



## Conference on ‘Changing dietary behaviour: physiology through to practice’ Symposium 1: Novel imaging and other methodologies for assessing health and behaviour: applications for nutrition

### Imaging methodologies and applications for nutrition research: what can functional MRI offer?‡

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Food intake is influenced by a complex regulatory system involving the integration of a wide variety of sensory inputs across multiple brain areas. Over the past decade, advances in neuroimaging using functional MRI (fMRI) have provided valuable insight into these pathways in the human brain. This review provides an outline of the methodology of fMRI, introducing the widely used blood oxygenation level-dependent contrast for fMRI and direct measures of cerebral blood flow using arterial spin labelling. A review of fMRI studies of the brain’s response to taste, aroma and oral somatosensation, and how fat is sensed and mapped in the brain in relation to the pleasantness of food, and appetite control is given. The influence of phenotype on individual variability in cortical responses is addressed, and an overview of fMRI studies investigating hormonal influences (e.g. peptide YY, cholecystokinin and ghrelin) on appetite-related brain processes provided. Finally, recent developments in MR technology at ultra-high field (7 T) are introduced, highlighting the advances this can provide for fMRI studies to investigate the neural underpinnings in nutrition research. In conclusion, neuroimaging methods provide valuable insight into the mechanisms of flavour perception and appetite behaviour.

**BOLD: Neuroimaging: Satiety: Obesity: Reward: Appetite: Food: Hypothalamus:  
Homeostatic**

Over the past decade, advances in neuroimaging techniques, particularly functional MRI (fMRI), have provided valuable insight into central food-related pathways in the human brain. This review outlines recent advances in fMRI to understand flavour perception and human appetitive behaviour. A brief overview of the method of fMRI and the blood oxygenation level-dependent (BOLD) contrast generally used in fMRI is provided, together with how more direct measures of cerebral blood flow (CBF) can be assessed. fMRI studies of the brain’s response to taste, aroma and flavour perception are outlined. The question of how fat is sensed and mapped in the brain in relation to the pleasantness of food, appetite control and

hormonal influences is addressed. The role of neuroimaging studies to assess eating behaviour in obesity will be outlined. Finally, recent developments in MR technology, and the advances they can provide for future fMRI studies to investigate the neural underpinnings in nutrition research will be described.

#### Principles of functional MRI

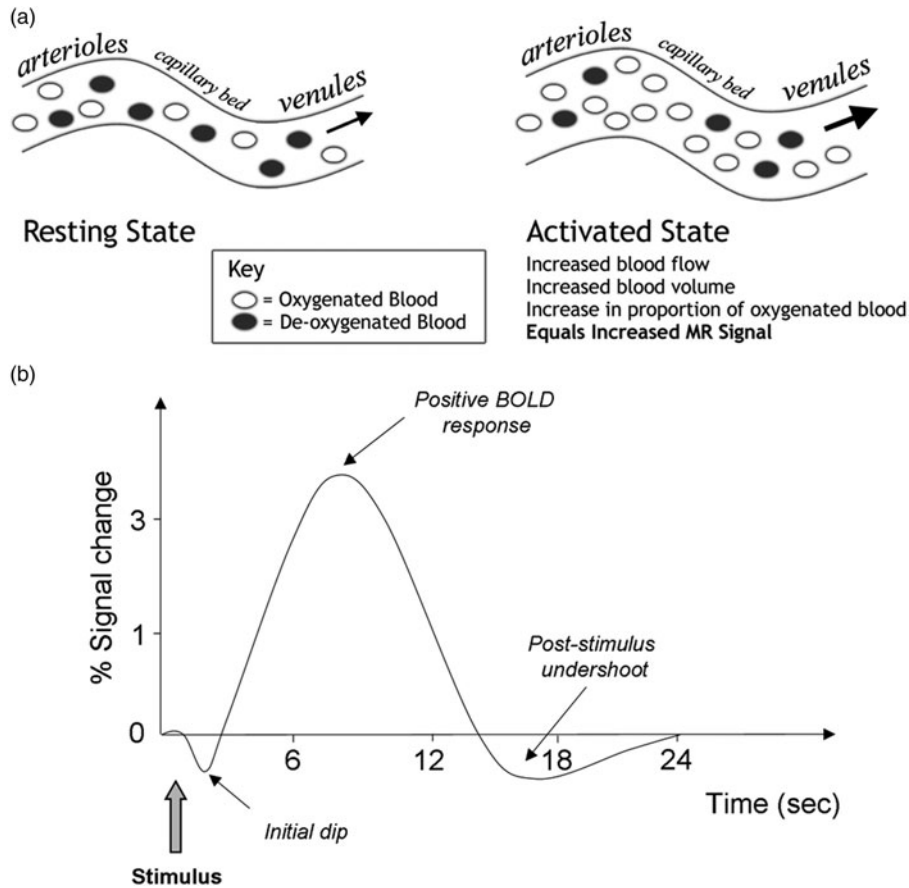
fMRI has revolutionised the research of functional brain mapping and is now the most widely used method for mapping brain activity. fMRI measures brain activity

**Abbreviations:** ACC, anterior cingulate cortex; BOLD, blood oxygenation level-dependent; CBF, cerebral blood flow; CCK, cholecystokinin; fMRI, functional MRI; OFC, orbitofrontal cortex; PROP, 6-*n*-propylthiouracil; PYY, peptide YY; UHF, ultra-high field.

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‡The original version of this article was published with incorrect conference details. A notice detailing this has been published and the error rectified in the online and print PDF and HTML copies.





**Fig. 1.** Schematic representation of (a) the haemodynamic changes which lead to a blood oxygenation level-dependent (BOLD) signal, and (b) the BOLD haemodynamic response function.

indirectly through the haemodynamic changes associated with neural activation, and typically uses the BOLD contrast. BOLD contrast was introduced in the early 1990s<sup>(1)</sup>, and relies on the different magnetic properties of oxygenated and deoxygenated blood, which are diamagnetic and paramagnetic, respectively<sup>(2)</sup>. Paramagnetic deoxyhaemoglobin leads to a local magnetic field distortion within and around vessels, causing the protons to dephase, reducing the  $T_2/T_2^*$  relaxation time and the MR signal compared with oxyhaemoglobin.

On brain activity, neural demand increases leading to an increase in glucose and oxygen consumption with an increase in both CBF and cerebral blood volume to deliver these nutrients. However, the increase in CBF, and hence the supply of oxygenated blood, increases to a level greater than that required by demand (over compensation). This leads to a local increase in blood oxygenation in active brain regions, resulting in a local increase in  $T_2/T_2^*$  relaxation time and thus a small, but detectable, increase in MR image intensity termed the BOLD response<sup>(3)</sup>, Fig. 1. This effect can be observed using  $T_2^*$  or  $T_2$  weighted imaging sequences using gradient-echo or spin-echo schemes, respectively. Although gradient-echo echo planar imaging is most typically used, the change in BOLD MR signal intensity has a characteristic

response, termed the haemodynamic response function, with the increase in MR signal typically delayed by 6 s following stimulus onset and having a 1–5 % signal change at a magnetic field strength of 3 T.

