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The functional human neuroanatomy of food pleasure cycles

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Abstract

Food ensures our survival and is a potential source of pleasure and general well-being. In order to survive, the human brain is required to optimize the resource allocation such that rewards are pursued when relevant. This means that food intake follows a similar cyclical time course to other rewards with phases related to expectation, consummation and satiety. Here we develop a multilevel model for the full cycle of eating behaviour based on the evidence for the brain networks and mechanisms initiating, sustaining and terminating the various phases of eating. We concentrate on how the underlying reward mechanisms of wanting, liking and learning lead to how human food intake is governed by both hedonic and homeostatic principles. We describe five of the main processing principles controlling food intake: hunger and attentional signal processing; motivation-independent discriminative processing; reward representations; learning-dependent multimodal sensory representations and hedonic experience. Overall, the evidence shows that while human food intake is complex, we are making progress in understanding the underlying mechanisms and that the brain networks supporting the food pleasure cycle are remarkably similar to those underlying the processing of other rewards.

Keywords: pleasure cycle, satiety, satiation, hedonic, pleasure, food, multimodal integration, insula, operculum, orbitofrontal cortex, cingulate cortex, wanting, liking, learning

Introduction

Food is essential to fulfil the evolutionary imperative of survival allowing species and organisms to replenish energy. Consummatory behaviour is rewarding in itself and, along with basic homeostatic regulation, hard-wired in even brainless species. In addition to food, the fundamental rewards afforded by biological evolution include sex and conspecifics. Pleasure and reward are key mechanisms ensuring that individuals and species seek the fundamental rewards allowing survival and procreation; and as such have been proposed as evolution's boldest trick (Kringelbach, 2005).

Food intake is complex, especially in mammals that must maintain a stable body temperature in a wide variety of often hostile climates (Berthoud, 2005). The relative sophistication of foraging in higher primates compared to other mammals indicates that significant parts of their large brains are dedicated to the required motivational, emotional and cognitive processing. In humans, it has been proposed that some of these cortical networks that evolved for the more advanced aspects of eating-related behaviour have been recycled and have come to underlie other higher cognitive functions (Kringelbach, 2004).

Understanding the functional neuroanatomy underlying food intake has to take into account the cyclical time course of eating with distinct phases related to expectation, consummation and satiety. These phases must in turn be related to the recent progress in *hedonia* research (from the ancient Greek word *hedone*, from the sweet taste of honey, *hedus*) demonstrating that pleasure consists of multiple brain networks and processes relating to *wanting*, *liking* and *learning* (Berridge and Kringelbach, 2008; Finlayson *et al.*, 2007; Robinson and Berridge, 1993, 2003) (see **Figure 1**).

Here, we discuss the evidence linking brain networks to initiating, sustaining and terminating the various wanting, liking and learning phases of the food pleasure cycle (see **Figure 2**). This allows an individual to obtain stable sensory information, evaluate desirability and select the appropriate behaviour. Some but not all of human eating behaviour is guided by basic homeostatic regulation. Other influences in eating behaviour include cognition, emotion and reward (Berthoud and Morrison, 2008) and may lead to eating beyond, or below homeostasis, e.g. obesity or anorexia respectively. Animal models have elucidated in great detail how mammals including humans share many sub-cortical circuits and molecules (Berthoud and Morrison, 2008; Saper *et al.*, 2002; Woods, 2009).

Human eating is not, however, governed solely by homeostatic processes, as illustrated by the current worldwide obesity pandemic, which has become a major health problem (Kohn and Booth, 2003). Instead, pleasure and reward mechanisms play a central role in the control of human food intake (Kringelbach, 2004). In addition, food intake is modulated by other factors such as genetics (O'Rahilly and Farooqi, 2006), circadian rhythms (Ramsey *et al.*, 2007), reproductive status (Eckel, 2004) and social factors. Evidence for the complexity of eating behaviour can be found in the influence of all five primary sensory systems as well as the visceral sensory system and gut-brain interactions (Aharon *et al.*, 2001; Batterham *et al.*, 2007; Critchley *et al.*, 2002; Frey *et al.*, 2000; Mayer, 2011; Rolls *et al.*, 2003b; Small *et al.*, 1999; Zatorre *et al.*, 1992).

This article reviews the evidence linking activity in human brain networks to the various parts of the food pleasure cycle. We develop a multilevel model of the control of human food intake which describes our current understanding of the interactions between the many different levels of systems involved. We concentrate on describing how the underlying reward mechanisms of wanting, liking and learning have given rise to a number of fundamental processing principles controlling human food intake. We compare the brain networks involved in food intake with those of other rewards.

Food intake cycles

The main challenge for the brain is to successfully balance resource allocation for survival and procreation (Lou *et al.*, 2011). The control of energy intake in humans is complex and much remains to be discovered (Kringelbach, 2004; Zheng *et al.*, 2009). In order to achieve this balance, different rewards compete for resources and therefore typically follow a cyclical time course (see **Figure 2**), where e.g. behaviours related to survival and procreation rarely occur simultaneously.

Here, we have expanded the basic cyclical model into a more elaborate multilevel model, which summarizes our current understanding of the episodic and tonic changes over time related to food intake (see **Figure 3**). This model involves the cyclical changes in hunger levels related to the initiation and termination of meals, and the way they interact with signals from the brain, gut-brain, oral cavity, stomach and intestines, liver and metabolites and body mass.

Satiation and satiety are key factors in this model which help control energy intake (Blundell and Burley, 1987). Satiation is the process that terminates eating (De Graaf *et al.*, 1999), while satiety is the feeling of fullness that persists after eating to suppress further eating. As such satiation and satiety are controlled by a cascade of sensory, cognitive, post-ingestive and post-absorptive signals that begin with the consumption of a food and continue as the food is digested and absorbed. All of this complex temporally dispersed information is processed and integrated in the brain.

Our multilevel model of food intake describes the changes over time in 1) the levels of hunger, 2) satiation/satiety cascade signals, 3) origin of signals, 4) signal carriers, 5) brain processes, 6) behavioural changes including in the digestive system and 7) general modulatory factors (see **Figure 3**).

Each of these levels clearly influence food intake, with many other excellent reviews describing the mechanisms of the changes after the termination of a meal. Examples from gut-brain interactions include signals from receptors in the digestive tract which are sensitive to calorie-rich nutrients (even in the absence of taste receptors) (De Araujo *et al.*, 2008; De Araujo and Simon, 2009) and signals from receptors in the circulatory system that are sensitive to changes in blood pressure or carbon dioxide gas in the blood and contribute to the control of eating (see **Figure 4**).

Here, however, we concentrate on the processing principles involved primarily in the initiation and termination of a meal. The control of food intake involves all of the five classic senses (vision, hearing, smell, taste, and touch), but smell and taste are perhaps the two most important senses involved in eating.

