradigm. During the fMRI examination, two different milkshake flavours (chocolate and strawberry) were administered. Larger post-prandial reductions in ghrelin plasma levels were associated with a reduced response to the chocolate milkshake in brain regions, including the midbrain, amygdala, pallidum, hippocampus, insula and medial OFC. Using the same paradigm, Li et al. (2012) investigated how ingested fat, glucose, protein, and water modulated brain activation in 14 healthy men. In line with previous findings (Sun et al., 2014), activation in the middle insula, amygdala and lateral OFC also correlated with changes in ghrelin levels after fat administration and glucose. Although this study did not demonstrate a direct correlation between cerebral activity and plasma ghrelin levels and appetite, it showed that ghrelin levels decreases after nutrient administration.

Leidy et al. (2013) used fMRI to confirm these results, by exploring brain activation in response to food cues in 20 late adolescent girls who consumed either a normal protein breakfast, a high protein breakfast, or who skipped breakfast continuously for six days. In agreement with previous evidence, ghrelin plasma levels decreased after the high protein breakfast, and reduced activation was observed in the amygdala, hippocampus and para-hippocampus.

Finally one PET study focused on ghrelin and brain-related neurochemical changes (Savage et al., 2014). This study included 8 subjects of normal weight and 19 obese subjects and investigated midbrain dopaminergic neurons (DA type 2/type 3 receptor (D2/D3R)). In healthy individuals, fasting ghrelin correlated negatively with dopaminergic binding potential in the midbrain and nucleus accumbens.

3.4. Effects of glucose and satiety inducing hormones on the brain: glucose, insulin, peptide YY, leptin, GLP-1, and CCK

19 fMRI studies used a food cue paradigm to explore the effect in

Table 1
Study characteristics.

Author and year	Nutrients received	Amount of nutrients received	Administration	Hormones investigated	Neuro-imagingmodality	Paradigm	Time after treatment administration
Batterham et al. (2007)	• PYY • Placebo	PYY was dissolved in 0.9% saline containing 5% by volume Haemaccel (Beacon)	Intravenous	• Ghrelin • Leptin • Insulin • PYY • Glucose	fMRI	On-off treatment related block design	Immediately
De Silva et al. (2011)	• Placebo • Standard breakfast • PYY • GLP-1 • PYY and GLP combined	• A 90 min saline infusion (fasted saline, control visit). • Standard breakfast, then a 90 min saline infusion (the fed saline visit). • A 90 min PYY3-36 infusion at 0.3 pmol/kg/min. • A 90 min GLP-1 7–36 amide infusion at 0.8 pmol/kg/min. • A 90 min combined PYY3-36 and GLP-1 7–36 amide infusion at 0.3 pmol/kg/min and 0.8 pmol/kg/min, respectively.	Intravenous	• PYY • GLP	fMRI	Food-cue	20 min after the start of the infusion
Douglas et al. (2015)	• Fiber–matched (MF) meal • Soy serving size–matched (SS) meal	400-kcal	Orally	• PYY • GLP	fMRI	Food-cue	Immediately
Eldeghaidy et al. (2016)	• High-fat meal • Water load • Fat	520 kcal	Orally	CCK	fMRI	On-off treatment related block design	45 min
Goldstone et al. (2014)	• Saline injection (Fed-Saline): before breakfast • Saline injection (Fasted-Saline): after breakfast • Acyl ghrelin (Fed-Ghrelin): after breakfast	3.6 nmol/kg	Intravenous	• Glucose, • PYY, • GLP-1 • Ghrelin • Insulin	fMRI	Food-cue	95 min.
Grosshans et al. (2012)	/	/	/	Leptin	fMRI	Food-cue	/
Heni et al. (2014)	• Glucose ingestion • Water ingestion	• 75 g glucose • 300 mL water	Orally	• Glucose • Insulin	fMRI	Food-cue	• 30 min • 120 min
Heni et al. (2015)	• Glucose ingestion • Water ingestion	• 75 g glucose • 300 mL water	Orally	• Glucose • Insulin	fMRI	Food-cue	• 30 min • 120 min
Hinkle et al. (2013)	• After a six weeks diet: 1. Leptin 2. Placebo (saline)	The leptin dose = leptin before the diet	Intravenous	Leptin	fMRI	Food-cue	5 weeks
Jastreboff et al. (2016)	• Glucose • Fructose	75 g	Beverage	• Glucose • Fructose • Leptin • Ghrelin	fMRI – ASL	Resting state	Immediately
Jones et al. (2012)	• Post-prandial state: 1. Ghrelin bolus 2. Saline • Fasting state:	• Ghrelin bolus (0.3 nmol/kg) • Ghrelin injection (1.25 pmol/kg/min)	Intravenous	Ghrelin	fMRI	On-off treatment related block design	Immediately

(continued on next page)

Table 1 *(continued)*

Author and year	Nutrients received	Amount of nutrients received	Administration	Hormones investigated	Neuro-imagingmodality	Paradigm	Time after treatment administration
	1. Ghrelin injection 2. C12 + Ghrelin						
Karra et al. (2013)	test meal	1840 kcal	Orally	Ghrelin	fMRI	Food-cue	45 min
Kroemer et al. (2013)	Glucose	75 g	Beverage	Ghrelin	fMRI	Food-cue	5 min.
Kroemer et al. (2013)	Glucose	75 g	Beverage	• Insulin • Glucose	fMRI	Food-cue	5 min.
Kroemer et al. (2015)	• Fasting 1. Placebo 2. Nicotine • Glucose: 1. Placebo 2. Nicotine	2 mg	Beverage	1. Leptin 2. Ghrelin	fMRI	Food-cue	6 min.
Lassman et al. (2010)	• Lipid (dodecanoic acid, 250 mL) • saline (control) • CCK-1 receptor antagonist dexloxiglumide (600 mg orally)	• Lipid (dodecanoic acid, 250 mL) • saline (control) • CCK-1 receptor antagonist dexloxiglumide (600 mg orally)	Intragastric	CCK	fMRI	On-off treatment related block design	Immediately
Leidy et al. (2013)	• 350-kcal NP (13 g protein) cereal-based breakfasts • 350-kcal HP egg- and beef-rich (35 g protein) breakfasts • breakfast skipping	• cereal-based breakfasts: 13 g protein • egg- and beef-rich breakfasts: 35 g protein	Orally	• Ghrelin • Peptide YY (PYY)	fMRI	Food-cue	6 days
Lennerz et al. (2013)	• High glycemic meal • Low glycemic meal	• High glycemic meal 84% of predictive glucose • Low glycemic meal 37% of predictive glucose	Orally	• Glucose • Insulin	fMRI – ASL	/	4 h
Li et al. (2012)	• glucose • soybean oil emulsion • whey protein • water	• glucose: 250 g • soybean oil emulsion: 111 g • whey protein: 257 g • water	Beverage	• Glucose • Insulin • Ghrelin • GLP-1 CCK	fMRI	On-off treatment related block design	Immediately
Little et al. (2014)	• 1 M glucose + predosing with dexloxiglumide (CCK1 receptor antagonist) • 1 M glucose + placebo • 0.9% saline (control) + placebo	• 250 gucose • 250 water • 600 mg of dexloxiglumide	Orally	CCK	fMRI	On-off treatment related block design	1h
Liu et al. (2000)	• D-dextrose • water	75 g	Beverage	Insulin	fMRI	On-off treatment related block design	Immediately
Malik et al. (2008)	• Ghrelin • Placebo	0.5 mg/kg for 20 min.	Intravenous	• Insulin • Glucose	fMRI	Food-cue	Immediately
Page et al. (2011)	• euglycemic-hypoglycemic (insulin) • euglycemic–euglycemic (glucose)	Insulin = 2 mU/kg/min + 20% glucose	Intravenous	• Leptin • Insulin • Ghrelin	fMRI	Food-cue	Immediately
Page et al. (2013)	• Glucose • Fructose	75 g	Beverage	• Glucose • Insulin	fMRI – ASL	Resting state	Immediately

(continued on next page)

Table 1 *(continued)*

Author and year	Nutrients received	Amount of nutrients received	Administration	Hormones investigated	Neuro-imagingmodality	Paradigm	Time after treatment administration
				• Leptin • Ghrelin • Peptide YY • GLP-1			
Page et al. (2009)	• Insuline • Glucose	• Euglycemia (plasma glucose ~95 mg/dl) • Hypoglicemia(plasma glucose ~50 mg/dl)	Intravenous	• Insuline • Glucose	fMRI – ASL	/	• 30 min after the start of the plasma glucose decline toward hypoglycemic levels • 90 min during the euglycemic session
Pannaciulli et al. (2007)	• Fasting state • Satiety state	Ensure-Plus 1.5 kcal/ml (1 Ca = 4.18 J)	Orally	• Glucose • Insulin • GLP-1	PET	/	25 min
Gautier et al. (2000)	• Fasting state • Satiety state	Ensure-Plus 1.5 kcal/ml (1 Ca = 4.18 J)	Orally	• Insulin • Leptin • GLP-1	PET	/	25 min
Purnell et al. (2011)	• Glucose • Fructose • Saline	0.3 mg/kg	Intravenous	• Insuline • Glucose	fMRI	On-off treatment related block design	Immediately
Rosenbaum et al. (2008)	• After a six weeks diet: 1. Leptin 2. Placebo (saline)	The leptin dose = leptin before the diet	Intravenous	Leptin	fMRI	Food-cue	5 weeks
Savage et al. (2014)	/	/	/	Ghrelin	PET	/	/
Schilling et al. (2014)	• Cortisol 1. Insulin 2. Placebo	• Cortisol: 30 mg • Insulin: 100 I.E./ml	• Cortisol: orally • Insulin Nasogastric tube	Insulin	fMRI – ASL	/	30 min
Spetter et al. (2014)	• Water • naso-gastric chocolate milk infusion • oral chocolate milk administration	per 100 mL: energy content of 354 kJ, 3.5 g proteins, 12 g mono and disaccharides, 2.5 fat g, 0.5 g fibres	• Nasogastric tube • Orally	• Insulin • Glucose • Ghrelin	fMRI	On-off treatment related block design	Immediately
Sun et al. (2014)	• Milkshake chocolate • Milkshake strawberry	• Milkshake chocolate • Milkshake strawberry	Orally	• Glucose • Insulin • Ghrelin	fMRI	On-off treatment related block design	30 min
Sun et al. (2015)	• Milkshake chocolate • Milkshake strawberry	• Milkshake chocolate (12 fl oz each of whole milk, Garelick Farms brand Chug Chocolate Milkshake, and Garelick Farms brand Chug Cookies and Cream Milkshake) • Milkshake strawberry (32 fl oz of whole milk to which 6 fl oz of Hershey's brand strawberry syrup was added)	Orally	• Glucose • Insulin • Ghrelin	fMRI	On-off odour (food-non food) block design	65 min
Tataranni et al. (1999)	• Fasting state • Satiety state	Ensure-Plus 1.5 kcal/ml (1 Ca = 4.18 J)	Orally	• Glucose • Insulin • GLP-1	PET	/	25 min
van Bloemendaal et al. (2014)	• GLP-1 receptor agonist exenatide	• Intravenous exendin 9–39 or placebo was	Intravenous	GLP-1	fMRI	Food-cue	Immediately