Since BOLD-fMRI is a non-invasive technique, it can be repeatedly used. The spatial resolution is typically 3 ml isotropic, but higher spatial resolution can be achieved at increasing magnetic field strength, such as at an ultra-high field (UHF) of 7 T. The main limitation of the BOLD technique arises from the vascular origin of the signal, which inherently limits its temporal resolution and quantitation<sup>(4,5)</sup>. In addition to developing stronger magnetic fields to enhance the spatial resolution of the BOLD response and brain mapping, measuring the direct change in CBF due to neuronal activation using arterial spin labelling provides absolute quantification of the signal change and hence neuronal activity.

In arterial spin labelling, arterial blood water is magnetically labelled before it reaches the tissue of interest by applying a single radiofrequency pulse<sup>(6,7)</sup> or train of pulses<sup>(8)</sup>. After a period of time (post-label delay), the labelled blood ‘endogenous tracer’ flows into the slice of interest, where it exchanges with tissue water. During this time, an image is taken (called the tag or label image). In this image, the blood water is in a

different magnetisation state from that of the static tissue water. In addition to the label image, a control image is acquired without labelling of inflowing arterial blood. Label and control images are then subtracted to yield a perfusion weighted image that can be quantified in terms of cerebral blood flow in ml/100 g per min<sup>(9)</sup>. Although directly measuring CBF using arterial spin labelling yields a better spatial correlation with the actual site of the active brain region than BOLD, its temporal resolution is lower than BOLD due to the time required to collect both a label and control pair. In addition, the signal-to-noise ratio and contrast-to-noise ratio are inherently lower than BOLD<sup>(10,11)</sup>; however increasing the field strength increases both of these measures due to longer longitudinal relaxation time ( $T_1$ ) at higher magnetic field strength.

### Functional MRI paradigm designs to study nutrition

In fMRI, various designs and approaches are used for studying the mechanism underlying food intake and appetite. One of the most direct methods is the presentation of taste, aroma or flavour stimuli or food images in a block design, where stimuli are presented for a period of time followed by a rest period. In an fMRI study, a set of BOLD images covering the whole brain (a brain volume) is typically collected each 2–3 s during the presentation of stimuli, and to increase the sensitivity to detect active brain areas, hundreds of brain volumes are acquired during many repeats of a stimulus. This leads to an fMRI paradigm typically taking 10–20 min. Signal averaging and statistical processing are required due to the difficulty in detecting the low BOLD signal changes against background physiological noise signal fluctuations<sup>(12)</sup>. However, BOLD sensitivity increases supra-linearly with magnetic strength, one reason for the current demand for UHF MR scanners.

Alternatively, the brains' response to food or food cues can be measured under different physiological conditions, such as the fasted state *v.* fed state, or the presence of exogenously administered or endogenously produced gut hormones. Another approach is to study the resting state signal fluctuations in the brain, where individuals do not perform any tasks during scanning (this is termed resting state fMRI). Subjects are scanned under different physiological conditions and the connectivity between different brain regions is studied. CBF-fMRI studies provide an alternative assessment of the effect of physiological state by measuring the absolute cerebral blood flow at different time points, which can then be compared with a baseline measure of CBF.

### Functional MRI responses to taste, aroma and oral somatosensation

The sensory properties of food and their hedonic effects are important drivers of food intake. The use of fMRI in recent years has improved the understanding of the cortical representation of sensory properties of food in

human subjects. Although taste stimulation has consistently activated the same brain regions across multiple fMRI studies, including insula and overlaying operculum, the transduction mechanisms remain incompletely characterised. Previous studies reported the primary taste cortex is located within the anterior insula/frontal operculum<sup>(13–15)</sup> with secondary projections to the orbitofrontal cortex (OFC)<sup>(16)</sup>, amygdala<sup>(17)</sup>, anterior cingulate cortex (ACC)<sup>(18)</sup>, ventral striatum<sup>(19)</sup> and dorsolateral prefrontal cortex<sup>(20)</sup>. O'Doherty *et al.* were the first to investigate the cortical response to pleasant (glucose) and aversive (salt) taste stimuli by assessing stimuli against a tasteless control stimulus<sup>(21)</sup>. In individual subject analysis, the OFC showed separate areas to be activated in response to these two tastes. Small *et al.* also highlighted activations in the OFC to sweet and aversive taste, and investigated the neural response to taste intensity when valence was held constant, showing activation of the amygdala and mid-insula<sup>(18)</sup>. Furthermore, the amygdala responded to both sweet and aversive taste (when intensity was held constant), with preferential activation to sweet taste, providing evidence that the amygdala is not solely involved in processing aversive taste. Other activations including ACC have been reported in many fMRI studies<sup>(16,18,21,22)</sup>, while the rolandic operculum of the parietal cortex has been identified as a part of the primary gustatory cortex<sup>(23,24)</sup>. A recent meta-analysis confirmed widespread activation of the insula and operculum in response to taste stimuli, diverging from posterior to the most anterior junction of insula and operculum, in addition to activation in medial OFC, pregenual ACC and mediodorsal thalamus<sup>(15)</sup>.

In response to aroma stimuli, fMRI studies report robust activation in higher-order olfactory areas, including the OFC, insula and ACC<sup>(16,25,26)</sup>. In contrast, the primary olfactory cortex has shown no<sup>(27,28)</sup> or inconsistent activations in some studies<sup>(25,29)</sup>. This may be due to its small structure, susceptibility artefacts in this region or habituation effects<sup>(30)</sup>.