In the following we show how these senses interact to facilitate and modulate decision making and hedonic experience. At least five processing principles exist for the interaction between sensory and hedonic processing controlling the initiation and termination of meals in humans: 1) Hunger and attentional processing; 2) motivation-independent discriminative processing of identity and intensity; 3) reward representations using state-dependent mechanisms; 4) formation of learning-dependent multimodal sensory representations and 5) representations of hedonic experience, monitoring/learning or direct behavioural change (Kringelbach, 2006).

Food reward processing

Food intake is driven by motivation and emotion which are in turn supported by reward and hedonic processing. Reward consists of multiple sub-components, including the dual aspect of hedonic impact and incentive salience. The former refers to the 'liking' or pleasure related to the reward, e.g., the experiences of eating, whereas the latter refers to the 'wanting' or desire to obtain the reward (Berridge, 1996; Berridge and Robinson, 1998). A third sub-component 'learning' is important for linking wanting and liking over time and usually, but not exclusively, follows consumption.

One might for example consume a certain food which is highly liked, but subsequently learn that this food causes an adverse effect such as an allergic reaction. Through learning one will be aware to avoid this liked substance in the future in order to avoid the negative outcome. Memories obtained through this Pavlovian learning remain stable over time until devaluation or until new information becomes available (Smith *et al.*, 2011; Zhang *et al.*, 2009).

Wanting is known to exhibit dynamic fluctuation corresponding to e.g. hunger states, but it can also shift from a reward food stimulus to a conditioned stimulus or cue. This cue itself could become highly wanted and thus become a motivational magnet. The immense attractive properties of such a motivational magnet can be seen when it is hard to ignore the cue and e.g. rats will try to consume an inedible cue that predicts the arrival of food instead of the food itself (Berridge, 2012).

The evidence from pleasure research thus suggests a tripartite framework for the wanting, liking and learning (Kringelbach and Berridge, 2009b), which in turn can be mapped onto the food pleasure cycle and the satiety/satiation cascades involved (Blundell and Burley, 1987) (see **Figures 2** and **3**).

Wanting and liking are difficult to tease apart in behavioural studies and there is an ongoing debate regarding how to best dissociate them (Havermans, 2012). Some of the best evidence comes from Berridge (2012) who has demonstrated a phenomenon which he terms "persistent 'miswanting'". In this case, wanting persists even when a food stimulus is disliked such as seen e.g. in drug addicts after bad drug experiences. Additionally, wanting and liking can be successfully dissociated by various pharmacological manipulations, of e.g. dopamine levels in select brain regions (Smith *et al.*, 2011).

Furthermore, we have introduced a behavioural wanting-liking paradigm where human participants indicate their subjective liking of a stimulus as well as their wanting measured by the amount of effort they are willing to put in to prolong or shorten the duration of the exposure to the stimulus (Parsons *et al.*, 2011). For example, this paradigm has been used to demonstrate that even though men and women differ in their liking

ratings of baby faces, they show similar viewing times (as a measure of wanting by exerted effort to influence viewing times).

In humans, neuroimaging offers a route to investigate the partly separable liking, wanting and learning components in the human brain with spatio-temporal monitoring of activity patterns in the different cortical regions regulating each of these components. For example, one way to investigate processing related to 'liking' is to correlate subjective hedonic ratings taken throughout a human neuroimaging experiment with changes in brain activity (De Araujo *et al.*, 2003a; De Araujo *et al.*, 2003b; Kringelbach *et al.*, 2003). This allows for a unique window on the hedonic processes evaluating the pleasantness of salient food stimuli.

Learning is an important component in decision-making regarding eating-related behaviour, where the brain must compare and evaluate the predicted reward value of various behaviours. This processing can be complex, as the estimations will vary in quality depending on the sampling rate of the behaviour and the variance of reward distributions. It is difficult to provide a reliable estimate of the reward value of a food that appears to be highly desirable and is high in nutritional value but is only rarely available and varies significantly in quality.

This raises a classic problem in animal learning, of how to optimize behaviour such that the amount of exploration is balanced with the amount of exploitation, where exploration is the time spent sampling the outcome of different behaviours and exploitation is the time spent using existing behaviours with known reward values.

Ultimately, pleasure can be thought of as an important tool to control this balancing act between exploitation and exploration. As reviewed below, the evidence from neuroimaging studies has linked regions of the human brain – and in particular the orbitofrontal cortex – to various aspects of eating and especially to the representation of the subjective pleasantness of foods (Kringelbach, 2004).

Hunger and other attentional processing

An important principle governing food intake relates to the way attention can signal the brain to start to reallocate resources for a change in ongoing behaviour. Hunger is a major attentional signal that along with other homeostatic signalling can influence the brain to initiate the food pleasure cycle, following the satiety phase from the previous meal. The information comes primarily from gut-brain interactions signalling if the nutrients eaten in the previous meal have yielded the expected amount of energy but learning and habit also play a large part. Signals from receptors in the gut and in the circulatory system are vital in initiating eating through conveying messages for the need of nutrients or energy uptake (Berthoud and Morrison, 2008; Lenard and Berthoud, 2008).

In normal adults, this system is balanced through careful monitoring and learning throughout life. In the presence of sufficient nutrients, healthy adults are able to maintain a stable body weight throughout life by careful management of nutrient uptake and energy needs and the balance with energy expenditure (Shin *et al.*, 2009). The homeostatic component of controlling energy balance and eating behaviour has been shown to relate to activity in hypothalamic circuits including the arcuate nucleus (Berthoud and Morrison, 2008; Lenard and Berthoud, 2008). Smeets and colleagues (2005) have shown a prolonged activity decrease in the

upper anterior hypothalamus using functional magnetic resonance imaging (fMRI). This effect furthermore was dependent on the glucose dose administered where a larger dose was associated with a larger signal decrease. The signal decrease in the upper posterior hypothalamus was however similar for both doses. However, Grill & Norgren (1978a) have shown that decerebrate rats are able to terminate food intake when fed to satiety suggesting that the caudal brainstem is responsible for some appropriate food intake behaviour.

Yet as shown below, this balance is not solely controlled by homeostasis and it has been suggested that malfunction to this control of energy balance can lead to eating disorders such as obesity, potentially through a mismatch between the expected pleasure compared to the actual energy uptake from food intake (Kringelbach, 2004; Zheng *et al.*, 2009).