(continued on next page)

Table 1 *(continued)*

Author and year	Nutrients received	Amount of nutrients received	Administration	Hormones investigated	Neuro-imagingmodality	Paradigm	Time after treatment administration
	• exenatide together with the GLP-1 receptor antagonist exendin 9–39	started 30 min after the start of the clamp at an infusion rate of 600 pmol/kg/min. • Intravenous exenatide or placebo infusion was started 60 min after the start of the clamp at an infusion rate of 50 ng/min for 30 min					
Wallner-Liebmann et al. (2010)	/	/	/	• Insulin • Glucose	fMRI	Food-cue	/
Wölnerhanssen et al. (2015)	• Glucose • Fructose • Placebo	• Glucose 75 g • Fructose 25 g • Placebo 300 m pure tap water	Nasogastric tube	• Glucose • Insulin • GLP-1	fMRI	Resting state	5 min
Wright et al. (2016)	• Fasted night • Standard breakfast (cornflakes, semiskimmed milk, toast, margarine, strawberry jam and orange juice)	• Fasted night • Standardize breakfast (531 kcal for females, 670 kcal for males)	Orally	Glucose	fMRI	Resting state	20 min
Zhang et al. (2015)	• fasted • liquid formula meal	Liquid meal:55% carbohydrate, 30% fat, 15% protein; Ensure-Plus 1.5 kcal/ml	Orally	• Glucose • Insulin	fMRI	Resting state	Immediately

Author and year	Sample size HC			Sample size Obese		
	N(m)	age	BMI (kg/m2)	N(m)	age	BMI
Batterham et al. (2007)	8(8)	29.6 ± 2.1	21.7 ± 0.7	/	/	/
De Silva et al. (2011)	15(10)	29.5	22.1	/	/	/
Douglas et al. (2015)	21(?)	23 ± 1	23.4 ± 0.6	/	/	/
Eldeghaidy et al. (2016)	17/11)	25 ± 2	22.4 ± 0.8	/	/	/
Goldstone et al. (2014)	22(17)	/	18.0–29.9	/	/	/
Grosshans et al. (2012)	23(8)	18–65	18.5–24.0	21(6)	18–65	36.9
Heni et al. (2014)	12(6)	21–29	19.4–22.5	12(6)	21–28	28.8–34.4
Heni et al. (2015)	12(6)	21–30	19.4–22.6	12(6)	21–29	28.8–34.5
Hinkle et al. (2013)	/	/	/	10(2)	38 ± 2	> 30
Jastreboff et al. (2016)	14(10)	15.8 ± 1.6	21.8 ± 2.3	24(11)	15.3 ± 1.8	34.4 ± 4.7
Jones et al. (2012)	20(?)	34.1	25.1			
Karra et al. (2013)	12AA(FTO)	23.0 ± 0.8	22.3 ± 0.5	12TT(FTO)	22.1 ± 1.0	21.6 ± 0.3
Kroemer et al. (2013)	26(13)	24.4 ± 3.4	18.5–24.9			
Kroemer et al. (2013)	26(13)	24.4 ± 3.5	18.5–24.10			
Kroemer et al. (2015)	26(13)	24.4 ± 3.6	18.5–24.11			
Lassman et al. (2010)	19					
Leidy et al. (2013)		19 ± 1	28.6 ± 0.7			
Lennerz et al. (2013)				12(12)	18–35	> 25
Li et al. (2012)	14(14)	21–25	21.2			
Little et al. (2014)						
Liu et al. (2000)	21(11)	34 ± 3				
Malik et al. (2008)	21(21)	24.1 ± 1.1	22.3 ± 0.7			

Table 1 (*continued*)

Author and year	Sample size HC			Sample size Obese		
	N(m)	age	BMI (kg/m2)	N(m)	age	BMI
Page et al. (2011)	21(12)	31.4 ± 7.9	25.2 ± 4			
Page et al. (2013)	20(10)	31 ± 7	22 ± 2.5			
Page et al. (2009)	9(8)	28 ± 5	23.6 ± 2			
Pannacciulli et al. (2007)	42(22)	31 ± 8	31 ± 9			
Gautier et al. (2000)	11(?)	35 ± 8	< 25	11(?)	27 ± 5	< 35
Purnell et al. (2011)	9(3)	29 ± 4.3	22.0 ± 2.2			
Rosenbaum et al. (2008)	/	/	/	6(2)	38 ± 2	> 30
Savage et al. (2014)	8(0)	38 ± 4.3	22	19(0)	/	38
Schilling et al. (2014)	48(48)	23.96 ± 3.4	20 < BMI < 25	/	/	/
Spetter et al. (2014)	16(16)	24.6 ± 3.8	22.3 ± 1.6			
Sun et al. (2014)	32(14)	25.5 ± 5.7	25.3 ± 4.4			
Sun et al. (2015)	20(9)	26 ± 5.9	21.7 ± 1.4	13(7)	28.2 ± 6.6	28.1 ± 2.5
Tataranni et al. (1999)	11(11)	35 ± 8	19 ± 6% body fat			
van Bloemendaal et al. (2014)	16(8)	57.8 ± 1.9	23.2 ± 0.4	16(?)	58.0 ± 2.1	32.6 ± 0.7
Wallner-Liebmann et al. (2010)	12(6)	18.3 ± 3.4	20.9 ± 1.6	12(6)	18.0 ± 3.7	34.1 ± 5.6
Wölnerhanssen et al. (2015)	12(12)	24.8	22.9			
Wright et al. (2016)	19(9)	24.8 ± 3.8	< 30			
Zhang et al. (2015)	20(20)		18.5–23.9	20(20)		> 28

healthy subjects of glucose and satiety hormones on brain activation (Table 3).

Six studies investigated the effects of glucose plasma levels on the brain. In 2011, Page et al. (2011) administered glucose and insulin to induce a hypoglycaemic or euglycemic status in 21 healthy subjects. A food cue paradigm was used to investigate brain responses during these two conditions. Hypoglycaemia preferentially activated limbic-striatal brain regions (such as the insula, putamen, hypothalamus, caudate) in response to food cues to produce greater desire for high calorie food, while euglycemia preferentially activated the medial prefrontal cortex and resulted in less interest in food stimuli.

In the milestone fMRI study of Liu et al. (2000), glucose was administered to 21 healthy volunteers in an 'on-off treatment related block design'. Temporal clustering analysis showed increased activation in the OFC, frontal lobe and decreased activation in the hypothalamus after glucose intake. Moreover, before glucose intake, plasma insulin levels correlated negatively with activity in the hypothalamus.

Woelnerhanssen et al. (2011) used an RS paradigm to explore the effects of acute glucose and fructose administration on the connectivity within the basal ganglia network of 12 healthy participants. They found that after glucose and fructose administration, a glucose-induced increase in rsFC was present in the left caudatus, left putamen, precuneus and lingual gyrus and − relative to placebo − the glucose-induced increase in functional connectivity within the basal ganglia/limbic network correlated positively with glucose-induced insulin release. Wright et al. (2016) confirmed these results by showing that the connectivity between the left hypothalamus and the superior frontal gyrus was negatively correlated with glucose plasma levels during fasting sessions.

In a 2009 study on nine healthy subjects (Page et al., 2009), Page used an fMRI-ASL sequence to show that increases in glucose blood levels lead to regional increases in cerebral blood flow (CBF) in the cerebellum and decreases in the hypothalamus, inferior frontal gyrus, and anterior cingulate cortex. In a study of 2013 (Page et al., 2013) on 20 HC, the author confirmed the previous results. After a drink containing glucose or fructose, regional CBF was reduced within the hypothalamus, thalamus, insula, anterior cingulate, and striatum after glucose or fructose compared to baseline. Moreover, changes in the levels of plasma insulin correlated negatively with changes in regional CBF in the caudate and putamen in response to glucose ingestion.

Seven studies investigated the effects of insulin plasma levels on brain activity.

In a study conducted in 2013 (Kroemer et al., 2013b), Kroemer used the "food cue paradigm" to investigate brain modifications after changes in insulin levels. fMRI was used to investigate reactivity to food cues after overnight fasting and following a standardised caloric intake (i.e., a 75 g oral glucose) in 26 participants. Increased plasma insulin levels correlated negatively with activity in the bilateral fusiform gyrus, superior temporal gyrus, medial frontal gyrus and the limbic system. In addition, activation in these regions was accompanied by lower subjective appetite ratings. In the same line, Wallner-Liebmann et al. (2010) showed that during high caloric food cues, insulin levels are positively associated with hippocampal activity and negatively with activity in the right superior frontal gyrus and left thalamus in 12 healthy adolescents.

Using an 'on-off treatment related block design' in a study on 14 healthy subjects, Li et al. (2012) showed that levels of plasma insulin after glucose administration correlated negatively with activity in the middle insula, thalamus, amygdala and lateral OFC, and – after protein administration – with activity in the caudate. In the same line, in the study of Purnell et al. (2011) on nine healthy individuals, increased activation in the OFC and increases in plasma glucose and insulin levels were observed during glucose infusion. Spetter et al. (2014) demonstrated that insulin responses following naso-gastric infusion of chocolate milk to 16 healthy individuals correlated positively with brain activation in the anterior cingulate cortex (ACC) and putamen and

Table 2
Effects of appetite-inducing hormones on the brain: Ghrelin. Decreased activation: "↓". Increased activation: "↑".