Oral somatosensation plays a crucial role in many aspects of flavour perception. fMRI studies have revealed brain regions involved in tactile components such as astringency<sup>(31)</sup>, burn<sup>(32)</sup> and temperature<sup>(33)</sup>. Textural properties of food are known to correlate with fat content, and fat may also act as a chemical stimulus, with NEFA stimulating taste receptor cells for the detection of fat<sup>(34,35)</sup>. Very few studies have investigated the cortical representation to oral viscosity and oral fat in the mouth. de Araujo and Rolls<sup>(36)</sup> and De Celis Alonso *et al.*<sup>(37)</sup> investigated the representation of oral viscosity (carboxymethyl cellulose) and manugel alginate gel, respectively. Both studies showed activation in the mid- and anterior insula, with the mid-insula representing the somatosensory properties of the oral activity (texture), other areas, including post-central gyrus and rolandic/parietal operculum were also reported<sup>(37)</sup>. In addition, the sensory and hedonic aspects of oral fat have been investigated in a number of studies using BOLD and CBF measures. Human responses to oral fat have been found to activate taste, texture and reward areas<sup>(36,38–40)</sup>. Responses to oral fat in the form of pure

fat have been found in the ACC extending to the OFC and hypothalamus, with the rostral ACC and medial OFC being activated independent of viscosity, leading to the suggestion that it is these areas that process the hedonic properties of fat<sup>(36)</sup>. Moreover, the subjective rating of texture and flavour pleasantness of oral fat was found to correlate with activity in the mid-OFC and ACC, areas thought to represent flavour pleasantness<sup>(39)</sup>. This study also suggested that the pregenual cingulate cortex is activated by converging flavour and fat signals, hence representing overall pleasantness. Further investigations on the effect of fat content on the cortical response show a positive correlation with increasing fat level/concentration in taste, texture and reward areas<sup>(38–40)</sup>. Most recently, the somatosensory cortex has been shown to be involved in the processing of oral flavoured fat through functional coupling with the OFC, for a high-fat pleasant sample compared with a low-fat food with the same flavour. It has been suggested that this may reflect the role of somatosensory cortex in the processing of pleasant-flavoured oral fat<sup>(41)</sup>. Understanding the cortical encoding of the perceived response to fat is important in relation to the pleasantness of food and appetite control, and it provides additional and valuable information to the food industry in order to improve the design of products that are lower in fat but still rewarding to eat, and hence decrease the risk of obesity and associated complications.

Flavour perception of foods or beverages is a complex multimodal process, engaging taste, olfaction and texture modalities, and does not result from the simple addition of these stimuli<sup>(14)</sup>. Despite taste, aroma and oral somatosensation systems being anatomically dissociated at the peripheral level, they are highly integrated at the cortical level, and the exact mechanisms that lead to flavour perception are still not well understood. Small<sup>(42)</sup> has suggested a model for flavour perception, which postulates that the oral somatomotor areas play the principal role in binding the taste, olfactory and associated tactile sensations into the unitary flavour percept. fMRI provides a great tool to understand the cortical association and integration between the different modalities. Evidence from recent fMRI studies show overlapping brain responses to taste and aroma in areas including anterior insula, ACC, OFC and amygdala<sup>(43–47)</sup>. Verhagen and Engelen performed a meta-analysis, which suggested the anterior insula to be a multi-modal area activated by both taste and aroma stimuli<sup>(48)</sup>. However, the mechanism of interaction is poorly understood. In addition, the cortical representation to oral somatosensation and taste was shown to overlap in the insula and operculum<sup>(31–33)</sup>. Although fMRI provides a powerful method in revealing the cortical response to flavour perception, much is still to be discovered in flavour perception.

### Phenotype and its modulation of functional MRI responses

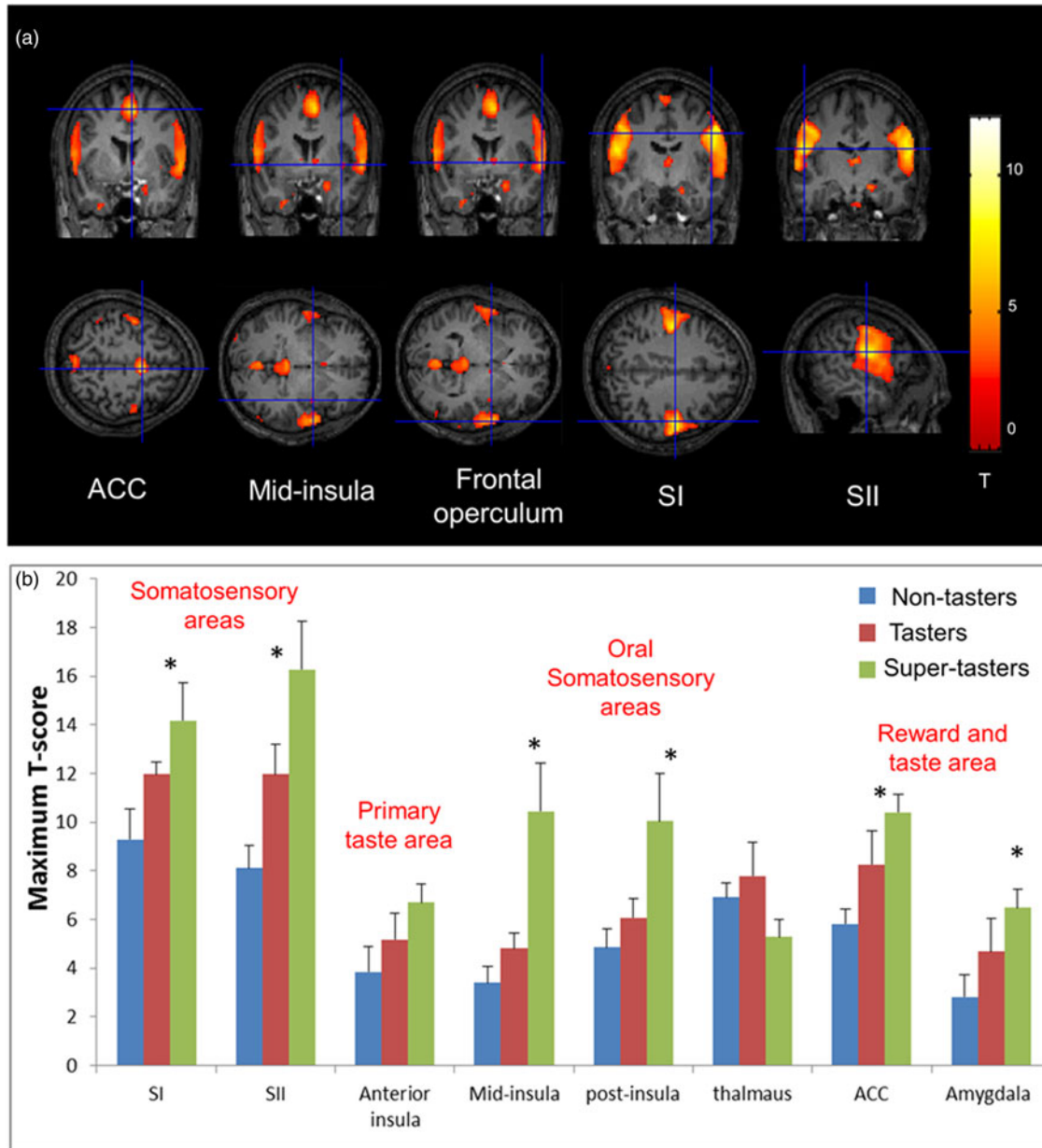
The perception of taste is known to vary widely across individuals. There are many factors that contribute to