Other important attentional factors influencing food intake include social interactions. The so-called social facilitation effect relates to the fact that people will eat more when surrounded by other people (e.g. during a dinner party). It has been suggested that this effect in part can be caused by diminished attention towards the food (De Graaf and Kok, 2010; Hetherington *et al.*, 2006). Concurrent with this finding is evidence that when explicit attention is given to a meal during consumption later appetite and subsequent snack intake is significantly lower. Furthermore when a meal is eaten with attention to its sensory properties, the memory of the meal is more vivid and negatively correlated with later snack intake (Higgs and Donohoe, 2011). The combination of attention and limited sensory exposure from e.g. fast foods may in turn cause a reduced or insufficient feeling of satiation, leading to increased food consumption. The increased food intake can subsequently lead to a surplus of energy and unused calories ultimately resulting in body weight increase. This mechanism has been proposed to be part of the problems involved in the current obesity pandemic (De Graaf and Kok, 2010).

Motivation-independent processing of identity and intensity

Once motivated to seek out food, the human brain has to obtain reliable sensory information about the available food in order to make sensible ingestion decisions. Eating-related behaviours have to be precisely controlled since erroneous evaluation of the sensory properties of foods can potentially be fatal if it results in swallowing toxins, micro organisms or non-food objects. Such decisions are so important that mammals have brainstem reflexes (stereotypical for each basic taste) that are based on rudimentary analyses of the chemical composition, and which are not altered even by the loss of all neural tissue above the level of the midbrain (Grill and Norgren, 1978b). In addition, as mentioned above, humans and other animals have therefore developed elaborate eating-related behaviours to balance conservative risk-minimising and life-preserving strategies (exploitation) with occasional novelty seeking (exploration) in the hope of discovering new, valuable sources of nutrients (Rozin, 2001).

All of the senses are involved in establishing the identity and intensity of a food – sometimes called a *flavour object* (Veldhuizen *et al.*, 2010). The evidence suggests that, at least in humans, it is a fundamental processing principle that the processing of flavour object is a multistage process where the brain activity related to identity is not modulated by motivational state, while the hedonic valence is assigned later (in higher order cortical regions).

This principle is perhaps best demonstrated with the evidence from primary taste processing. Neuroimaging and neuropsychological studies in humans with brain lesions indicate that the primary taste area in humans is located in the anterior insula/frontal operculum (Kinomura *et al.*, 1994; O'Doherty *et al.*, 2001; Small *et al.*, 1997; Small *et al.*, 1999). This is also consistent with the findings in primates (Kringelbach *et al.*, 2004; Pritchard *et al.*, 2005).

The largest fMRI study of taste processing to date used forty datasets from thirty-eight right-handed subjects with 1) identical delivery of the taste stimuli, 2) the same control procedure in which a tasteless solution was delivered after every taste stimulus, and 3) event-related interleaved designs (Kringelbach *et al.*, 2004). A total of eight unimodal and six multimodal taste stimuli (oral stimuli that produce typically gustatory, olfactory and somatosensory stimulation) ranging from pleasant to unpleasant were used in the four experiments. Stringent analysis of taste activity across the forty datasets revealed three cortical activity foci in response to the main effects of taste in the human brain (see **Figure 5A** and **5B**).

The results showed bilateral activity in the anterior insular/frontal opercular cortex with a slightly stronger response on the right side. This slight asymmetry in bilateral taste processing fits with an early meta-analysis of gustatory responses gathered from neuroimaging studies suggesting that the preponderance of activity peaks to taste fall in the right hemisphere (Small *et al.*, 1999). Taste stimuli also produced activity in the medial caudal orbitofrontal cortex, which is likely to coincide with the secondary taste cortex.

Similar to the processing of taste stimuli, neuroimaging studies of pure olfactory stimuli reveal dissociable brain regions for motivation-independent representations of reinforcer identity and for hedonic representations. Representations of olfactory identity occur in primary olfactory cortices (Anderson *et al.*, 2003; Gottfried *et al.*, 2002; O'Doherty *et al.*, 2000; Rolls *et al.*, 2003a; Royet *et al.*, 2001; Zald and Pardo, 1997), which are distinct from the later hedonic representations found in other brain regions including the orbitofrontal cortex.

In general, the experiments in humans and non-human primates clearly demonstrate that the primary sensory areas for taste and smell are not modulated by motivational state, and that hedonic processing occurs in higher-order, multi-modal areas such as the orbitofrontal cortex and regions of mid-insular cortex.

Reward representations of sensory stimuli

The valence of food is assigned subsequently to identifying the motivation-independent representation of food and is another fundamental processing principle. Neuroimaging studies have found that affective valence is encoded in a network of brain regions. For example, in a neuroimaging taste study, a dissociation was found between the brain regions responding to the intensity of the taste and its affective valence (Small *et al.*, 2003). Brain regions responding to intensity regardless of valence included the cerebellum, pons, middle insular cortex, and amygdala, whereas valence-specific responses were observed in the orbitofrontal cortex, with the right caudolateral orbitofrontal cortex responding preferentially to pleasant compared to unpleasant taste, irrespective of intensity. Another neuroimaging study found that the subjective ratings of taste pleasantness (but not intensity) correlated with activity in the medial orbitofrontal cortex and in the anterior cingulate cortex (De Araujo *et al.*, 2003b). Moreover, in the same study it was found that activity in the me-

dial orbitofrontal cortex and a region of mid-insula correlated with subjective pleasantness ratings of water during thirst and subsequent replenishment (see **Figure 5E**).

Further evidence of neural correlates of subjective experience of pure taste was found in an experiment investigating true taste synergism, which is the phenomenon whereby the intensity of a taste is dramatically enhanced by adding minute doses of another taste. The results of this neuroimaging experiment showed that the strong subjective enhancement of the pleasantness of umami taste that occurs when 0.005 M inosine 5'-monophosphate is added to 0.5 M monosodium glutamate (compared to both delivered separately) correlated with increased activity in the mid-anterior part of the orbitofrontal cortex (see **Figure 5G**) (De Araujo *et al.*, 2003a).

Several neuroimaging studies on olfaction have found dissociable encoding of the intensity and pleasantness of olfactory stimuli, with the intensity encoded in the amygdala and nearby regions, and the pleasantness correlated with activity in the medial orbitofrontal cortex and anterior cingulate cortex (Anderson *et al.*, 2003; Gottfried *et al.*, 2002; Rolls *et al.*, 2003a). This finding is consistent with studies that have found that hedonic judgments are correlated with activity in the medial orbitofrontal cortex (Royet *et al.*, 2001) and that the unpleasantness of aversive odours correlates with activity in the lateral orbitofrontal cortex (Zald and Pardo, 1997). Furthermore, it has been found that the orbitofrontal cortex represents the sensory-specific decrease of smell (O'Doherty *et al.*, 2000), which is clear evidence that the reward value of olfactory stimuli is represented in the orbitofrontal cortex.