Authors and year of publication	Neuro-imaging modality	Brain region investigated	Type of analysis	Threshold	Results (HC, if not indicated otherwise)
Batterham et al. (2007)	fMRI	Whole brain + ROIs (Hypothalamus, substantia nigra, nucleus accumbens, solitary nucleus and tract, parabrachial nucleus)	GLM	Uncorrected	• Hypothalamus ↓ • VTA ↓ • Brainstem ↓
Goldstone et al. (2014)	fMRI	ROIs (Orbito-frontal cortex, hippocampus, nucleus accumbens, caudate, anterior insula, amygdala)	GLM	FDR at $P < 0.05$	• Ghrelin: orbitofrontal cortex↑, Hippocampus↑
Jastreboff et al. (2016)	fMRI – ASL	Whole brain analyses	GLM	$p < 0.05$, FWE whole-brain corrected	• Main effect: Ghrelin: putamen↑, thalamus↑, insula↑, hypothalamus ↑ • Obese vs. lean: Ghrelin: hypothalamus↑, thalamus↑ , hippocampus ↑
Jones et al. (2012)	fMRI	Whole brain analyses	GLM	$p < 0.05$, FWE whole-brain corrected	• Post-prandial state, ghrelin vs. saline: 1. decrease medulla, midbrain and pons regions of the brainstem↓, cerebellum↓, hypothalamus (upper)↓, insula↓, parahippocampal gyrus (amygdala/ hippocampus), postcentral gyrus, thalamus (ventral anterior nucleus)↓ 2. motor cortex and precentral gyrus↑ • Pre-prandial state, ghrelin vs. saline: 1. decrease medulla, midbrain and pons regions of the brainstem↑, cerebellum↑, hypothalamus (upper) ↑, insula↑, parahippocampal gyrus (amygdala/ hippocampus), postcentral gyrus, thalamus (ventral anterior nucleus) ↑ • Effects of ghrelin on C12-induced BOLD signal: 1. In the midbrain, pons and hypothalamus, ghrelin blocked the increase in BOLD signal in response to C12, and in the insula and amygdala/hippocampus the C12 response was reduced by ghrelin to baseline
Karra et al. (2013)	fMRI	Whole brain analyses	Regression	$p < 0.05$, FWE whole-brain corrected	• Fasted condition: 1. TT group: hypothalamus↑, nucleus accumbens↑ 2. AA group: hypothalamus↓, nucleus accumbens↓ • Fed condition (ghrelin suppression): 1. TT group: fusiform gyrus↑, the postcentral gyrus↑, the cuneus↑, caudate ↓ 2. AA group: fusiform gyrus↓, the postcentral gyrus↓, the cuneus↓, caudate ↑
Kroemer et al. (2013)	fMRI	Whole brain + ROIs (ventral striatum, hypothalamus, midbrain)	• GLM • Correlations	whole brain uncorrected $P < 0.001$/ROIs FWE correction	• Middle occipital/temporal gyrus ↑ • Fusiform gyrus ↑ • Superior/medial frontal gyrus ↑ • Middle occipital/temporal gyrus R ↑ • Inferior frontal gyrus L ↑ • Postcentral g., supramarginal gyrus, rolandic operculum L ↑ • Midbrain (i.e. substantia nigra, red nuclei, mammilary bodies, ventral tegmental area) L ↑ • Subthalamic nucleus R ↑ • Thalamus R ↑ • Hypothalamus R ↑ • Superior occipital gyrus L ↑ • Middle frontal gyrus R ↑ • Pallidum, amygdala L ↑ • Inferior frontal gyrus R ↑ • Inferior temporal g., fusiform gyrus L ↑ • Caudate body R ↑ • Thalamus (anterior nucleus) L ↑ • Middle/superior frontal gyrus L ↑ • Medial/superior frontal gyrus, anterior cingulate ↑
Kroemer et al. (2015)	fMRI	Whole brain + ROIs (ventral striatum, hypothalamus, midbrain)	• GLM • Correlations	whole brain/ROIs uncorrected $P < 0.001$	• Fasting state: 1. Hypothalamus ↑ 2. Nicotine administration impact on ghrelin: 3. nucleus accumbens ↓ 4. amygdala ↓ 5. right hypothalamus ↓ • Fed state: 1. Nucleus accumbens L ↑ 2. Amygdala R ↑ 3. Hypothalamus R ↑ 4. Ventro-medial pre-frontal cortex ↑
Leidy et al. (2013)	fMRI	ROIs	GLM	$p < 0.05$, multiple comparisons corrected	• Amygdala ↓ • Hippocampus ↓

(continued on next page)

Table 2 *(continued)*

Authors and year of publication	Neuro-imaging modality	Brain region investigated	Type of analysis	Threshold	Results (HC, if not indicated otherwise)
Li et al. (2012)	fMRI	ROIs (hypothalamus, insula, thalamus, parahippocampal/hippocampal cortex, caudate, putamen, amygdala, and OFC)	• GLM • Correlations	P < 0.05 corrected with Monte Carlo simulations	• Middle Frontal Gyrus ↓ 1 Soybean oil emulsion: • Middle insula↑ • Amygdala↑ • Latera orbito-frontal cortex↑ 1 Glucose: • Middle insula↑ • Latera orbito-frontal cortex↑ 1 Whey protein: • Amygdala↑
Malik et al. (2008)	fMRI	Whole brain	• GLM • Correlations	p < 001 uncorrected	• Amygdala↑ • Orbitofrontal cortex ↑ • substantia nigra↑ • ventral tegmental area↑ • caudate↑ • hippocampus ↑ • insula↑ • occipital gyrus↑ • left pulvinar ↑ • left fusiform ↑
Savage et al. (2014)	PET	ROIs (substantia nigra)	Correlations	P < 0.05	• HC: ○ Substantia nigra↑ • Obese: • no correlation
Sun et al. (2014)	fMRI	Whole brain + ROIs (insula, hippocampus, amygdala, caudate, putamen, midbrain, pallidum, nucleus accumbens, and hypothalamus)	• GLM • Correlations	p < 0.05 Family Wise Error	• Midbrain↑ • Amygdala↑ • Pallidum↑ • Insula↑ • Hippocampus↑ • Middle orbito-frontal cortex ↑
Sun et al. (2015)	fMRI	Whole brain + ROIs (insula, amygdala)	• GLM • Correlations	p < 0.05 Family Wise Error	• Odor > OL • Higher satiety than hunger • cerebellum ↓

negatively in the insula.

The opposite results were found by Schilling et al. (2014) using fMRI-ASL. Intranasal administration of insulin led to increased CSF in the insular cortex and putamen in 48 male volunteers.

Finally, one study used PET to investigate the effects of insulin plasma changes on brain activity. Tataranni et al. (1999) investigated brain neurochemical changes after satiation (liquid meal intake) or in the fasting state in 11 healthy subjects. Satiation was associated with increased CBF in the ventromedial prefrontal cortex, dorsolateral prefrontal cortex, and inferior parietal lobule. Furthermore, changes in plasma insulin concentrations in response to the meal were negatively correlated with changes in CBF in the insular and OFC.

A recent study of Kromer, as previously discussed (Kroemer et al., 2015), used fMRI to investigate effects of leptin on food-cue reactivity before and after a caloric load (oral glucose tolerance test, OGTT) in 26 healthy normal weight never-smokers. During fasting, nicotine administration increased correlations between leptin levels and activation in the mesocorticolimbic system. After the OGTT, nicotine increased the effects of leptin on food-induced neural activity, positively correlating with activity in the ventromedial prefrontal cortex (vmPFC) and the amygdala. Nicotine therefore enhances the effect of leptin, which might in turn reduce appetite.

Five studies investigated the effects of PYY and GLP-1 plasma levels on the brain.

De Silva et al. (2012), using the “food cue paradigm” during fMRI examination, and demonstrated that PYY and GLP-17-36 administration to 16 healthy subjects reduced appetite and in turn altered brain activity was present in areas as the amygdala, caudate, insula, nucleus accumbens, OFC and putamen. Similar findings were also found in the study of Leidy, as previously described (Leidy et al., 2013), which demonstrated that increased PYY plasma concentrations were negatively correlated with activity in the amygdala, hippocampal and para-hippocampal areas. Douglas et al. (2015) confirmed these results, using the same paradigm, and showed that high protein meal (beef lunch) increased GLP-1 and PYY3-36 plasma levels and in turn reduced activity in the anterior cingulate and insula in 21 healthy subjects. Moreover, GLP-1 levels correlated negatively with activation in the middle insula and lateral OFC after both glucose and protein administration. On the contrary, Batterham et al. (2007), using the ‘on-off treatment related block design’, showed that with high plasma PYY concentrations, mimicking the fed state, there was increased neural activity in the caudolateral OFC (as insula and anterior cingulate cortex).

In a fMRI-ASL on 42 healthy participants, Pannacciulli et al. (2007) showed that, in the postprandial state, there was an increased plasma concentration of GLP-1, which was positively correlated with increased rCBF in the left dorsolateral prefrontal cortex (including the left middle and inferior frontal gyri) and hypothalamus.

Finally, four studies investigated CCK effects at the brain level. A study previously reported by Li et al. (2012) using an ‘on-off treatment related block design’ on 14 healthy subjects, showed that levels of plasma CCK after glucose administration correlated negatively with activity in the caudate and in the thalamus. Moreover, in a work of Eldeghaidy on 17 healthy adults, an fMRI examination was performed assessing how prior consumption of an HFM or water load modulates reward, homeostatic, and taste brain responses to the subsequent delivery of oral fat. Their findings show that an individual’s plasma CCK concentration correlated negatively with brain activation in taste and oral somatosensory areas, insula, amygdala and thalamus. A similar study of Little et al. (2014) administering to 12 healthy subjects an intragastric infusion (250 mL) of 1 M glucose and predosing with dexloxiglumide (CCK receptor antagonist) or 1 M glucose + placebo, or 0.9% saline (control) + placebo, highlighted a CCK1-receptor

Table 3
Effects of satiety inducing hormones and nutrients on the brain: glucose, insulin, peptide YY, leptin and GLP-1. Decreased activation: "↓". Increased activation: "↑".