an individual's taste perception and subsequent food preferences and energy intake, including the density of taste papillae on the tongue and genetic differences in taste receptors<sup>(49)</sup>. The most well-researched taste phenotyping is the perception of the bitterness taste. In behavioural studies, this can be assessed by measuring a subjects' sensitivity to a bitter chemical called 6-*n*-propylthiouracil (PROP). Subjects are asked to taste a filter paper soaked in super saturated PROP solution and rate for bitterness intensity on a Generalised Labelled Magnitude Scale<sup>(50)</sup>. Non-tasters cannot taste the bitterness of PROP (about 25 % of the population), medium tasters (about 50 %) sense the bitterness while accepting it and super-tasters (about 25 %) find the taste of PROP unacceptable. Tasters (medium- and super-tasters) are more sensitive than non-tasters to the bitterness of caffeine, and to the sweetness of sucrose<sup>(51)</sup>, some artificial sweeteners<sup>(49)</sup> and salt taste<sup>(52)</sup>. Moreover, some studies have also shown that PROP tasters are also more sensitive to fat<sup>(53)</sup>, oral irritation<sup>(54)</sup> and oral temperature<sup>(55)</sup>. Variability in PROP taster status is, in part, explained by the TAS2R receptor gene family<sup>(56)</sup>. Previous research showed that the density of fungiform papillae is significantly higher in PROP super-tasters<sup>(56,57)</sup> suggesting that this could be the source of increased sensitivity to taste stimuli and oral sensitivity. Essick *et al.* showed a strong correlation between PROP tasters and oral somatosensation<sup>(58)</sup>, with supertasters having improved lingual tactile spatial acuity (to embossed letters) compared with medium tasters or non-tasters.

Recently, a new taste phenotype known as thermal taster status has been described<sup>(59)</sup>. Thermal stimulation of small areas of the tongue was found to elicit a 'phantom' taste in some individuals. Thermal sourness and/or saltiness can be perceived by cooling the tongue, whereas re-warming the tongue from an initial cooling period can evoke a sweetness taste. In addition, thermal tasters were found to be more sensitive than thermal non-tasters to taste and olfactory stimuli<sup>(60)</sup>, and oral stimulation including temperature<sup>(61)</sup>. The mechanism underlying this is still under investigation, and appears to not be associated with fungiform papillae density, as no correlation has been found previously. Fungiform papillae are surrounded and sometimes innervated by the trigeminal nerve, which carries information from the tongue related to chemical and physical properties of foods, and this may lead to a correlation between PROP tasters and thermal tasters. Recent studies also show there is a relationship between the trigeminal system and PROP taster status<sup>(61)</sup>.

Very few studies have investigated the impact of taste phenotype on the primary gustatory cortex and oral somatosensory areas. Eldeghaidy *et al.* showed that the cortical response to oral fat in PROP tasters was highly correlated in key taste, texture, and reward processing areas, with a significant increase in BOLD response with PROP taster status (super-taster>taster>non-taster)<sup>(38)</sup>, Fig. 2. More recently, Clark *et al.*, showed that the cortical response to taste and carbonation in thermal tasters was significantly higher in several cortical areas involved in flavour processing compared with



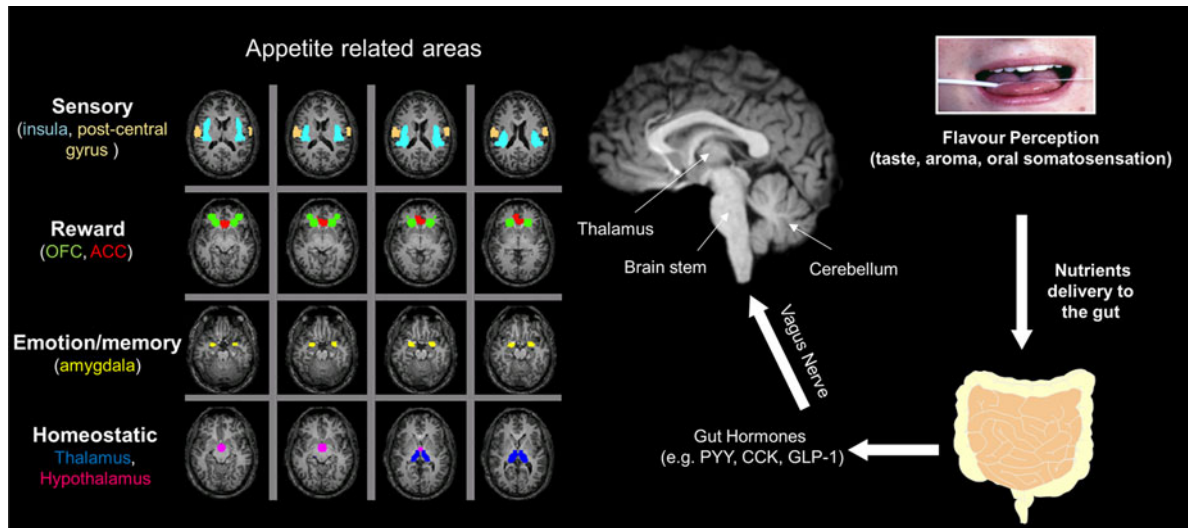


**Fig. 2.** (colour online) Cortical response to oral fat. (a) Blood oxygenation level-dependent response to oral fat delivery, shown with false discovery rate (FDR) corrected at  $P < 0.05$ , overlaid on a  $T_1$ -weighted image. (b) Region of interest analysis of the  $T$ -scores showing a significant increase in the oral somatosensory (SI, SII and mid-insula) and reward area (amygdala) in 6-*n*-propylthiouracil supertasters<sup>(38)</sup>. ACC, anterior cingulate cortex.

thermal non-tasters<sup>(62)</sup>. Furthermore, the variation in genotype, such as the  $\alpha$ -synuclein gene and TaqIA A1, has also been shown to be associated with the BOLD response to taste stimuli in the OFC and striatum<sup>(63,64)</sup> and regions known to be rich in dopaminergic axon terminals, including ACC, amygdala, thalamus and putamen<sup>(65)</sup>. These results highlight new information about the cortical features of different phenotypes, and emphasise the importance of phenotyping participants for fMRI taste studies to increase the statistical power of group analysis.