Other strong evidence for the role of the orbitofrontal cortex in the representation of the reward value of olfactory stimuli comes from an appetitive conditioning neuroimaging experiment in which brain activity related to two arbitrary visual stimuli was measured both before and after olfactory devaluation, i.e. where the reward value of a stimulus is temporarily devalued by e.g. eating it to satiety (Gottfried *et al.*, 2003). In the amygdala and the orbitofrontal cortex, responses evoked by a predictive target stimulus decreased after devaluation, whereas responses to the non-devalued stimulus were maintained.

Similar evidence exists with regard to gustatory stimuli, where the medial and lateral regions of the orbitofrontal cortex are shown to be involved in goal-directed learning and subsequent decision making about devalued food stimuli (Valentin *et al.*, 2007), i.e. the devaluation of a food stimulus changes the reward prediction of that stimulus resulting in altered behaviour or decision making. This is in accordance with a study by O'Doherty and colleagues (2003) who showed that significantly increased activity in the orbitofrontal cortex is associated with behavioural choice.

It would thus appear that differential activity in the amygdala and the orbitofrontal cortex encodes the current value of reward representations accessible to predictive cues. Furthermore the orbitofrontal cortex seems to exhibit functional heterogeneity including, in addition to representation of stimulus-reward values, behavioural control as well as signalling changes in reinforcement outcomes.

This evidence is compatible with studies in non-human primates with lesions of the orbitofrontal cortex. In one study, lesioned monkeys responded normally to associations between food and conditioners but failed to modify their behaviour to the cues when the incentive value of the food was reduced (Butter *et al.*, 1963), and, in another study, lesioned monkeys displayed altered food preferences (Baylis and Gaffan, 1991). Simi-

larly, monkey with unilateral lesions of the orbitofrontal cortex on one side and of the basolateral part of the amygdala on the other side displayed disrupted stimulus devaluation in a procedure in which the incentive value of a food was reduced by satiation on that specific food (Baxter *et al.*, 2000).

Formation of learning-dependent multimodal sensory representations.

Another fundamental processing principle governing food intake relates the formation of learning-dependent multimodal sensory representations. Decisions about food intake also integrate somatosensory information from the oral and nasal cavities in addition to the integration of information from taste and smell. The sensory information includes temperature, viscosity, texture, fat contents, pungency and irritation and is mediated by a large variety of neural systems (De Araujo and Simon, 2009).

Neuroimaging investigations of such learning-dependent multimodal integration have found that one of the critical brain regions is the human orbitofrontal cortex, where activity is elicited by auditory (Frey *et al.*, 2000), gustatory (Small *et al.*, 1999), olfactory (Zatorre *et al.*, 1992), somatosensory (Rolls *et al.*, 2003b) and visual (Aharon *et al.*, 2001) inputs, as well as information from the visceral sensory system (Critchley *et al.*, 2002).

This is consistent with neurophysiological recordings finding that the non-human primate orbitofrontal cortex receives input from all of the five senses (Rolls, 1999). These sensory inputs enter the orbitofrontal cortex mostly through its posterior parts. The interaction between taste and smell revealed by neuroimaging is found in slightly more anterior parts of the orbitofrontal cortex and nearby agranular insula (De Araujo *et al.*, 2003c; Kringelbach *et al.*, 2003; Small *et al.*, 1997).

A good example of multimodal integration is how subjective olfactory experience appears different depending on whether a smell reaches the olfactory epithelium in the nasal cavity through the nose (orthonasal) or mouth via the posterior nares of the nasopharynx (retronasal) (Pierce and Halpern, 1996; Van Hartevelt and Kringelbach, 2011). These are likely to be related to differences in somatosensory influences (e.g. mastication). Several neuroimaging studies have found corresponding differences in cortical activity patterns between ortho- and retronasal olfaction in the orbitofrontal cortex and related brain regions (Cerf-Ducastel and Murphy, 2001; De Araujo *et al.*, 2003a; Small *et al.*, 2005). According to Rozin (1982) orthonasal and retronasal smell have different behavioural consequences.

While an odour entering the nose can come from any object in the environment, an odour coming through the mouth is highly likely to be part of food consumption. Furthermore, a study using ultrasound recordings of swallowing showed that orthonasal and retronasal odour stimulation differentially influence swallowing (Welge-Lüssen *et al.*, 2009). This study showed that swallowing was initiated faster and more frequently after a retronasally presented vanillin odour as a food odour in combination with gustatory sucrose stimulation. Whether this holds true for non-food odours is unknown, although it could be hypothesized that a reverse effect should be found as a non-food or unpleasant odour could signal potential danger (toxicity) if ingested.

Representations of hedonic experience

Finally, a key fundamental processing principle for food intake relates to the role of subjective hedonic experience, constituting a large part of the liking component in the food intake cycle. The evidence from neuroimaging studies of pure taste and smell cited above shows that activity in the medial orbitofrontal cortex is consistently correlated with the subjective pleasantness ratings of a biologically relevant stimulus. Therefore, it is to be expected that studies using multi-modal combinations of taste and smell as well as state-dependent changes in pleasantness should find correlations between subjective pleasantness and activity in the orbitofrontal cortex.

Compelling evidence for a region encoding the subjective pleasantness of food comes from a selective-satiety neuroimaging study in which a region of the mid-anterior orbitofrontal cortex showed not only a selective decrease in the reward value to the food eaten to satiety (and not to the food not eaten), but also a correlation with pleasantness ratings (see **Figure 5F**) (Kringelbach *et al.*, 2003). This result indicates that the reward value of the taste, olfactory, and somatosensory components of a food are represented in the orbitofrontal cortex and, therefore, that the subjective pleasantness of food might be represented in this region.

Further evidence for the convergence of the hedonic processing of taste and smell comes from a study investigating the non-specific satiation effects of chocolate (with both olfactory and gustatory components) which found a correlation between the decrease in pleasantness and activity in the orbitofrontal cortex (Small *et al.*, 2001). Another multimodal study investigating the link between olfaction and vision found activity in the anterior orbitofrontal cortex for semantically congruent trials (Gottfried and Dolan, 2003). Finally, when investigating the synergistic enhancement of a matched taste and retronasal smell it was again found that a region of the orbitofrontal cortex was significantly active (see **Figure 5H**) (De Araujo *et al.*, 2003c). This region was located very near to the region of the orbitofrontal cortex activated by the synergistic combinations of umami described above (De Araujo *et al.*, 2003a).

It is an open but interesting question whether the orbitofrontal cortex and perhaps even sub-regions thereof are both necessary and sufficient for the experience of pleasure. The evidence from psychosurgery studies of last century is not illuminating because of the usually crude psychological measurements and because the lack of neuroimaging or careful post-mortem investigations meant that the surgical lesions were not adequately described. One study of patients with relatively circumscribed lesions suggests that white-matter lesions that disconnect the orbitofrontal cortex can lead to serious emotional changes (Hornak *et al.*, 2003). Direct tests of the lack of pleasure, anhedonia, linked to lesions to the orbitofrontal cortex have, however, not been carried out.