Authors and year of publication	Neuroimaging modality	Tested hormone	Brain region investigated	Type of analysis	Threshold	Results (HC, if not indicated otherwise)
Batterham et al. (2007)	fMRI	PYY	Whole brain + ROIs (Hypothalamus, substantia nigra, nucleus accumbens, solitary nucleus and tract, parabrachial nucleus)	GLM	$p < 0.05$ cluster-level corrected	• Cerebellum ↑ • Anterior cerebellum ↑ • Cingulate ↑ • Anterior cingulate ↑ • Globus pallidus ↑ • Inferior parietal lobule ↑ • Middle frontal gyrus ↑ • Medial superior frontal gyrus ↑ • Caudolateral orbitofrontal cortex ↑ • Peri-aqueductal grey ↑ • Precentral gyrus ↑ • Substantia nigra ↑ • Ventral tegmental area ↑
De Silva et al. (2011)	fMRI	PYY	ROIs (amygdala, caudate, insula, nucleus accumbens, orbitofrontal cortex and putamen)	GLM	$p < 0.05$ cluster-level corrected	• Insula ↓ • ACC ↓
Douglas et al. (2015)	fMRI	PYY/GLP-1	Whole brain	GLM	$P = 0.01$ cluster-level, $a = 0.05$ corrected	Insula, ACC, but no direct link between the hormones and the studies
Eldeghaidy et al. (2016)	fMRI	CCK	ROIs (amygdala, caudate, insula, nucleus accumbens, orbitofrontal cortex and hypothalamus)	GLM	$p < 0.05$ cluster-level corrected	• Supramarginal gyrus ↑ • Insula ↑ • Amygdala ↑ • Operculum ↑ • Temporal gyrus ↑ • Cerebellum ↑ • Thalamus ↑
Grosshans et al. (2012)	fMRI	Leptin	Whole brain + ROIs (striatum)	Correlations	$P < 0.005$, uncorrected; cluster size ≥ 10 voxels	Ventral striatum ↑
Heni et al. (2014)	fMRI	• Glucose • Insulin	Whole brain	Regressions	$P < 0.05$, corrected for multiple comparisons	• Correlations: 1. Plasma glucose * brain response to high caloric food cues 30 min post load: Hypothalamus↓ 2. Plasma insulin * brain response to high caloric food cues 120 min post load: Inferior frontal gyrus↓, middle frontal gyrus↓, cingulate gyrus↓, Inferior parietal gyrus↓
Heni et al. (2015)	fMRI	GLP-1	Whole brain	Regressions	$P < 0.05$, corrected for multiple comparisons	• Correlations: 1. In lean subjects: Plasma glucose * brain response to glucose 30 min post load: orbitofrontal cortex↓ 2. In lean and obese subjects: Plasma glucose * brain response to high caloric food cues 120 min post load: orbitofrontal cortex↓
Hinkle et al. (2013)	fMRI	Leptin	• Whole brain, seeds: 1. Hypothalamus 2. Nucleus accumbens	PPI	$p < 0.05$ and cluster-level corrections	• Right mid- and posterior insula↑, right central and parietal operculae↑, precunous↑ • Frontal Pole↓, superior frontal gyrus↓, dorsal anterior cingulate cortex↓, superior division of the lateral occipital cortex↓, inferior parietal lobule↓, orbital frontal cortex↓, medial frontal gyrus↓
Jastreboff et al. (2016)	fMRI – ASL	• Insulin • Leptin	Whole brain	• GLM • Correlations	$p < 0.05$ and cluster-level corrections	• Main effect: Insulin: visual regions ↑ Leptin: no effects • Obese vs. lean: Insulin: hypothalamus↑, thalamus↑, hippocampus ↑ Leptin: PFC ↓
Kroemer et al. (2013)	fMRI	Insulin	Whole brain	• GLM • Correlations	whole brain uncorrected $P < 0.001$/ROIs FWE correction	• Cerebellum, parahippocampal gyrus L ↓ • Precentral gyrus ↓ • Middle frontal gyrus L ↓ • Superior temporal gyrus L ↓ • Thalamus↓ • Amygdala↓ Hippocampus↓

(continued on next page)

Table 3 *(continued)*

Authors and year of publication	Neuroimaging modality	Tested hormone	Brain region investigated	Type of analysis	Threshold	Results (HC, if not indicated otherwise)
						• Superior temporal gyrus R ↓ • Cerebellum R ↓ • Precentral gyrus↓ • Middle frontal gyrus ↓ Insula L ↓ • Cingulate cortex, anterior cingulate cortex L ↓ • Fusiform gyrus ↓ • Caudate nucleus body ↓ • Middle temporal gyrus, posterior cingulate ↓ • Precuneus, cuneus ↓ • Inferior/middle frontal gyrus ↓ • Putamen ↓ • Precentral gyrus L ↓ • Superior frontal gyrus L↓ • Parahippocampal gyrus L ↓
Kroemer et al. (2015)	fMRI	Leptin	Whole brain + ROIs (ventral striatum, hipothalamus, midbrain)	• GLM • Correlations	whole brain/ROIs uncorrected P < 0.001	• Fasting state: 1. Nicotine administration impact on leptin: vmPFC↑ Nucleus accumbens↑ Dorsal striatum↑, amygdala↑ Ventral tegmental area↑ Hypothalamus↑ • Fed state: ○ Middle temporal gyrus↓ Thalamus↓ Inferior parietal lobule↓ ○ Midbrain↓ Orbitofrontal cortex↓ Amygdala↓
						• Fasting state: 1. Nicotine administration impact on leptin: vmPFC↑ Nucleus accumbens↑ Dorsal striatum↑, Amygdala↑ Ventral tegmental area↑ Hypothalamus↑ • Fed state: ○ Middle temporal gyrus↓ Thalamus↓ Inferior parietal lobule↓ ○ Midbrain↓ Orbitofrontal cortex↓ Amygdala↓
Lassman et al. (2010)	fMRI	CCK	Whole brain	Correlations	Uncorrected P < 0.005	• Brain stem ↑ • Hypothalamus ↑ • Motor cortex ↑ • Precuneus ↑ • Cingulate gyrus ↑ • Temporal gyrus, middle ↑ • Caudate ↑ • Thalamus ↑
Leidy et al. (2013)	fMRI	PYY	ROIs (hippocampus, insula, amygdala, cingulate, striatum, OFC and PFC)	• GLM • Correlations	ROIs corrected P < 0.01	Amygdala – Hippocampus-Middle – Frontal Gyrus↓
Lennerz et al. (2013)	fMRI	• Glucose • Insulin	Whole brain + ROIs (ventral striatum, hipothalamus, midbrain)	• GLM • Correlations	whole brain/Bonferroni corrected P < 0.002	Nucleus accumbens↑
Li et al. (2012)	fMRI	Insulin • Ghrelin • GLP-1	ROIs (hypothalamus, insula, thalamus, parahippocampal/hippocampal cortex, caudate, putamen, amygdala, and OFC)	• GLM • Correlations	P < 0.05 corrected with Monte Carlo simulations	• glucose: 1. Insuline: Middle insula↓ Thalamus↓ Amygdala↓ 2. Latera orbito-frontal cortex↓ 3. Glucose/CCK: Thalamus↓ 4. GLP-1: Middle insula↓ Latera orbito-frontal cortex↓ • whey protein: 1. Insulin/CCK: Caudate↓ 2. GLP-1: Lateral orbito-frontal cortex↓
Little et al. (2014)	fMRI	CCK	Whole brain	Correlations	False Discovery Rate level (pFDR < 0.05)	Motor cortex↓
Liu et al. (2000)	fMRI	Insulin	Hypothalamus	Temporal clustering analysis		• glucose: 1. Insuline:

(continued on next page)

Table 3 *(continued)*

Authors and year of publication	Neuroimaging modality	Tested hormone	Brain region investigated	Type of analysis	Threshold	Results (HC, if not indicated otherwise)
						• the orbitofrontal cortex ↑ • pre-frontal cortex ↑ • hypothalamus ↓
Page et al. (2011)	fMRI	Glucose	Whole brain	• GLM • Correlations	FWE correction for multiple comparisons	ventromedial-preforntal corex/anterior cingulate cortex↑
Page et al. (2013)	fMRI – ASL	Insulin	Whole brain/hypothalamus	• GLM • Correlations	FWE correction for multiple comparisons	• Glucose: ○ Insula↓ ○ Putamen↓ ○ Anterior cingulate cortex↓ ○ Hypothalamus↓ ○ Caudate↓ • Insulin: • Putamen L↑
Page et al. (2009)	fMRI – ASL	• Glucose • Insulin	Whole brain/hypothalamus	Whole brain analyses	/	• Hypoglicemic vs. euglicemic: ○ Hypothalamus↑ ○ Inferior frontal gyrus L↑ ○ Right anterior cingulate cortex↑ ○ Caudate ↑ ○ Superior temporal gyrus L↑ ○ Pars triangolaris L↑ ○ Viasual association cortex L↑ ○ Cerebellum↓ ○ Medial Frontal Gyrus↓
Pannaciulli et al. (2007)	PET	GLP-1	Whole brain	Correlations	P ≤ 0.001 uncorrected for multiple comparisons	• Hypoglicemic vs. euglicemic: ○ Middle frontal gyrus L↑ ○ Inferior frontal gyrus L↑ ○ Hypothalamus ↑
Gautier et al. (2000)	PET	• Insulin • Glucose	ROIs (from main effect results)	Correlations	P ≤ 0.005 uncorrected for multiple comparisons	• Obese subjects: 1. Insulin: posterior orbitofrontal cortex L ↓ Hippocampus L↓ Precunoeus R↓ Putamen R↓ Thalamus L ↓ • Lean subjects: 1. Insulin: posterior orbitofrontal cortex L ↓ Hippocampus ↓ Precuneus ↑ Putamen ↓ Thalamus L↓ Dorsolateral prefrontal cortex L↑ Dorsolateral prefrontal cortex R↓ 2. Glucose: Anterior prefrontal cortex ↓
Purnell et al. (2011)	fMRI	Glucose	Hypothalamus	GLM – hormone absorption	p < 0.002 uncorrected	Cortical control areas(as the orbitofrontal cortex, pre-frontal cortex)↑
Rosenbaum et al. (2008)	fMRI	Leptin	Whole brain/hypothalamus	GLM	*p* values of 0.005 corrected for multiple comparisons	• Leptin > Placebo: ○ Cingulate gyrus ↑ Hypothalamus ↑ Inferior frontal gyrus ↑ ○ Lingual gyrus ↑ Middle frontal gyrus ↑ Middle temporal gyrus ↑ Postcentral gyrus ↑ Precuneus ↑ Putamen ↑ Thalamus ↑ • Placebo > Leptin ○ Brain stem ↑ Cingulate gyrus ↑ Inferior frontal gyrus ↑ ○ Insula ↑ Lingual gyrus ↑ Middle frontal gyrus ↑ Middle temporal gyrus ↑ Middle occipital gyrus ↑ Precuneus ↑ ○ Superior frontal gyrus ↑ Superior temporal gyrus ↑
Schilling et al. (2014)	fMRI – ASL	Insulin	Whole brain + ROIs (insula, hippocampus, putamen)	GLM	*p* values of 0.05 corrected for multiple comparisons	• Insulin: ○ Insula↑ ○ Putamen↑ ○ Caudate nucleus↑ ○ Inferior frontal gyrus↑
Spetter et al. (2015)	fMRI	Insulin	ROIs (amygdala, insula, inferior frontal gyrus, anterior cingulate cortex, hypothalamus and	Correlations	p < 0.05 FWE-corrected for multiple comparisons	• Insulin: ○ Anterior cingulate cortex↑ Putamen↑ Insula ↓

(continued on next page)