### Effect of hunger and satiety on functional MRI response

A number of fMRI studies have investigated the cortical modulation to satiation. Most studies show increased activation in insula, amygdala, OFC parahippocampal cortex, thalamus, hypothalamus, ACC and caudate in a hunger/fasting state, compared with increased activation in prefrontal cortex and inferior parietal lobe in a satiated/fed state (areas that show decreased activation in fasting/hunger areas). Viewing food images when hungry modulates the response in appetite-related brain



**Fig. 3.** (colour online) A simplified illustration of the gut–brain axis and appetite and homeostatic brain areas modulated by food intake. OFC, the orbitofrontal cortex; ACC, anterior cingulate cortex; PYY, peptide YY, GLP-1, glucagon-like peptide 1; CCK, chole cystokinin.

regions, including the amygdala, parahippocampal gyrus and lateral OFC, compared with the fed state<sup>(66–69)</sup>. In addition, manipulating food motivation by varying energy content of food images is associated with fMRI activation in hypothalamus, ventral striatum, cerebellum and frontal middle gyrus to high-energy food images compared with low-energy images<sup>(66,69–71)</sup>.

In addition to visual stimulation with food images, studies using oral food cues have also shown modulation of brain responses by satiation. Key brain areas attenuated due to satiation include the insula, amygdala, striatum and OFC. Suppression in OFC, amygdala, ventral striatum is reported in many studies and may reflect the decrease in pleasantness and desire to eat<sup>(25,72,73)</sup>. Suppression in the anterior insula activity on satiation suggests its role in feeding behaviour in addition to its taste sensory processing<sup>(22,25,74–76)</sup>. The hypothalamus is widely recognised as the gatekeeper to control food intake, highly influenced by nutrients, with evidence that hypothalamic dysfunction may lead to obesity<sup>(77)</sup>. Prior studies have shown the hypothalamus is modulated by satiety<sup>(76,78)</sup>; however this modulation is inconsistent across BOLD studies, and may be due to its small structure, variability in position and close proximity to the sinus cavity. Recent CBF studies show a decrease in activation of the hypothalamus after the consumption of glucose<sup>(79)</sup> and a high-fat meal<sup>(40)</sup> compared with baseline. In addition, the decrease in hypothalamus CBF correlated positively with the insula gustatory brain region<sup>(40)</sup>, indicating the interaction between homeostatic and taste areas in response to a high-fat meal.

### How do hormonal responses influence the cortex?

Food intake and its termination are affected by internal and external factors. The homeostatic system controls appetite and food intake via anorectic and appetitive hormones connecting to the neural circuitry, and

converging through the hypothalamus to stimulate or inhibit food intake<sup>(80)</sup>. The non-homeostatic mechanisms including food palatability (through sight, smell and taste sensory), habitual, sociocultural, emotional and economic influences also drive food intake and appetite. It is now widely accepted that, there is extensive cross-modulation between homeostatic and non-homeostatic systems, with regard to appetite control. Fig. 3 shows a simplified schematic of the gut–brain axis and the appetite and homeostatic brain areas modulated by food intake.

Peptide YY (PYY), glucagon-like peptide 1 and cholecystokinin (CCK) are anorectic hormones secreted by the gut and intestine following a meal ingestion, leading to inhibition of food intake. Prior BOLD-fMRI studies have assessed the brain response to an intravenous infusion of PYY, and showed a modulation in OFC, posterior insula, ACC, striatum and homeostatic regions of the brainstem and hypothalamus<sup>(81)</sup>. The subjects' energy intake correlated negatively with OFC signal change after the PYY infusion and positively with hypothalamus activity after saline infusion. These authors postulated the presence of PYY switched the regulation of food intake from a homeostatic brain region (hypothalamus) to a hedonic region (OFC). In a more recent study, the combined administration of PYY and glucagon-like peptide 1 to fasted human subjects attenuated brain areas that control appetitive behaviour, including amygdala, caudate, insula, nucleus accumbens, OFC and putamen<sup>(82)</sup>.

CCK is released within minutes of eating, as a function of the presence of fat (long-chain NEFA) or protein, and thought to play a role in meal termination<sup>(83,84)</sup>. The satiety effects of CCK are mediated in part by the vagal nerve<sup>(85,86)</sup>, to activate the brainstem nucleus tractus solitarius which projects to brain regions controlling food intake (e.g. hypothalamus and amygdala)<sup>(87)</sup>. Very few studies have assessed the brains' response to nutrients and the role of CCK in mediating such a response. The intra-gastric infusion of lipids has been shown to lead



to a CCK-dependent increase in BOLD signal in the brainstem, pons, hypothalamus, cerebellum and motor cortical areas<sup>(88)</sup>. Li *et al.* investigated the brain response to different macronutrients (fat, glucose and protein) and measured the associated gut hormone concentrations, including ghrelin (appetitive hormone), CCK, and glucagon-like peptide 1, in both fed and fasted states<sup>(89)</sup>. The BOLD response reduced when fed in the middle insula, thalamus, parahippocampal cortex, caudate, and lateral OFC, compared with the hunger state<sup>(89)</sup>. However, amygdala activation was modulated following protein ingestion but not after fat or glucose, suggesting it may play a more important role than other regions in mediating dietary protein-induced satiety. BOLD signal changes were positively correlated with circulating ghrelin concentrations and were negatively correlated with circulating insulin, CCK and glucagon-like peptide 1 concentrations. More recently, the CCK plasma values have been showed to correlate negatively with BOLD response in reward (amygdala) and taste (insula) regions in response to ingestion of a high-fat meal<sup>(90)</sup>. A number of studies have also investigated the cortical response to ghrelin<sup>(91–93)</sup>.

#### Effect of obesity on the cortical response

There is now extensive literature on using fMRI to examine how obesity influences the cortical response to food. Recent fMRI studies showed that brain activity of obese people is significantly different from that of normal-weight control subjects in several brain regions implicated in food reward, emotion/memory and sensory/motor processing, with greater activation in the obese group paired with hypo-activity in areas associated with homeostatic satiety and cognitive control/attention. Szalay *et al.* showed that obese subjects had high levels of activation in taste and reward areas (amygdala, nucleus accumbens for sweet, fatty or quinone samples, whereas control healthy subjects varied their response depending on the taste of the sample<sup>(94)</sup>. The authors postulated that the dysfunction in reward circuitry in obese subjects may have a distinguished role in overeating due to their altered responsiveness to tastes. Other studies<sup>(95,96)</sup> demonstrated that food motivation associated with viewing high- and low-energy food images in obese women is different from healthy weighted subjects, with an enhanced activation to high-energy food images in dorsal striatal regions (reward areas). Moreover, increasing body BMI positively correlated with BOLD signal for the high-energy condition in anterior insula (taste region), OFC (reward and secondary taste area), posterior cingulate, dorsal striatum and post-central gyrus. A more recent functional connectivity analysis study showed a relative deficiency in the reward network in obese women, with a deficit in amygdala modulated activation of both OFC and nucleus accumbens, but a tendency towards excessive modulation of the nucleus accumbens by the OFC<sup>(97)</sup>. These results show it may not only be the hyper-activation of the reward system in obese individuals that increases the motivational values of food, but also

differences in the interaction of regions within the reward network. Together these studies demonstrate unique patterns of brain activation in obese compared to healthy control individuals when food motivation is manipulated by varying food content.