Conclusions

Food is essential to sustain life, but must compete with other rewards for time and resources. This leads to complex resource allocation problems in the human brain, especially related to the problem of successfully balancing exploration and exploitation to ensure survival. Decisions have to be made with regard to which

reward to pursue when, and whether to initiate, sustain and terminate the wanting, liking and learning phases involved in the pleasure cycle for a given reward (Kringelbach and Berridge, 2009a).

In this review we have described some of the basic underlying mechanisms for food intake and proposed a multilevel model of the episodic and tonic changes over time related to food intake (see **Figure 3**). This review has mostly concentrated on recent evidence from human neuroimaging related to the brain processing principles involved primarily in the initiation and termination of a meal. The model, however, demonstrates the cyclical changes in hunger levels related to the initiation and termination of meals, as they relate to signals from the brain, gut-brain, oral cavity, stomach and intestines, liver and metabolites and body mass.

Moreover, appetite and subsequent initiation of food intake also depends on the vividness of a memory of the previous meal and the attention paid while consuming the previous meal. There is convincing evidence that decerebrate rats terminate food intake after sufficient calorie intake (Grill and Norgren, 1978a), which indicates that, at least in rats, brainstem mechanisms may be sufficient for food intake guided by homeostasis. As pointed out in this review however, human eating behaviour is more complex and depends also on hedonic principles where subsequent meal initiation is not solely dependent on hunger and satiety states, such as for example when humans are shown to increase food intake in social situation where no or little attention is given to the food (De Graaf and Kok, 2010).

In this review, we have discussed some of the underlying brain processes which integrate information not only from the primary sensory systems, but also from gut-brain interactions as well as attention and memory. We have proposed five main processing principles: 1) Hunger and attentional processing; 2) motivation-independent processing of identity and intensity; 3) reward representations; 4) formation of learning-dependent multimodal sensory representations and 5) representations of hedonic experience. These five processing principles constitute the wanting, liking and learning phases of the food intake cycle.

We have identified that regions in the orbitofrontal cortex are associated with virtually all of the processing principles mentioned and, together with subcortical and brainstem structures, plays a major role in human eating behaviour. The orbitofrontal cortex shows activity related to the different processing principles in anatomically closely related areas. The importance of the processing principles regarding the reward and pleasure or hedonic experience of food in relation to human eating behaviour can be seen through the effect on learning (e.g. Pavlovian learning) and are thus of great influence in future food intake behaviour. By linking reward and pleasure as well as nutrient information from gut-brain systems to certain food stimuli, humans are able to adapt their eating behaviour in terms of balancing exploitation and exploration.

In line with earlier proposals (Kringelbach, 2004), we propose a possible model which implements these processing principles for the interaction between sensory and hedonic systems in the human brain (see **Figure 6**). This model of the functional neuroanatomy underlying food intake focuses on the orbitofrontal cortex and the interaction with other brain regions, including the brainstem and subcortical structures, in the control of human food intake. There are multiple modulatory brain-loops with other important structures such as the anterior cingulate, insular cortex, nucleus accumbens, ventral pallidum, hippocampus, amygdala and hypothalamus, as well as modulation with autonomic input from the gut. The evidence presented in this review

suggests that the orbitofrontal cortex is an important nexus for food pleasure and the food intake cycle as a whole, including learning, monitoring and subjective food evaluation.

Interestingly, the evidence shows that other fundamental rewards such as sex give rise to similar pleasure cycles and are being processed by similar brain networks (Georgiadis and Kringelbach, Submitted). There are important differences, however, in terms of the subjective experience. For example, during the liking phase of food intake, there can be multiple peaks of pleasure which, in contrast to the pleasure of orgasm during sex, do not necessarily signal immediate termination of the liking phase.

Nevertheless, as we have gained more insight into the brain networks involved in food intake, it has become clear that the underlying brain networks are remarkable similar to those involved in processing other rewards. Furthermore, more research into the brain mechanisms of the reward of food is likely to yield new insights into eating disorders, which can be conceptualised as problems in initiating, sustaining or terminating the different phases of food intake. In time, a better understanding of the relationship between the wanting, liking and learning components of food intake may potentially lead to new treatments.

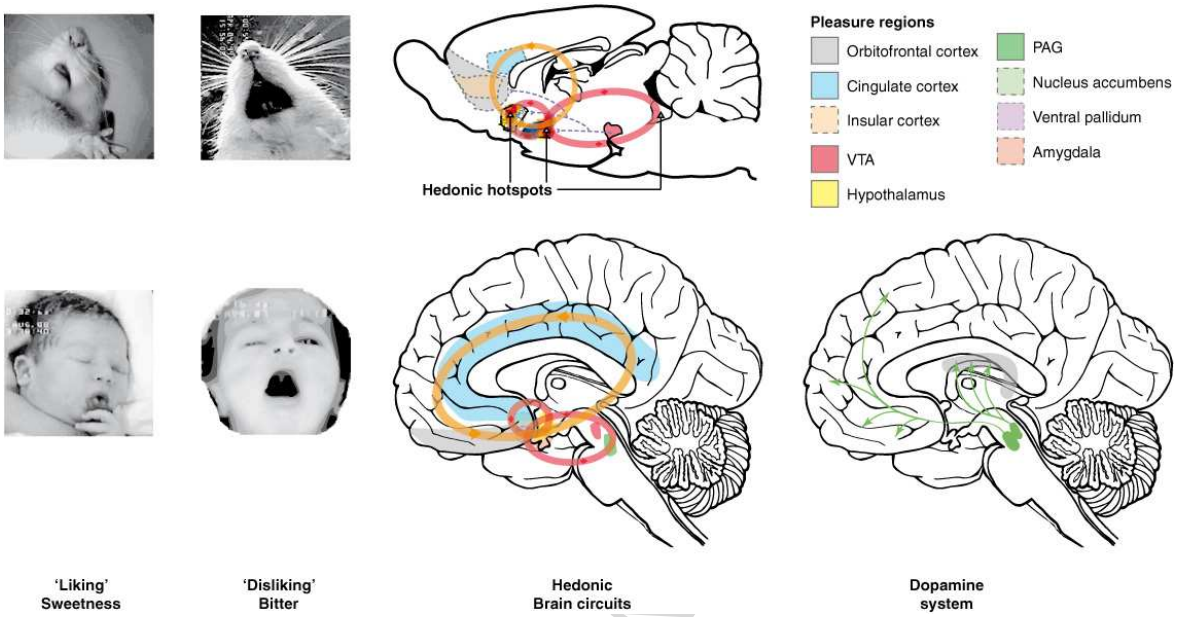

Figure 1. Pleasure networks in the mammalian brain. The figure shows pleasure regions in the adult rat (upper) and human (lower) brains. The hedonic circuitries have been revealed using behavioural and subjective measures of pleasure to food stimuli (Berridge and Kringelbach, 2008). The pleasure networks (in the middle panel) include the orbitofrontal cortex (grey), the cingulate cortex (light blue), ventral tegmental area in the brainstem (light red), hypothalamus (yellow), periventricular gray/periacqueductal gray (PVG/PAG, green), nucleus accumbens (light green), ventral pallidum (light purple), amygdala (light red) and the insular cortices (not shown). The right-most panel shows the dopaminergic system in the human brain.