Table 3 *(continued)*

Authors and year of publication	Neuroimaging modality	Tested hormone	Brain region investigated	Type of analysis	Threshold	Results (HC, if not indicated otherwise)
			striatum)			
Tataranni et a. 1999)	PET	Insulin	Whole brain	Correlations	$p \leq 0.001$ uncorrected for multiple comparisons	● Satiation insulin changes ○ Insula L ↓ Orbitofrontal cortex L↓
van Bloemendaal et al. (2014)	fMRI	● GLP-1 ● insulin	ROIs (insula, striatum, amygdala, and OFC)	● GLM ● Correlations	$p < 0.05$ FWE-corrected for multiple comparisons	● GLP-1 Obese: ○ Amygdala↑ ○ Insula↑
Wallner-Liebmann et al. (2010)	fMRI	● Insulin ● Glucose	ROIs (frontal lobe and the limbic system including: amygdala, thamalus hippocampus, nucleus caudatus,putamen, and gyrus cinguli)	● GLM ● Correlations	$p > 0.001$ with a minimum cluster size of 15 voxels	● High caloric food images, insulin: ○ Hippocampus R ↑ Insula L↑ Superior frontal gyrus R ↓ ○ Thalamus L ↓
Wölnerhanssen et al. (2015)	fMRI	Insulin	ROIs (Thalamus)	● Dual regression ● Correlations	$p < 0.05$ uncorrected	● Thalamus ↑
Wright et al. (2016)	fMRI	Glucose	Whole brain	Seed based functional connectivity (insula)	$p < 0.05$ FWE corrected	● Glucose (fed state vs. fasting state): ○ L Insula – Superior frontal gyrus ↓ ○ Middle insula – Posterior cingulate cortex↑
Zhang et al. (2015)	fMRI	Insulin	ROIs (dACC and precuneus)	● Low-frequency fluctuations ● Correlations	$p < 0.05$ Monte Carlo corrected	dACC ↓

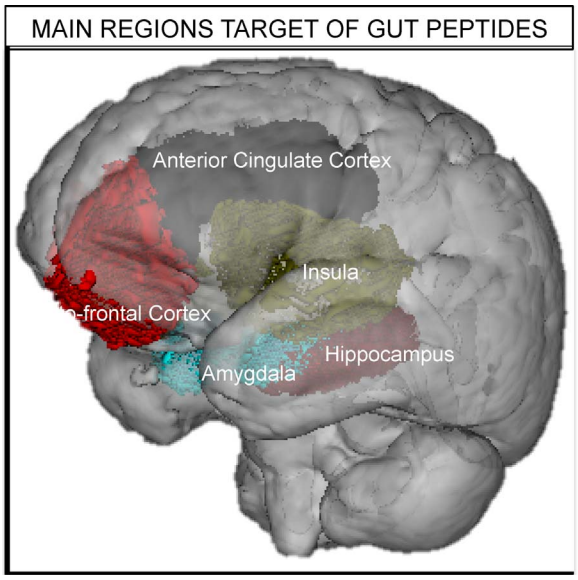

Fig. 2. Main target regions of gut peptides.

dependent increase in Blood oxygenation level dependent (BOLD) signal in the motor cortex. Lastly, a study of Lassman et al. (2010), investigating the brain activation responses to ingested lipid (dodecanoic acid) or saline (control) on 19 healthy subjects with and without prior administration of the CCK receptor antagonist dexloxiglumide, showed significant interaction of dexloxiglumide before treatment on brain stem, hypothalamus, precuneus, cingulate cortex, temporal gyrus and caudate.

The main areas involved in the neural circuit of appetite and target of the gut peptides are shown in Fig. 2.

3.5. *Effects of gut peptides on the brain in patients with obesity*

13 of the included studies focused on the neural effects of gut peptides in obese subjects (van Bloemendaal et al., 2014; Gautier et al., 2000; Grosshans et al., 2012; Heni et al., 2014, 2015; Hinkle et al., 2013; Jastreboff et al., 2016; Lennerz et al., 2013; Rosenbaum et al., 2008; Savage et al., 2014; Sun et al., 2015; Wallner-Liebmann et al., 2010; Zhang et al., 2015). Three studies were conducted to test the effects of ghrelin on brain areas of obese subjects in comparison to lean subjects (Jastreboff et al., 2016; Karra et al., 2013; Savage et al., 2014). Karra et al. (2013) investigated the relation between changes in plasma ghrelin concentrations and obesity, focusing on the obesity-associated gene (FTO). This fMRI study examined how brain responses to food cues differed between 12 carriers of the AA genotype and 12 carriers of the TT allele after consumption of a standard meal. During the fasted state, activation in the hypothalamus, nucleus accumbens, cingulate gyrus and OFC correlated positively with ghrelin levels in the AA group and with greater feelings of hunger. These results show that the FTO gene and ghrelin are key mediators of ingestive behaviour.

Jastreboff et al. (2016) tested how glucose and fructose administration modulated brain perfusion in 14 lean and 24 obese subjects. Obese patients showed high levels of perfusion in the hypothalamus and thalamus that was related to high plasma concentrations of ghrelin, while low levels of perfusion in the prefrontal cortex and anterior cingulate cortex were linked to low plasma levels of ghrelin (Jastreboff et al., 2016; Savage et al., 2014). Furthermore, Savage and colleagues found different brain responses between lean and obese subjects with respect to ghrelin plasma levels (Savage et al., 2014). Using positron emission tomography (PET) imaging, they investigated the expression of DA type 2/t 3 receptors (D2/D3R) in eight subjects with normal weight compared to 19 obese subjects. Ghrelin levels and D2/D3R binding potential (BPND) in the substantia nigra were positively

correlated in normal weight but not in obese participants.

On the other hand, 11 studies investigated differences in brain activation in obese subjects compared to lean subjects in relation to changes in glucose and satiety hormones (van Bloemendaal et al., 2014; Gautier et al., 2000; Grosshans et al., 2012; Heni et al., 2014, 2015; Hinkle et al., 2013; Jastreboff et al., 2016; Karra et al., 2013; Lennerz et al., 2013; Rosenbaum et al., 2008; Zhang et al., 2015). In one study, both ghrelin and insulin were measured (Jastreboff et al., 2016).

Lennerz et al. (2013) focussed on glucose plasma levels and explored resting state connectivity in 12 overweight men after a high glycaemic (high GI) or a low glycaemic meal (low GI). Compared with a low GI meal, a high GI meal decreased plasma glucose, increased hunger and enhanced activation in the nucleus accumbens, striatum and olfactory area.

Heni et al. (2014, 2015) explored the effects of glucose ingestion on brain activity in 12 lean and 12 obese subjects, using a fMRI food-induced paradigm. The hypothalamic response to high caloric food cues correlated negatively with changes in blood glucose levels 30 min after glucose ingestion, while activation in the ACC and OFC correlated negatively with increased plasma insulin levels 120 min after glucose ingestion. These effects can be observed in both the obese and lean groups. In a similar study, Jastreboff et al. (2016), confirmed these results, by showing that obese adolescents exhibited decreased CBF in the PFC, striatum and hypothalamus after drinking glucose. The hippocampus, an area implicated in the processing of high caloric food pictures, was also identified by Wallner-Liebmann et al. (2010)), which found a positive correlation between hippocampus activity and waist circumference.

Insulin-related brain changes were also investigated by Gautier et al. (2000) in a study on 11 lean and 11 obese subjects, that combined PET and fMRI-ASL sequences after fasting or satiation (liquid meal). A converse correlation was found between changes in plasma insulin concentrations and changes in rCBF in the precuneus, orbitofrontal cortex, putamen and thalamus in obese and lean subjects. This study raises the possibility that activation in OFC (involved in the inhibition of inappropriate response tendencies) and limbic/paralimbic areas (associated with the regulation of emotion) during eating may be different in obese and lean men.

As regards leptin, and using fMRI in a food cue paradigm, Grosshans et al. (2012) showed that plasma leptin levels were associated with brain activation in the ventral striatum and with BMI in 21 obese subjects. According to this study, leptin is therefore a satiety hormone linked to increased activation in subcortical regions and to weight gain.

In the same line, and with fMRI in a food-cue paradigm, Rosenbaum et al. (2008) examined how brain responses to food cues were modulated after subcutaneous injection of leptin in six obese subjects following a diet. During weight loss, leptin-related increases in neural activity in response to visual food cues were observed in the brain stem, parahippocampal gyrus, inferior and middle frontal gyri, middle temporal gyrus, and lingual gyrus. Leptin-related decreases were observed in the hypothalamus, cingulate gyrus, and middle frontal gyrus.

A recent study by Hinkle et al. (2013) confirms these results and investigated changes in the connectivity of the right hypothalamus in respect to leptin plasma levels in 10 obese subjects. Using fMRI with a food cue paradigm, the functional connectivity of the right hypothalamus with the mid-insula and the central and parietal operculae increased after leptin injections, while it decreased with the OFC, frontal pole and the dorsal ACC.

Apart from insulin, effects of changes in GLP-1 plasma levels on the brain have also been investigated in obese subjects. van Bloemendaal et al. (2014) explored how the administration of the GLP-1 receptor agonist exenatide modulated brain responses to food pictures during a somatostatin pancreatic-pituitary clamp in 16 obese and 16 normal-weight subjects. Relative to lean subjects, obese subjects showed increased brain responses to food pictures in the insula, amygdala, putamen, and OFC. In the same line, in a second study performed in 2015, Heni et al. (2015) administered 75 g of glucose to promote GLP-1 secretion. Food cue-induced brain activity was assessed with fMRI and GLP-1 concentrations measured before, 30 and 120 min after glucose intake. The significant increase in GLP-1 levels correlated negatively with a change in the food cue-induced brain activity in the OFC in lean and overweight participants. In contrast, postprandial changes in plasma insulin were associated with OFC activations in lean individuals only. Finally, using rsfMRI, Zhang et al. (2015) investigated the amplitude of low frequency fluctuations of spontaneous signals during both hunger and satiety states in 20 lean and 20 obese males. Before food intake, obese men had significantly higher baseline activity in the precuneus and lower activity in the dorsal anterior cingulate cortex (dACC) relative to lean subjects. After food intake, obese males had significantly lower activity in the dorsal anterior cingulate cortex (dACC) than lean males. Moreover a significant positive correlation was found between precuneus activation and hunger ratings before food intake, while dACC activity was negatively correlated with plasma insulin levels before and after food intake in both groups. These results indicated that both precuneus and dACC may play an important role in eating behaviour. While precuneus seemed to mediate subjective satiety, dACC activation rather reflected indirect measures of glucose utilisation.