#### What can ultra-high field offer to functional MRI studies of nutrition?

The studies described in this review demonstrate the application of fMRI to reveal brain regions involved in food perception, and provide a powerful method to study the interactions between homeostatic and hedonic signals controlling eating mechanism. In addition, these studies suggest that the neural circuitry involved in the control of food intake is not limited to the hypothalamus and brainstem, but involves hedonic brain regions. However, there is still much research needed to understand the neural underpinnings in nutrition research in the human brain. One of the major gains of UHF (7 T) MR is the increased BOLD contrast-to-noise ratio. The use of such UHF scanners will improve the spatial mapping, and allow better differentiation of cortical areas involved in uni-modal and multi-modal processing, for example in the primary gustatory cortex. Furthermore, the increased BOLD contrast-to-noise ratio can be applied to study single trial BOLD responses and habituation, thus allowing the delivery of more natural stimuli and reduced adaptation effects.

#### Conclusion

In conclusion, neuroimaging methods have been shown to provide valuable insight into improving the understanding of flavour processing and the dependence of phenotype of the cortical response. fMRI studies have begun to demonstrate how the homeostatic system controls appetite and food, and allow the study of the effect of obesity at the cortical level.

#### Financial Support

None.

#### Conflicts of Interest

None.

#### Authorship

S. T. F and S. E. wrote the paper. Both authors have read and approved the final manuscript.



## References

1. Ogawa S, Lee TM, Kay AR *et al.* (1990) Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proc Natl Acad Sci USA* **87**, 9868–9872.
2. Okada YC (1983) Inferences concerning anatomy and physiology of the human brain based on its magnetic field. *Il Nuovo Cimento D* **2**, 379–409.
3. Thulborn KR, Waterton JC, Matthews PM *et al.* (1982) Oxygenation dependence of the transverse relaxation time of water protons in whole blood at high field. *Biochim Biophys Acta* **714**, 265–270.
4. Buxton RB, Uludag K, Dubowitz DJ *et al.* (2004) Modeling the hemodynamic response to brain activation. *Neuroimage* **23**, S220–S233.
5. Hoge RD, Atkinson J, Gill B *et al.* (1999) Investigation of BOLD signal dependence on cerebral blood flow and oxygen consumption: the deoxyhemoglobin dilution model. *Magn Reson Med* **42**, 849–863.
6. Edelman RR, Siewert B, Darby DG *et al.* (1994) Qualitative mapping of cerebral blood flow and functional localization with echo-planar MR imaging and signal targeting with alternating radio frequency. *Radiology* **192**, 513–520.
7. Kim SG (1995) Quantification of relative cerebral blood flow change by flow-sensitive alternating inversion recovery (FAIR) technique: application to functional mapping. *Magn Reson Med* **34**, 293–301.
8. Wu W-C, Fernandez-Seara M, Detre JA *et al.* (2007) A theoretical and experimental investigation of the tagging efficiency of pseudocontinuous arterial spin labeling. *Magn Reson Med* **58**, 1020–1027.
9. Buxton RB, Wong EC & Frank LR (1998) Dynamics of blood flow and oxygenation changes during brain activation: the balloon model. *Magn Reson Med* **39**, 855–864.
10. Silva AC, Lee SP, Yang G *et al.* (1999) Simultaneous blood oxygenation level-dependent and cerebral blood flow functional magnetic resonance imaging during forepaw stimulation in the rat. *J Cerebr Blood F Met* **19**, 871–879.
11. Duong TQ, Kim DS, Ugurbil K *et al.* (2000) Spatiotemporal dynamics of the BOLD fMRI signals: toward mapping submillimeter cortical columns using the early negative response. *Magn Reson Med* **44**, 231–242.
12. Purdon PL & Weisskoff RM (1998) Effect of temporal autocorrelation due to physiological noise and stimulus paradigm on voxel-level false-positive rates in fMRI. *Hum Brain Mapp* **6**, 239–249.
13. Small DM, Zald DH, Jones-Gotman M *et al.* (1999) Human cortical gustatory areas: a review of functional neuroimaging data. *Neuroreport* **10**, 7–13.
14. Small DM, Jones-Gotman M, Zatorre RJ *et al.* (1997) Flavor processing: more than the sum of its parts. *Neuroreport* **8**, 3913–3917.
15. Veldhuizen MG, Albrecht J, Zelano C *et al.* (2011) Identification of human gustatory cortex by activation likelihood estimation. *Hum Brain Mapp* **32**, 2256–2266.
16. Francis S, Rolls ET, Bowtell R *et al.* (1999) The representation of pleasant touch in the brain and its relationship with taste and olfactory areas. *Neuroreport* **10**, 453–459.
17. O'Doherty J, Rolls ET, Francis S *et al.* (2001) Representation of pleasant and aversive taste in the human brain. *J Neurophysiol* **85**, 1315–1321.
18. Small DM, Gregory MD, Mak YE *et al.* (2003) Dissociation of neural representation of intensity and affective valuation in human gustation. *Neuron* **39**, 701–711.
19. O'Doherty JP, Dayan P, Friston K *et al.* (2003) Temporal difference models and reward-related learning in the human brain. *Neuron* **38**, 329–337.
20. Kringelbach ML, de Araujo IET & Rolls ET (2004) Taste-related activity in the human dorsolateral prefrontal cortex. *Neuroimage* **21**, 781–788.
21. O'Doherty J, Rolls E, Francis S *et al.* (2001) Representation of pleasant and aversive taste in the human brain. *J Neurophysiol* **85**, 1315–1321.
22. de Araujo IE, Kringelbach M, Rolls E *et al.* (2003) Human cortical responses to water in the mouth, and the effects of thirst. *J Neurophysiol* **90**, 1865–1876.
23. Ogawa H, Wakita M, Hasegawa K *et al.* (2005) Functional MRI detection of activation in the primary gustatory cortices in humans. *Chem Senses* **30**, 583–592.
24. Faurion A, Cerf B, Van De Moortele PF *et al.* (1999) Human taste cortical areas studied with functional magnetic resonance imaging: evidence of functional lateralization related to handedness. *Neurosci Lett* **277**, 189–192.
25. O'Doherty J, Rolls ET, Francis S *et al.* (2000) Sensory-specific satiety-related olfactory activation of the human orbitofrontal cortex. *Neuroreport* **11**, 893–897.
26. Savic I, Gulyas B, Larsson M *et al.* (2000) Olfactory functions are mediated by parallel and hierarchical processing. *Neuron* **26**, 735–745.
27. Yousem DM, Williams SCR, Howard RO *et al.* (1997) Functional MR imaging during odor stimulation: preliminary data. *Radiology* **204**, 833–838.
28. Fulbright RK, Skudlarski P, Lacadie CM *et al.* (1998) Functional MR imaging of regional brain responses to pleasant and unpleasant odors. *AJNR Am J Neuroradiol* **19**, 1721–1726.
29. Weismann M, Yousry I, Heuberger E *et al.* (2001) Functional magnetic resonance imaging of human olfaction. *Neuroimaging Clin N Am* **11**, 237–250.
30. Poellinger A, Thomas R, Lio P *et al.* (2001) Activation and habituation in olfaction—an fMRI study. *NeuroImage* **13**.
31. Cerf-Ducastel B, Van de Moortele PF, MacLeod P *et al.* (2001) Interaction of gustatory and lingual somatosensory perceptions at the cortical level in the human: a functional magnetic resonance imaging study. *Chem Senses* **26**, 371–383.
32. Rudenga K, Green BG, Nachtigal D *et al.* (2010) Evidence for an integrated oral sensory module in the human ventral insula. *Chem Senses* **35**, 693–703.
33. Guest S, Grabenhorst F, Essick G *et al.* (2007) Human cortical representation of oral temperature. *Physiol Behav* **92**, 975–984.
34. Gilbertson TA (1998) Gustatory mechanisms for the detection of fat. *Curr Opin Neurobiol* **8**, 447–452.
35. Mattes RD (2005) Fat taste and lipid metabolism in humans. *Physiol Behav* **86**, 691–697.
36. de Araujo IE & Rolls ET (2004) Representation in the human brain of food texture and oral fat. *J Neurosci* **24**, 3086–3093.
37. De Celis Alonso B, Marciani L, Head K *et al.* (2007) Functional Magnetic Resonance imaging assessment of the cortical representation of oral viscosity. *J Texture Stud* **38**, 725–737.
38. Eldeghaidy S, Marciani L, McGlone F *et al.* (2011) The cortical response to the oral perception of fat emulsions and the effect of taster status. *J Neurophysiol* **105**, 2572–2581.
39. Grabenhorst F, Rolls ET, Parris BA *et al.* (2010) How the brain represents the reward value of fat in the mouth. *Cereb Cortex* **20**, 1082–1091.
40. Frank S, Linder K, Kullmann S *et al.* (2012) Fat intake modulates cerebral blood flow in homeostatic and gustatory brain areas in humans. *Am J Clin Nutr* **95**, 1342–1349.
41. Grabenhorst F & Rolls ET (2014) The representation of oral fat texture in the human somatosensory cortex. *Hum Brain Mapp* **35**, 2521–2530.