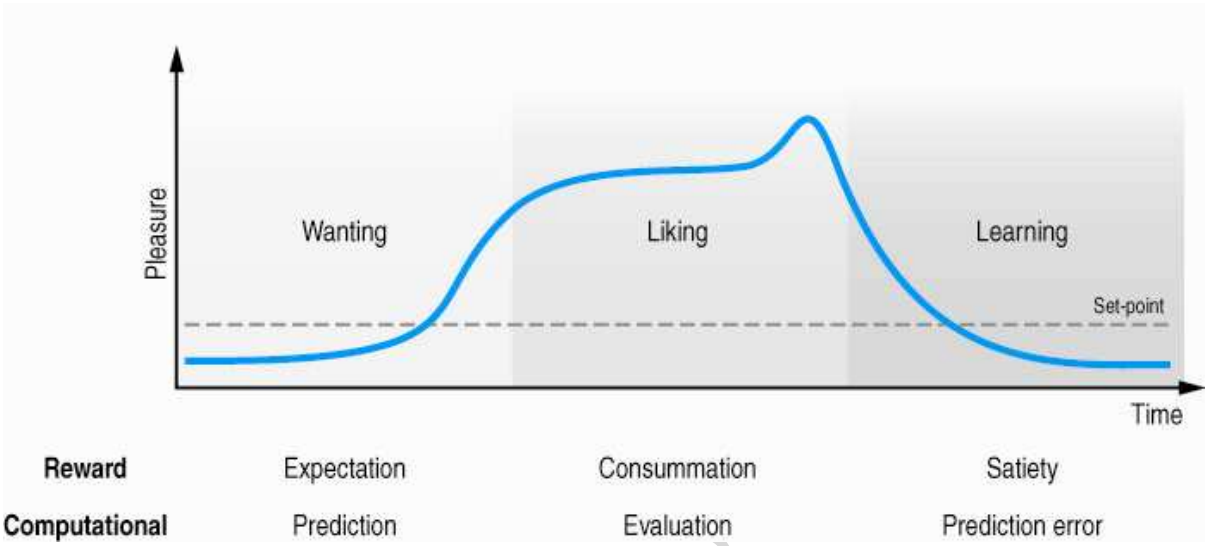

Figure 2: Food pleasure cycle. Fundamental (i.e. rewards associated with behaviour necessary for species survival) and higher order pleasures are associated with a cyclical time course. Typically, rewarding moments go through a phase of expectation or wanting for a reward, which sometimes leads to a phase of consummation or liking of the reward which can have a peak level of pleasure (e.g. encountering a loved one, a tasty meal, sexual orgasm, drug rush, winning a gambling bet). This can be followed by a satiety or learning phase, where one learns and updates predictions for the reward but note that learning obviously can take place throughout the cycle. These various phases have been identified at many levels of investigation of which the recent research on the computational mechanisms underlying prediction, evaluation and prediction error are particularly interesting (Friston and Kiebel, 2009; Zhang *et al.*, 2009). Note, however, that a very few rewards might possibly lack a satiety phase (suggested candidates for brief or missing satiety phase have included money, some abstract rewards and some drug and brain stimulation rewards that activate dopamine systems rather directly).

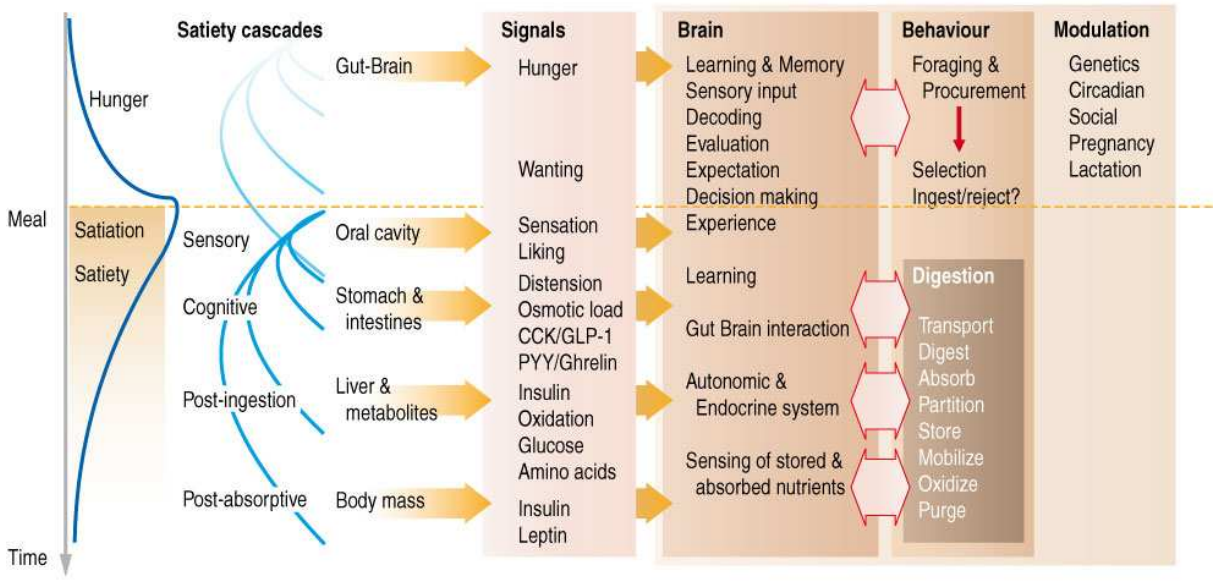

Figure 3: Multilevel model for the satiation/satiety cascade involved in the control of food intake. From left to right, the columns summarize the episodic and tonic changes over time: changes before, during and after meals in 1) the levels of hunger, 2) satiation/satiety cascade (sensory, cognitive, post-ingestion and post-absorptive signals), 3) origin of signals (gut-brain, oral cavity, stomach and intestines, liver and metabolites and body mass), 4) signal carriers, 5) brain processes, 6) behavioural changes including digestive system and 7) general modulatory factors.