4. Discussion

To our knowledge, this is the first study to systematically review the effects of different gut peptides on brain activation in healthy and obese subjects. Forty original studies were retrieved, which addressed how key gut hormones or nutrients, such as ghrelin, glucose, insulin, leptin, PYY, GLP-1 and CCK, modulate functional brain activation after food intake. Plasma levels of the appetite-promoting gut hormone ghrelin positively correlate with activity in the PFC, amygdala and insula and negatively correlate with activity in subcortical areas such as the hypothalamus. In contrast, satiety-regulating gut hormones or nutrients like glucose, insulin, letpin, PYY, GLP-1 and CCK affect the same brain regions in the opposite directions. Nevertheless, the lack of reproducible studies and the existence of multiple methodological approaches prevent definitive conclusions and explains some discrepancies in the results between the different studies. The present review is to be considered as the basis for a future meta-analysis of brain-gut interactions.

4.1. Nutrient administration

Individual nutrients were administered to stimulate the plasma release of the investigated hormones. In particular, 22 studies used direct administration of the target substance (i.e. glucose) (Batterham et al., 2007; van Bloemendaal et al., 2014; De Silva et al., 2011; Eldeghaidy et al., 2016; Goldstone et al., 2014; Heni et al., 2014, 2015; Hinkle et al., 2013; Jastreboff et al., 2016; Jones et al., 2012; Kroemer et al., 2013a,b, 2015; Lennerz et al., 2013; Malik et al., 2008 Page et al., 2009, 2011, 2013, p. 200; Purnell et al., 2011; Rosenbaum et al., 2008; Schilling et al., 2014; Wölnerhanssen et al., 2015) and 16 the administration of a nutrient (for instance chocolate milkshake) that subsequently stimulated the production of gut peptides (i.e. ghrelin and PYY) (Douglas et al., 2015; Gautier et al., 2000; Grosshans et al., 2012; Karra et al., 2013; Leidy et al., 2013; Li et al., 2012; Liu et al., 2000; Pannacciulli et al., 2007; Savage et al., 2014; Spetter et al., 2014; Sun et al., 2014, 2015; Tataranni et al., 1999; Wallner-Liebmann et al., 2010; Wright et al., 2016; Zhang et al., 2015). Studies also employed different administration schemes: while in 12 studies the administration was intragastric or intravenous (Batterham et al., 2007; van Bloemendaal et al., 2014; De Silva et al., 2012; Goldstone et al., 2014; Hinkle et al., 2013; Jones et al., 2012; Malik et al., 2008; Page et al., 2009, 2011; Purnell et al., 2011; Rosenbaum et al., 2008; Schilling et al., 2014; Wölnerhanssen et al., 2015), in 24 investigations the

nutrients were ingested orally (Douglas et al., 2015; Eldeghaidy et al., 2016; Gautier et al., 2000; Grosshans et al., 2012; Heni et al., 2014, 2015; Jastreboff et al., 2016; Karra et al., 2013; Kroemer et al., 2013a,b, 2015; Leidy et al., 2013; Lennerz et al., 2013; Li et al., 2012; Liu et al., 2000; Page et al., 2013; Pannacciulli et al., 2007; Savage et al., 2014; Spetter et al., 2014; Sun et al., 2014, 2015; Tataranni et al., 1999; Wallner-Liebmann et al., 2010; Wright et al., 2016; Zhang et al., 2015). Oral intake aimed to mimic the consumption of daily meals, whereas intragastric/intravenous administration aimed to directly assess the effects of the target hormones. The difference in the acquisition procedure leads to two main consequences in the comparison of the studies: a) intragastric/intravenous administration could lead to uncomfortable feelings and therefore influence data acquisition, b) differences in the timing of nutrient absorption leads to differences in the timing of the fMRI examination (immediately after nutrient administration or after 10, 30, 120 min).

4.2. Differences in the paradigm during the fMRI examination

Different paradigms were used during the neuroimaging examination to investigate the effects of gut peptides on brain activation. 16 studies (van Bloemendaal et al., 2014; De Silva et al., 2011; Douglas et al., 2015; Goldstone et al., 2014; Grosshans et al., 2012; Heni et al., 2014, 2015; Hinkle et al., 2013; Karra et al., 2013; Kroemer et al., 2013a,b, 2015; Leidy et al., 2013; Malik et al., 2008; Page et al., 2011; Rosenbaum et al., 2008; Wallner-Liebmann et al., 2010) used a “food-cue paradigm” to investigate effects of gut peptides on feelings of appetite and neural activity during high and low caloric food cues. The “food-cue paradigm” refers to a block design in which high/low energy dense food pictures were shown alternatively to non-food pictures in a randomised fashion during the fMRI examination.

On the other hand, 9 studies (Batterham et al., 2007; Eldeghaidy et al., 2016; Jones et al., 2012; Li et al., 2012; Liu et al., 2000; Purnell et al., 2011; Spetter et al., 2014; Sun et al., 2014, 2015) used an ‘on-off treatment related block design’ to assess the direct effect of the target compound on the brain. Nutrients are administered during the fMRI examination and the timing of hormonal plasma absorption is used to investigate the brain response. The best example is a milestone study by Liu et al. (2000), in which the statistical model to investigate the BOLD signal is based on the increasing insulin plasma levels after glucose administration. The last paradigm used during fMRI examination was that of the classical resting state. At the highest point of plasma hormone absorption, an fMRI sequence is performed; the subjects had to relax and not think about anything in particular. Differences within brain networks involved in appetite and satiety regulation were then investigated.

Although these paradigms are different, the absence of any cognitive tasks makes the results rather comparable. The focus is on brain activity changes associated with variations in hormonal plasma concentrations.

4.3. Neuroimaging results

In line with subjective feelings of appetite, neuroimaging results demonstrate that the two classes of gut hormones have opposite effects on the neural circuit of appetite. In particular, activation in frontocortical regions, such as OFC, ACC and insula correlates positively with ghrelin plasma levels, and with increased hunger feelings. Subcortical areas like the thalamus, hippocampus, striatum and hypothalamus correlated negatively with ghrelin levels. These results have consistently been reported in 8 studies (Batterham et al., 2007; Goldstone et al., 2014; Jones et al., 2012; Kroemer et al., 2013a, 2015; Li et al., 2012; Sun et al., 2014, 2015, p. 2), while 2 studies (Leidy et al., 2013; Savage et al., 2014) found associations in different directions. This discrepancy can perhaps be explained by the use of the food-cue paradigm that could discriminate between high caloric and low caloric food cues and therefore be more specific.

In contrast, plasma levels of satiety-stimulating hormones correlate negatively with the same cortical areas and positively with subcortical areas.

The present findings fit with a model proposed by Woods (Woods et al., 1998), which embeds gut-brain interactions during food-intake within the framework of homeostasis regulation. After food intake, the circulating adipose signals (ghrelin and insulin) penetrate the blood brain barrier and stimulate receptors on neurons in the hypothalamus (Woods et al., 1998). Satiety signals generated by ingested food enter subcortical areas, such as amygdala and striatum, where they influence reflexes related to the acceptance or rejection of food. In a second step, the hypothalamus sends signals to cortical areas, such as the OFC, ACC and insula, as part of the reward mechanism, where cognitive information is integrated with adiposity signals. A higher cognitive evaluation is performed and the prospective eating behaviour is determined. This model of integration between gut peptides, brain responses and subjective feelings explains the opposite direction of the correlations between cortical and subcortical brain activation, subjective satiety and appetite feelings and hormonal plasma levels.

Increased activity of adiposity signals enhances the ability of satiety signals to terminate a meal or of appetite signals to continue eating.

Although this pattern is clear in the majority of the included studies (De Silva et al., 2012; Douglas et al., 2015; Gautier et al., 2000; Grosshans et al., 2012; Heni et al., 2014, 2015; Hinkle et al., 2013; Jastreboff et al., 2016; Kroemer et al., 2013b, 2015; Lennerz et al., 2013; Li et al., 2012; Page et al., 2013; Rosenbaum et al., 2008; Spetter et al., 2014, p. 20; Tataranni et al., 1999; Wright et al., 2016; Zhang et al., 2015), discrepancies across studies may be due to the peculiarity of the different satiety stimulating hormones that have intrinsic properties and therefore affect different brain areas in different ways.

4.4. Differences between a clinical obese and a healthy lean population

Finally, our last result concerns the effects of gut peptides on brain activation in obese subjects. The included studies provide little, if any, evidence for alterations in obese compared to lean subjects. In particular, the results of gut hormones on brain regional activity in the obese population is not reproduced by any study using the same amount of ingested nutrients and the same paradigm. Moreover, it is very hard to compare brain changes in obese and lean subjects due to a lack of statistical comparisons between the two groups within each study.

Moreover, the discrepancies of results can be explained by methodological issues (the different nutrients administered, different peptides investigated and different paradigms used during the fMRI examination) and by the low number of studies performed and the lack of reproducibility of the results. Further investigations on the differential effects of gut peptides on the appetite circuit between obese and lean population are therefore needed.

4.5. Limitations

A first limitation that we want to highlight is that most studies didn’t control for possible pre-existing preferences for the participants for certain type of foods and this can impact the studies results. Moreover, the results might be influenced by psychopathological states, such as mood disturbances, which have not been systematically assessed in the included studies. Also the use of cannabinoids or psychoactive substances was self-reported and consequently not necessarily accurate (Becker et al., 2015). These factors may confound the neuroimaging results.

The amount of nutrients ingested varied in several studies and this hampers comparability. Moreover, the timing of the fMRI examination was very different across studies. It varied from an examination immediately after substance intake to 6 weeks post-administration. Although (as stated above) the timing was in accordance with the aim

of the investigation, it cannot be denied that this may result in a confounding factor and make the studies poorly comparable. Furthermore, in neuroimaging studies addressing brain-gut interactions in healthy subjects, the sample sizes were modest because the design of the study makes recruitment of subjects relatively difficult.

Finally, we suggest that studies including randomised samples that express preferences for specific food have to be conducted. Moreover, psychopathological states, such as mood disturbances in the participants, have to be previously screened in order to avoid confounding factors that can affect the results. Furthermore, studies on eating disorders, such as anorexia and bulimia, can greatly enhance the clinical relevance of studies of the effects of specific nutrients on brain regions regulating appetite. It would also be interesting to investigate cognitive changes (such as working memory performance) after nutrient administration, as shown by pioneering studies (Borgwardt et al., 2012; Schmidt et al., 2014).