42. Small DM (2008) Flavor and the formation of category-specific processing in olfaction. *Chem Percept* **1**, 136–146.
43. Small DM, Voss J, Mak YE *et al.* (2004) Experience-dependent neural integration of taste and smell in the human brain. *J Neurophysiol* **92**, 1892–1903.
44. De Araujo IET, Rolls ET, Kringelbach ML *et al.* (2003) Taste-olfactory convergence, and the representation of the pleasantness of flavour, in the human brain. *Eur J Neurosci* **18**, 2059–2068.
45. Eldeghaidy S, Marciani L, Pfeiffer J *et al.* (2011) Use of an immediate swallow protocol to assess taste and aroma integration in fMRI studies. *Chemosens Percept* **4**, 163–174.
46. Small DM & Prescott J (2005) Odor/taste integration and the perception of flavor. *Exp Brain Res* **166**, 345–357.
47. McCabe C & Rolls ET (2007) Umami: a delicious flavor formed by convergence of taste and olfactory pathways in the human brain. *Eur J Neurosci* **25**, 1855–1864.
48. Verhagen JV & Engelen L (2006) The neurocognitive bases of human multimodal food perception: sensory integration. *Neurosci Biobehav Rev* **30**, 613–665.
49. Bartoshuk LM, Duffy VB & Miller IJ (1994) PTC/PROP tasting: anatomy, psychophysics, and sex effects. *Physiol Behav* **56**, 1165–1171.
50. Bartoshuk LM, Duffy VB, Fast K *et al.* (2003) Labeled scales (eg, category, Likert, VAS) and invalid across-group comparisons: what we have learned from genetic variation in taste. *Food Qual Prefer* **14**, 125–138.
51. Chang WI, Chung JW, Kim YK *et al.* (2006) The relationship between phenylthiocarbamide (PTC) and 6-n-propylthiouracil (PROP) taster status and taste thresholds for sucrose and quinine. *Arch Oral Biol* **51**, 427–432.
52. Miller IJ & Reedy FE (1990) Variations in human taste bud density and taste intensity perception. *Physiol Behav* **47**, 1213–1219.
53. Duffy VB, Bartoshuk LM, Lucchina LA *et al.* (1996) Supertasters of PROP (6-n-propylthiouracil) rate the highest creaminess to high-fat milk products. *Chem Senses* **21**, 598.
54. Duffy VB, Peterson J & Bartoshuk L (2004) Associations between taste genetics, oral sensation and alcohol intake. *Physiol Behav* **82**, 435–445.
55. Manrique S & Zald DH (2006) Individual differences in oral thermosensation. *Physiol Behav* **88**, 417–424.
56. Duffy VB, Davidson AC, Kidd JR *et al.* (2004) Bitter receptor gene (TAS2R38), 6-n-propylthiouracil (PROP) bitterness and alcohol intake. *Alcohol Clin Exp Res* **28**, 1629–1637.
57. Duffy BV & Bartoshuk LM (2000) Food acceptance and genetic variation in taste. *J Am Diet Assoc* **100**, 647–655.
58. Essick GK, Chopra A, Guest S *et al.* (2003) Lingual tactile acuity, taste perception, and the density and diameter of fungiform papillae in female subjects. *Physiol Behav* **80**, 289–302.
59. Cruz A & Green BG (2000) Thermal stimulation of taste. *Nature* **403**, 889–892.
60. Green BG & George P (2004) Thermal taste' predicts higher responsiveness to chemical taste and flavor. *Chem Senses* **29**, 617–628.
61. Bajec MR & Pickering G (2008) Thermal taste, PROP responsiveness, and perception of oral sensations. *Physiol Behav* **95**, 581–590.
62. Clark R, Francis S, Bealin-Kelly F *et al.* (2011) The cortical response to carbonation and its interaction with taste perception. In *9th Pangborn Sensory Science Symp.*
63. Stice E, Spoor S, Bohon C *et al.* (2008) Relation of reward from food intake and anticipated food intake to obesity: a functional magnetic resonance imaging study. *J Abnorm Psychol* **117**, 924–935.
64. Felsted JA, Ren X, Chouinard-Decorte F *et al.* (2010) Genetically determined differences in brain response to a primary food reward. *J Neurosci* **30**, 2428–2432.
65. Wilcox CE, Claus ED, Blaine SK *et al.* (2013) Genetic variation in the alpha synuclein gene (SNCA) is associated with BOLD response to alcohol cues. *J Stud Alcohol Drugs* **74**, 233–244.
66. Fuhrer D, Zysset S & Stumvoll M (2008) Brain activity in hunger and satiety: an exploratory visually stimulated fMRI study. *Obesity (Silver Spring)* **16**, 945–950.
67. LaBar KS, Gitelman DR, Parrish TB *et al.* (2001) Hunger selectively modulates corticolimbic activation to food stimuli in humans. *Behav Neurosci* **115**, 493–500.
68. Mohanty A, Gitelman DR, Small DM *et al.* (2008) The spatial attention network interacts with limbic and monoaminergic systems to modulate motivation-induced attention shifts. *Cereb Cortex* **18**, 2604–2613.
69. van der Laan LN, de Ridder DTD, Viergever MA *et al.* (2011) The first taste is always with the eyes: a meta-analysis on the neural correlates of processing visual food cues. *NeuroImage* **55**, 296–303.
70. Killgore WD, Young AD, Femia LA *et al.* (2003) Cortical and limbic activation during viewing of high- versus low-calorie food. *Neuroimage* **19**, 1381–1394.
71. Goldstone AP, de Hernandez CG, Beaver JD *et al.* (2009) Fasting biases brain reward systems towards high-calorie foods. *Eur J Neurosci* **30**, 1625–1635.
72. Smeets P, Graaf C, Stafleu A *et al.* (2006) Effect of satiety on brain activation during chocolate tasting in men and women. *Am J Clin Nutr* **83**, 1297–1305.
73. Smeets PAM, Weijzen P, de Graaf C *et al.* (2011) Consumption of caloric and non-caloric versions of a soft drink differentially affects brain activation during tasting. *Neuroimage* **54**, 1367–1367.
74. Small D, Zatorre R, Dagher A *et al.* (2001) Changes in brain activity related to eating chocolate From pleasure to aversion. *Brain* **124**, 1720–1733.
75. Tataranni P & DelParigi A (2003) Functional neuroimaging: a new generation of human brain studies in obesity research. *Obes Rev* **4**, 229–238.
76. Gautier J, Del Parigi A, Chen K *et al.* (2001) Effect of satiation on brain activity in obese and lean women. *Obes Res* **9**, 676–684.
77. Thaler JP & Schwartz MW (2010) Minireview: inflammation and obesity pathogenesis: the hypothalamus heats up. *Endocrinology* **151**, 4109–4115.
78. Smeets P, de Graaf C, Stafleu A *et al.* (2005) Functional MRI of human hypothalamic responses following glucose ingestion. *Neuroimage* **24**, 363–368.
79. Page KA, Chan O, Arora J *et al.* (2013) Effects of fructose vs glucose on regional cerebral blood flow in brain regions involved with appetite and reward pathways. *J Am Med Assoc* **309**, 63–70.
80. von Ruesten A, Steffen A, Floegel A *et al.* (2011) Trend in obesity prevalence in European adult cohort populations during follow-up since 1996 and their predictions to 2015. *PLoS ONE* **11**, e27455.
81. Batterham R, Ffytche D, Rosenthal J *et al.* (2007) PYY modulation of cortical and hypothalamic brain areas predicts feeding behaviour in humans. *Nature* **450**, 106–109.
82. De Silva A, Salem V, Long CJ *et al.* (2011) The gut hormones PYY 3–36 and GLP-1 7–36 amide reduce food intake and modulate brain activity in appetite centers in humans. *Cell Metab* **14**, 700–706.
83. Moran TH & Kinzig KP (2004) Gastrointestinal satiety signals II. Cholecystokinin. *Am J Physiol Gastrointest Liver Physiol* **286**, G183–G188.