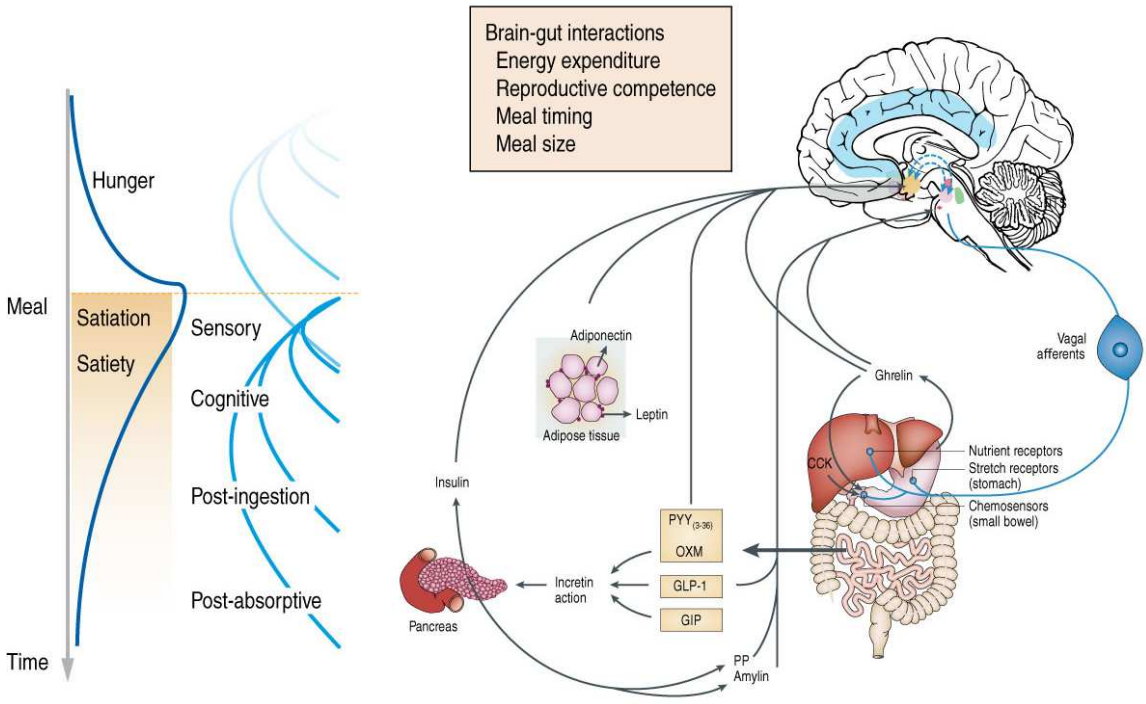

Figure 4: Brain-gut interactions. The figure shows the hunger/satiety cycles as well as the satiation/satiety cycles (Blundell and Burley, 1987) (far left). The right-most diagram shows interactions between brain and gut for the various peripheral signals relating to energy stores and the satiation/satiety cycles (redrawn from figures in Badman and Flier, 2005; Kringelbach, 2004).