Finally, studies using a standardised amount of ingested nutrient should be performed, since the amount of ingested nutrients can also lead to differences in the strength of brain activation

5. Conclusion

The present article systematically reviewed the existing literature investigating how gut peptides influence brain regions regulating appetite and satiety in healthy and obese subjects. The activation of brain areas controlling the brain-gut matrix occurs in opposite directions in respect to satiety or appetite regulation. The present review can enhance our understanding of the physiology of eating behaviour and the pathophysiology of obesity and eating disorders and is the basis for a future meta-analysis in the field.

Funding

No funding.

Acknowledgments

The authors declare no competing interests.

References

Abizaid, A., Liu, Z.-W., Andrews, Z.B., Shanabrough, M., Borok, E., Elsworth, J.D., Roth, R.H., Sleeman, M.W., Picciotto, M.R., Tschöp, M.H., Gao, X.-B., Horvath, T.L., 2006. Ghrelin modulates the activity and synaptic input organization of midbrain dopamine neurons while promoting appetite. J. Clin. Invest. 116, 3229–3239. http://dx.doi.org/10.1172/JCI29867.

Batterham, R.L., ffytche, D.H., Rosenthal, J.M., Zelaya, F.O., Barker, G.J., Withers, D.J., Williams, S.C.R., 2007. PYY modulation of cortical and hypothalamic brain areas predicts feeding behaviour in humans. Nature 450, 106–109. http://dx.doi.org/10.1038/nature06212.

Becker, B., Wagner, D., Koester, P., Tittgemeyer, M., Mercer-Chalmers-Bender, K., Hurlemann, R., Zhang, J., Gouzoulis-Mayfrank, E., Kendrick, K.M., Daumann, J., 2015. Smaller amygdala and medial prefrontal cortex predict escalating stimulant use. Brain 138, 2074–2086. http://dx.doi.org/10.1093/brain/awv113.

Borgwardt, S., Hammann, F., Scheffler, K., Kreuter, M., Drewe, J., Beglinger, C., 2012. Neural effects of green tea extract on dorsolateral prefrontal cortex. Eur. J. Clin. Nutr. 66, 1187–1192. http://dx.doi.org/10.1038/ejcn.2012.105.

Cummings, D.E., Purnell, J.Q., Frayo, R.S., Schmidova, K., Wisse, B.E., Weigle, D.S., 2001. A preprandial rise in plasma ghrelin levels suggests a role in meal initiation in humans. Diabetes 50, 1714–1719.

De Silva, A., Salem, V., Long, C.J., Makwana, A., Newbould, R.D., Rabiner, E.A., Ghatei, M.A., Bloom, S.R., Matthews, P.M., Beaver, J.D., Dhillo, W.S., 2011. The gut hormones PYY3-36 and GLP-17-36 amide reduce food intake and modulate brain activity in appetite centers in humans. Cell Metab. 14, 700–706. http://dx.doi.org/10.1016/j.cmet.2011.09.010.

De Silva, A., Salem, V., Matthews, P.M., Dhillo, W.S., De Silva, A., Salem, V., Matthews, P.M., Dhillo, W.S., 2012. The use of functional MRI to study appetite control in the CNS, the use of functional MRI to study appetite control in the CNS. J. Diabetes Res. J. Diabetes Res. 2012 (2012), e764017. http://dx.doi.org/10.1155/2012/764017.

Diano, S., Farr, S.A., Benoit, S.C., McNay, E.C., da Silva, I., Horvath, B., Gaskin, F.S., Nonaka, N., Jaeger, L.B., Banks, W.A., Morley, J.E., Pinto, S., Sherwin, R.S., Xu, L., Yamada, K.A., Sleeman, M.W., Tschöp, M.H., Horvath, T.L., 2006. Ghrelin controls hippocampal spine synapse density and memory performance. Nat. Neurosci. 9, 381–388. http://dx.doi.org/10.1038/nn1656.

Douglas, S.M., Lasley, T.R., Leidy, H.J., 2015. Consuming beef vs. soy protein has little effect on appetite, satiety, and food intake in healthy adults. J. Nutr.. http://dx.doi.org/10.3945/jn.114.206987. jn206987.

Eldeghaidy, S., Marciani, L., Hort, J., Hollowood, T., Singh, G., Bush, D., Foster, T., Taylor, A.J., Busch, J., Spiller, R.C., Gowland, P.A., Francis, S.T., 2016. Prior consumption of a fat meal in healthy adults modulates the brain's response to fat. J. Nutr.. http://dx.doi.org/10.3945/jn.116.234104. jn234104.

Figlewicz, D.P., 2003. Adiposity signals and food reward: expanding the CNS roles of insulin and leptin. Am. J. Physiol. Regul. Integr. Comp. Physiol. 284, R882–892. http://dx.doi.org/10.1152/ajpregu.00602.2002.

Gautier, J.F., Chen, K., Salbe, A.D., Bandy, D., Pratley, R.E., Heiman, M., Ravussin, E., Reiman, E.M., Tataranni, P.A., 2000. Differential brain responses to satiation in obese and lean men. Diabetes 49, 838–846.

Goldstone, A.P., Prechtl, C.G., Scholtz, S., Miras, A.D., Chhina, N., Durighel, G., Deliran, S.S., Beckmann, C., Ghatei, M.A., Ashby, D.R., Waldman, A.D., Gaylinn, B.D., Thorner, M.O., Frost, G.S., Bloom, S.R., Bell, J.D., 2014. Ghrelin mimics fasting to enhance human hedonic, orbitofrontal cortex, and hippocampal responses to food. Am. J. Clin. Nutr. 99, 1319–1330. http://dx.doi.org/10.3945/ajcn.113.075291.

Grosshans, M., Vollmert, C., Vollstädt-Klein, S., Tost, H., Leber, S., Bach, P., Bühler, M., von der Goltz, C., Mutschler, J., Loeber, S., Hermann, D., Wiedemann, K., Meyer-Lindenberg, A., Kiefer, F., 2012. Association of leptin with food cue-induced activation in human reward pathways. Arch. Gen. Psychiatry 69, 529–537. http://dx.doi.org/10.1001/archgenpsychiatry.2011.1586.

Heni, M., Kullmann, S., Ketterer, C., Guthoff, M., Bayer, M., Staiger, H., Machicao, F., Häring, H.-U., Preissl, H., Veit, R., Fritsche, A., 2014. Differential effect of glucose ingestion on the neural processing of food stimuli in lean and overweight adults. Hum. Brain Mapp. 35, 918–928. http://dx.doi.org/10.1002/hbm.22223.

Heni, M., Kullmann, S., Gallwitz, B., Häring, H.-U., Preissl, H., Fritsche, A., 2015. Dissociation of GLP-1 and insulin association with food processing in the brain: GLP-1 sensitivity despite insulin resistance in obese humans. Mol. Metab. 4, 971–976. http://dx.doi.org/10.1016/j.molmet.2015.09.007.

Hinkle, W., Cordell, M., Leibel, R., Rosenbaum, M., Hirsch, J., 2013. Effects of reduced weight maintenance and leptin repletion on functional connectivity of the hypothalamus in obese humans. PLoS One 8. http://dx.doi.org/10.1371/journal.pone.0059114.

Huda, M.S.B., Wilding, J.P.H., Pinkney, J.H., 2006. Gut peptides and the regulation of appetite. Obes. Rev. Off. J. Int. Assoc. Study Obes. 7, 163–182. http://dx.doi.org/10.1111/j.1467-789X.2006.00245.x.

Jastreboff, A.M., Sinha, R., Arora, J., Giannini, C., Kubat, J., Malik, S., Van Name, M.A., Santoro, N., Savoye, M., Duran, E.J., Pierpont, B., Cline, G., Constable, R.T., Sherwin, R.S., Caprio, S., 2016. Altered brain response to drinking glucose and fructose in obese adolescents. Diabetes. http://dx.doi.org/10.2337/db15-1216.

Jenkins, D.J., Wolever, T.M., Collier, G.R., Ocana, A., Rao, A.V., Buckley, G., Lam, Y., Mayer, A., Thompson, L.U., 1987. Metabolic effects of a low-glycemic-index diet. Am. J. Clin. Nutr. 46, 968–975.

Jones, R.B., McKie, S., Astbury, N., Little, T.J., Tivey, S., Lassman, D.J., McLaughlin, J., Luckman, S., Williams, S.R., Dockray, G.J., Thompson, D.G., 2012. Functional neuroimaging demonstrates that ghrelin inhibits the central nervous system response to ingested lipid. Gut. http://dx.doi.org/10.1136/gutjnl-2011-301323. gutjnl-2011-301323.

Karra, E., O'Daly, O.G., Choudhury, A.I., Yousseif, A., Millership, S., Neary, M.T., Scott, W.R., Chandarana, K., Manning, S., Hess, M.E., Iwakura, H., Akamizu, T., Millet, Q., Gelegen, C., Drew, M.E., Rahman, S., Emmanuel, J.J., Williams, S.C.R., Rüther, U.U., Brüning, J.C., Withers, D.J., Zelaya, F.O., Batterham, R.L., 2013. A link between FTO, ghrelin, and impaired brain food-cue responsivity. J. Clin. Invest. 123, 3539–3551. http://dx.doi.org/10.1172/JCI44403.

Kojima, M., Hosoda, H., Date, Y., Nakazato, M., Matsuo, H., Kangawa, K., 1999. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. Nature 402, 656–660. http://dx.doi.org/10.1038/45230.

Kroemer, N.B., Krebs, L., Kobiella, A., Grimm, O., Pilhatsch, M., Bidlingmaier, M., Zimmermann, U.S., Smolka, M.N., 2013a. Fasting levels of ghrelin covary with the brain response to food pictures. Addict. Biol. 18, 855–862. http://dx.doi.org/10.1111/j.1369-1600.2012.00489.x.

Kroemer, N.B., Krebs, L., Kobiella, A., Grimm, O., Vollstädt-Klein, S., Wolfensteller, U., Kling, R., Bidlingmaier, M., Zimmermann, U.S., Smolka, M.N., 2013b. (Still) longing for food: insulin reactivity modulates response to food pictures. Hum. Brain Mapp. 34, 2367–2380. http://dx.doi.org/10.1002/hbm.22071.

Kroemer, N.B., Wuttig, F., Bidlingmaier, M., Zimmermann, U.S., Smolka, M.N., 2015. Nicotine enhances modulation of food-cue reactivity by leptin and ghrelin in the ventromedial prefrontal cortex. Addict. Biol. 20, 832–844. http://dx.doi.org/10.1111/adb.12167.

Lassman, D.J., McKie, S., Gregory, L.J., Lal, S., D'Amato, M., Steele, I., Varro, A., Dockray, G.J., Williams, S.C.R., Thompson, D.G., 2010. Defining the role of cholecystokinin in the lipid-induced human brain activation matrix. Gastroenterology 138, 1514–1524. http://dx.doi.org/10.1053/j.gastro.2009.12.060.