84. Liddle RA, Goldfine ID, Rosen MS *et al.* (1985) Cholecystokinin bioactivity in human plasma. Molecular forms, responses to feeding, and relationship to gallbladder contraction. *J Clin Invest* **75**, 1144–1152.
85. Batterham R, Cowley M, Small C *et al.* (2002) Gut hormone PYY3–36 physiologically inhibits food intake. *Nature* **418**, 650–654.
86. Degen L, Matzinger D, Drewe J *et al.* (2001) The effect of cholecystokinin in controlling appetite and food intake in humans. *Peptides* **22**, 1265–1269.
87. Petrovich G, Setlow B, Holland P *et al.* (2002) Amygdalo-hypothalamic circuit allows learned cues to override satiety and promote eating. *J Neurosci* **22**, 8748–8753.
88. Lassman D, Mckie S, Gregory L *et al.* (2010) Defining the role of cholecystokinin in the lipid-induced human brain activation matrix. *Gastroenterology* **138**, 1514–1524.
89. Li J, An R, Zhang Y *et al.* (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.
90. Eldeghaidy S, Marciani L, Hort J *et al.* (2014) Prior feeding of fat modulates the cortical response to fat in the mouth in humans. In *Joint Annual Meeting ISMRM-ESMRMB*.
91. Sun X, Veldhuizen MG, Wray AE *et al.* (2014) The neural signature of satiation is associated with ghrelin response and triglyceride metabolism. *Physiol Behav*.
92. Goldstone AP, Precht CG, Scholtz S *et al.* (2014) Ghrelin mimics fasting to enhance human hedonic, orbitofrontal cortex, and hippocampal responses to food. *Am J Clin Nutr* **99**, 1319–1330.
93. Malik S, McGlone F, Bedrossian D *et al.* (2008) Ghrelin modulates brain activity in areas that control appetitive behavior. *Cell Metab* **7**, 400–409.
94. Szalay C, Aradi M, Schwarcz A *et al.* (2012) Gustatory perception alterations in obesity: an fMRI study. *Brain Res* **1473**, 131–140.
95. Rothmund Y, Preuschhof C, Bohner G *et al.* (2007) Differential activation of the dorsal striatum by high-calorie visual food stimuli in obese individuals. *Neuroimage* **37**, 410–421.
96. Stoeckel LE, Weller RE, Cook EW *et al.* (2008) Widespread reward-system activation in obese women in response to pictures of high-calorie foods. *Neuroimage* **41**, 636–647.
97. Stoeckel LE, Kim J, Weller RE *et al.* (2009) Effective connectivity of a reward network in obese women. *Brain Res Bull* **79**, 388–395.