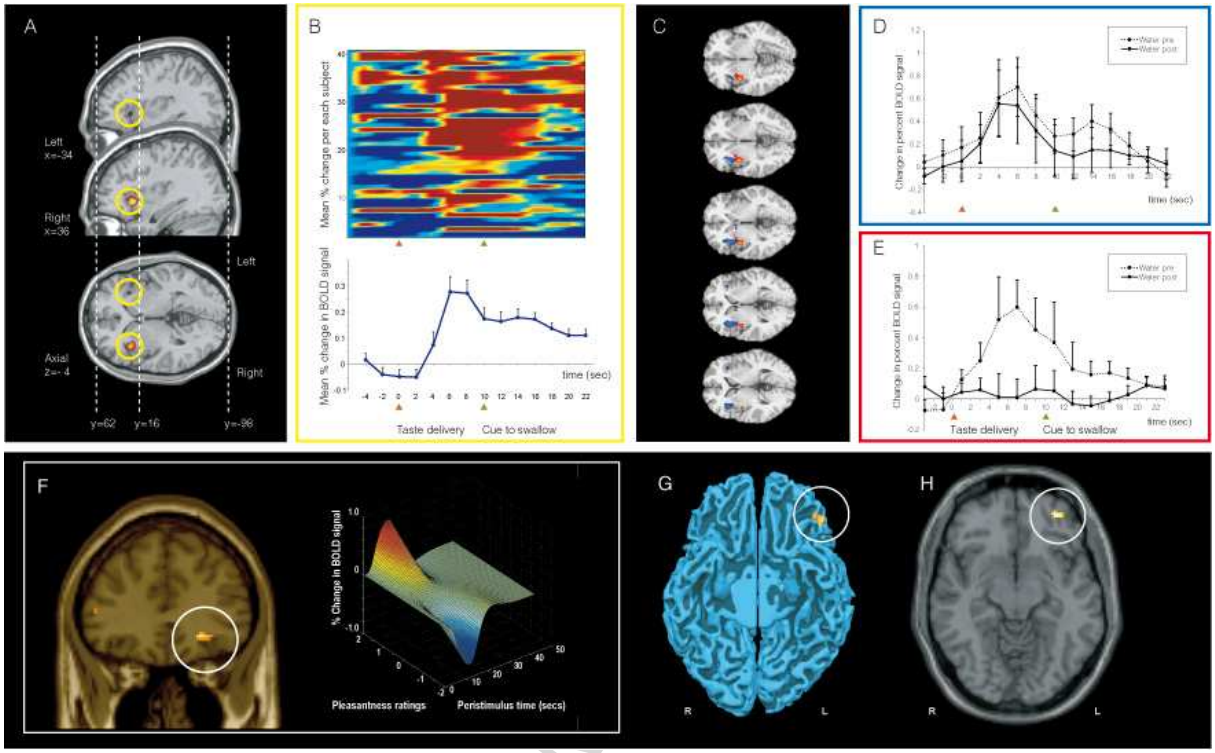

Figure 5. Principles of taste processing and pleasure. Activity in human primary taste cortex in the insula/operculum has not been found to be modulated by motivational state. **A)** Neuroimaging has located the primary human taste cortex in bilateral anterior insular/frontal opercular cortices (yellow circles) with peak MNI coordinates of [x,y,z: 38,20,–4] and [x,y,z: –32,22,0] (top two sagittal and axial slices) (Kringelbach *et al.*, 2004). This is based on 40 dataset from four experiments with eight unimodal and six multimodal taste stimuli ranging from pleasant to unpleasant and found, in concordance with data from non-human primates. **B)** The time course of blood oxygen-level detection (BOLD) activity in right primary taste cortex is shown for all forty subjects (top), and averaged across all (bottom) (for taste minus tasteless solution). **C.** In contrast dissociable parts of the insula were active in the multistage processing of identity and valance. Axial slices showing the extent of primary taste cortex (in blue) which is *not* modulated by thirst. This in contrast to a region of right mid-insula (in red) which is modulated by thirst (De Araujo *et al.*, 2003b). **D)** Time courses of activity extracted from the cluster in right primary taste cortex (blue) with respect to the delivery of water shown separately for the pre-satiety and post-satiety states. **E)** Time courses from the cluster in mid-insula cortex (red) showing significantly modulatory effects of water between motivational states when satiated and thirsty. **F)** The subjective pleasure of food has been found to be represented by the activity in a mid-anterior site of the orbitofrontal cortex in a study of selective-satiety (Kringelbach *et al.*, 2003), **G)** in a study of supra-additive effects combining the umami tastants monosodium glutamate and inosine monophosphate (De Araujo *et al.*, 2003a), and **H**) in a study of supra-additive effects combining strawberry odor with sucrose taste solution (De Araujo *et al.*, 2003b).

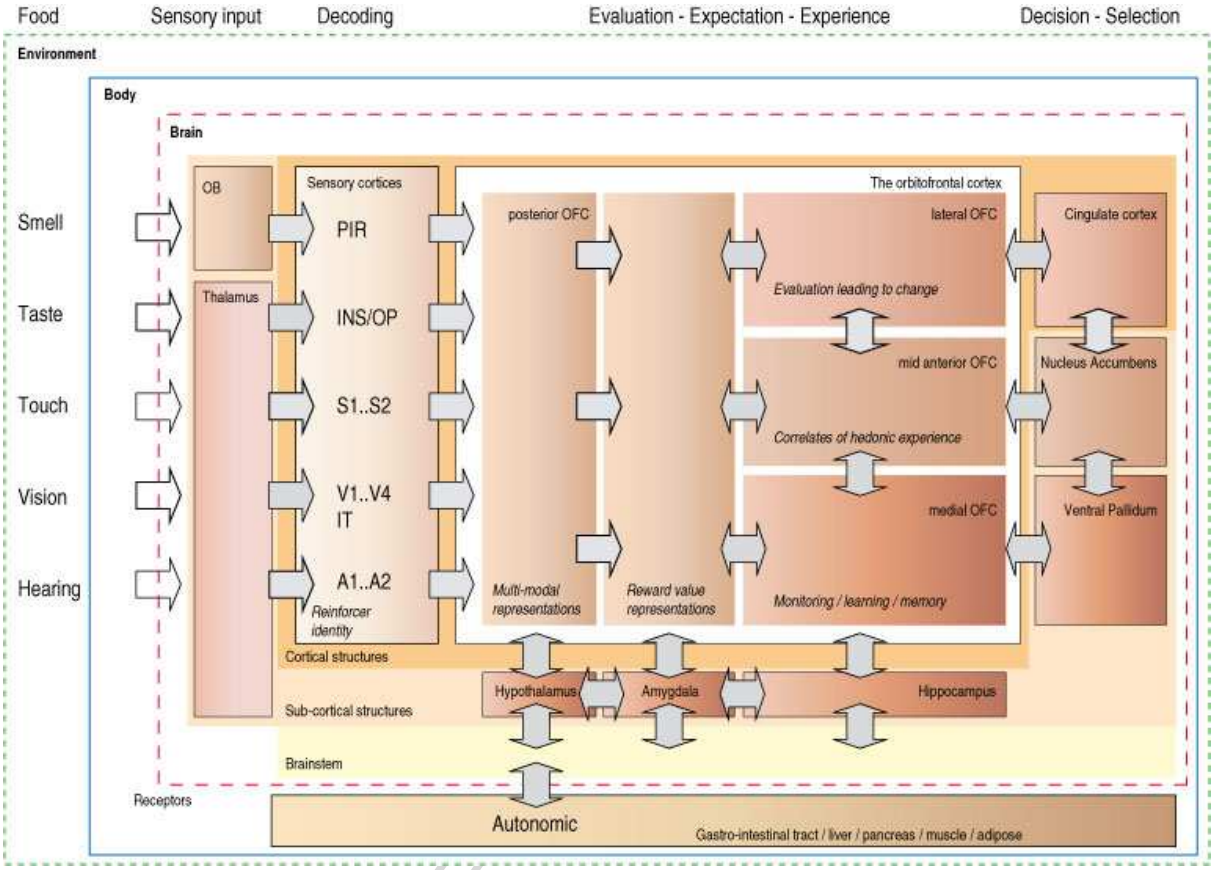

Figure 6. Converging brain pathways in the brain processing of food stimuli.

The figure summarises the interactions with environment to procure suitable food sources with a special focus on the role of the orbitofrontal cortex. Potential food sources are identified on the basis of the sensory input, which through the appropriate receptors are relayed to the orbitofrontal cortex, where processing is taking place of evaluation, expectation, experience as well as decision and selection. Here the input is processed in the primary sensory cortices via the thalamus (except for olfaction) and made available for pattern-association between primary (e.g. taste) and secondary (e.g. visual) reinforcers. Stimulus sensory identities are then processed for multimodal perceptual integration in the posterior orbitofrontal cortex. Hedonic reward value is represented in more anterior parts of orbitofrontal cortex, from where it can then be used to influence subsequent behaviour (in lateral parts of the anterior orbitofrontal cortex with connections to anterior cingulate cortex), stored for valence learning/memory (in medial parts of the anterior orbitofrontal cortex) and made available for subjective hedonic experience (in mid-anterior orbitofrontal cortex). There are multiple modulatory brain-loops with other important structures such as the nucleus accumbens, ventral pallidum, hippocampus, amygdala and hypothalamus, as well as modulation with autonomic input from the gut. *Abbreviations: V1, V2, V4, primary and secondary visual areas; SS, somatosensory cortex (3,1,2); A1..A2, auditory cortex; INS/OP, insular cortex/frontal operculum; IT, inferior temporal visual cortex; PIR, piriform cortex; OB, olfactory bulb; OFC, orbitofrontal cortex. From (Kringelbach and Stein, 2010).*

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Highlights

>> Food ensures survival as a source of pleasure and well-being >> In order to survive, brain must optimize resource allocation for reward pursuit. >> Food intake follows a similar cyclical time course to other rewards with phases related to expectation, consummation and satiety. >> Multilevel model for the full cycle of eating behaviour with mechanisms initiating, sustaining and terminating eating. >> Focus on how wanting, liking and learning governs human food intake. >> Five of main processing principles controlling food intake are presented. >>Progress is being made in understanding brain networks supporting the food pleasure cycle.