Leidy, H.J., Ortinau, L.C., Douglas, S.M., Hoertel, H.A., 2013. Beneficial effects of a higher-protein breakfast on the appetitive, hormonal, and neural signals controlling energy intake regulation in overweight/obese, breakfast-skipping, late-adolescent girls. Am. J. Clin. Nutr. 97, 677–688. http://dx.doi.org/10.3945/ajcn.112.053116.

Lennerz, B.S., Alsop, D.C., Holsen, L.M., Stern, E., Rojas, R., Ebbeling, C.B., Goldstein, J.M., Ludwig, D.S., 2013. Effects of dietary glycemic index on brain regions related to reward and craving in men1234. Am. J. Clin. Nutr. 98, 641–647. http://dx.doi.org/10.3945/ajcn.113.064113.

Li, J., An, R., Zhang, Y., Li, X., Wang, S., 2012. Correlations of macronutrient-induced functional magnetic resonance imaging signal changes in human brain and gut

hormone responses. Am. J. Clin. Nutr. 96, 275–282. http://dx.doi.org/10.3945/ajcn.112.037440.
Little, T.J., McKie, S., Jones, R.B., D'Amato, M., Smith, C., Kiss, O., Thompson, D.G., McLaughlin, J.T., 2014. Mapping glucose-mediated gut-to-brain signalling pathways in humans. Neuroimage 96, 1–11. http://dx.doi.org/10.1016/j.neuroimage.2014.03.059.
Liu, Y., Gao, J.H., Liu, H.L., Fox, P.T., 2000. The temporal response of the brain after eating revealed by functional MRI. Nature 405, 1058–1062. http://dx.doi.org/10.1038/35016590.
Malik, S., McGlone, F., Bedrossian, D., Dagher, A., 2008. Ghrelin modulates brain activity in areas that control appetitive behavior. Cell Metab. 7, 400–409. http://dx.doi.org/10.1016/j.cmet.2008.03.007.
Moher, D., Shamseer, L., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., Shekelle, P., Stewart, L.A., PRISMA-P Group, 2015. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst. Rev. 4, 1. http://dx.doi.org/10.1186/2046-4053-4-1.
Nakazato, M., Murakami, N., Date, Y., Kojima, M., Matsuo, H., Kangawa, K., Matsukura, S., 2001. A role for ghrelin in the central regulation of feeding. Nature 409, 194–198. http://dx.doi.org/10.1038/35051587.
Page, K.A., Arora, J., Qiu, M., Relwani, R., Constable, R.T., Sherwin, R.S., 2009. Small decrements in systemic glucose provoke increases in hypothalamic blood flow prior to the release of counterregulatory hormones. Diabetes 58, 448–452. http://dx.doi.org/10.2337/db08-1224.
Page, K.A., Seo, D., Belfort-DeAguiar, R., Lacadie, C., Dzuira, J., Naik, S., Amarnath, S., Constable, R.T., Sherwin, R.S., Sinha, R., 2011. Circulating glucose levels modulate neural control of desire for high-calorie foods in humans. J. Clin. Invest. 121, 4161–4169. http://dx.doi.org/10.1172/JCI57873.
Page, K.A., Chan, O., Arora, J., Belfort-Deaguiar, R., Dzuira, J., Roehmholdt, B., Cline, G.W., Naik, S., Sinha, R., Constable, R.T., Sherwin, R.S., 2013. Effects of fructose vs glucose on regional cerebral blood flow in brain regions involved with appetite and reward pathways. JAMA 309, 63–70. http://dx.doi.org/10.1001/jama.2012.116975.
Pannacciulli, N., Le, D.S.N.T., Salbe, A.D., Chen, K., Reiman, E.M., Tataranni, P.A., Krakoff, J., 2007. Postprandial glucagon-like peptide-1 (GLP-1) response is positively associated with changes in neuronal activity of brain areas implicated in satiety and food intake regulation in humans. Neuroimage 35, 511–517. http://dx.doi.org/10.1016/j.neuroimage.2006.12.035.
Purnell, J.Q., Klopfenstein, B.A., Stevens, A.A., Havel, P.J., Adams, S.H., Dunn, T.N., Krisky, C., Rooney, W.D., 2011. Brain functional magnetic resonance imaging response to glucose and fructose infusions in humans. Diabetes Obes. Metab. 13, 229–234. http://dx.doi.org/10.1111/j.1463-1326.2010.01340.x.
Rosenbaum, M., Sy, M., Pavlovich, K., Leibel, R.L., Hirsch, J., 2008. Leptin reverses weight loss–induced changes in regional neural activity responses to visual food stimuli. J. Clin. Invest. 118, 2583–2591. http://dx.doi.org/10.1172/JCI35055.
Savage, S.W., Zald, D.H., Cowan, R.L., Volkow, N.D., Marks-Shulman, P.A., Kessler, R.M., Abumrad, N.N., Dunn, J.P., 2014. Regulation of novelty seeking by midbrain dopamine D2/D3 signaling and ghrelin is altered in obesity. Obes. Silver Spring Md. 22, 1452–1457. http://dx.doi.org/10.1002/oby.20690.
Schilling, T.M., Ferreira de Sá, D.S., Westerhausen, R., Strelzyk, F., Larra, M.F., Hallschmid, M., Savaskan, E., Oitzl, M.S., Busch, H.-P., Naumann, E., Schächinger, H., 2014. Intranasal insulin increases regional cerebral blood flow in the insular cortex in men independently of cortisol manipulation. Hum. Brain Mapp. 35, 1944–1956. http://dx.doi.org/10.1002/hbm.22304.
Schmidt, A., Hammann, F., Wölnerhanssen, B., Meyer-Gerspach, A.C., Drewe, J., Beglinger, C., Borgwardt, S., 2014. Green tea extract enhances parieto-frontal connectivity during working memory processing. Psychopharmacology (Berl.) 231, 3879–3888. http://dx.doi.org/10.1007/s00213-014-3526-1.
Spetter, M.S., de Graaf, C., Mars, M., Viergever, M.A., Smeets, P.A.M., 2014. The sum of its Parts—Effects of gastric distention, nutrient content and sensory stimulation on brain activation. PLoS One 9. http://dx.doi.org/10.1371/journal.pone.0090872.
Steinert, R.E., Feinle-Bisset, C., Asarian, L., Horowitz, M., Beglinger, C., Geary, N., 2017. Ghrelin, CCK, GLP-1, and PYY(3–36): secretory controls and physiological roles in eating and glycemia in health, obesity, and after RYGB. Physiol. Rev. 97, 411–463. http://dx.doi.org/10.1152/physrev.00031.2014.
Sun, X., Veldhuizen, M.G., Wray, A.E., de Araujo, I.E., Sherwin, R.S., Sinha, R., Small, D.M., 2014. The neural signature of satiation is associated with ghrelin response and triglyceride metabolism. Physiol. Behav. 0, 63–73. http://dx.doi.org/10.1016/j.physbeh.2014.04.017.
Sun, X., Kroemer, N.B., Veldhuizen, M.G., Babbs, A.E., Araujo, I.E., Gitelman, de, Sherwin, D.R., Sinha, R.S., Small, R., 2015. Basolateral amygdala response to food cues in the absence of hunger is associated with weight gain susceptibility. J. Neurosci 35, 7964–7976. http://dx.doi.org/10.1523/jneurosci.3884-14.2015.
Tataranni, P.A., Gautier, J.-F., Chen, K., Uecker, A., Bandy, D., Salbe, A.D., Pratley, R.E., Lawson, M., Reiman, E.M., Ravussin, E., 1999. Neuroanatomical correlates of hunger and satiation in humans using positron emission tomography. Proc. Natl. Acad. Sci. U. S. A. 96, 4569–4574.
van Bloemendaal, L., Izerman, J., Kulve, R.G., ten, J.S., Barkhof, F., Konrad, R.J., Drent, M.L., Veltman, D.J., Diamant, M., 2014. GLP-1 receptor activation modulates appetite- and reward-related brain areas in humans. Diabetes 63, 4186–4196. http://dx.doi.org/10.2337/db14-0849.
Wölnerhanssen, B.K., Meyer-Gerspach, A.C., Schmidt, A., Zimak, N., Peterli, R., Beglinger, C., Borgwardt, S., 2015. Dissociable behavioral, physiological and neural effects of acute glucose and fructose ingestion: a pilot study. PLoS One 10, e0130280. http://dx.doi.org/10.1371/journal.pone.0130280.
Wallner-Liebmann, S., Koschutnig, K., Reishofer, G., Sorantin, E., Blaschitz, B., Kruschitz, R., Unterrainer, H.F., Gasser, R., Freytag, F., Bauer-Denk, C., Schienle, A., Schäfer, A., Mangge, H., 2010. Insulin and hippocampus activation in response to images of high-calorie food in normal weight and obese adolescents. Obes. Silver Spring Md. 18, 1552–1557. http://dx.doi.org/10.1038/oby.2010.26.
Woelnerhanssen, B., Peterli, R., Steinert, R.E., Peters, T., Borbély, Y., Beglinger, C., 2011. Effects of postbariatric surgery weight loss on adipokines and metabolic parameters: comparison of laparoscopic Roux-en-Y gastric bypass and laparoscopic sleeve gastrectomy-a prospective randomized trial. Surg. Obes. Relat. Dis. Off. J. Am. Soc. Bariatr. Surg. 7, 561–568. http://dx.doi.org/10.1016/j.soard.2011.01.044.
Woods, S.C., Seeley, R.J., Porte, D., Schwartz, M.W., 1998. Signals that regulate food intake and energy homeostasis. Science 280, 1378–1383. http://dx.doi.org/10.1126/science.280.5368.1378.
Wren, A.M., Bloom, S.R., 2007. Gut hormones and appetite control. Gastroenterology 132, 2116–2130. http://dx.doi.org/10.1053/j.gastro.2007.03.048.
Wright, H., Li, X., Fallon, N.B., Crookall, R., Giesbrecht, T., Thomas, A., Halford, J.C.G., Harrold, J., Stancak, A., 2016. Differential effects of hunger and satiety on insular cortex and hypothalamic functional connectivity. Eur. J. Neurosci. 43, 1181–1189. http://dx.doi.org/10.1111/ejn.13182.
Zhang, B., Tian, D., Yu, C., Li, M., Zang, Y., Liu, Y., Walter, M., 2015. Altered baseline brain activity differentiates regional mechanisms subserving biological and psychological alterations in obese men. Sci. Rep. 5. http://dx.doi.org/10.1038/srep11563.