

## CHAPTER

## 2

# Cortical Systems Involved in Appetite and Food Consumption

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Food intake consumption and the control of appetite rely on cortical processing in humans and other primates to a much larger degree than other mammals. This review describes the evidence from neurophysiology, neuropsychology, and neuroimaging. Four main computational principles are proposed: (1) motivation-independent processing of identity and intensity; (2) formation of learning-dependent multimodal sensory representations; (3) reward representations using mechanisms including selective satiation, and (4) representations of hedonic experience, monitoring/learning, or direct behavioral change. A model incorporating these computational principles is proposed for

the orbitofrontal cortex, which is one of the most important nodes linking sensory and hedonic systems involved in appetite and food consumption in the human brain.

## I. INTRODUCTION

Human food intake relies on a complex hierarchy of cortical processing which include obtaining stable sensory information, evaluation for desirability, and choosing the appropriate behavior. Part of this processing is linked to basic homeostatic regulation, which has been elucidated in great details in animal models with mammals, including humans sharing many

subcortical circuits and molecules (such as leptin and ghrelin) as outlined elsewhere in this book and in other recent reviews (Saper et al., 2002).

However, human food intake is not only regulated by homeostatic processes as illustrated by our easy overindulgence on sweet foods beyond homeostatic needs and the epidemic proportions of obesity, which has become a major health problem (Kohn and Booth, 2003). Instead the regulation of human food intake relies on the interaction between homeostatic regulation and hedonic pleasure. This complex subcortical and cortical processing involves higher order processing, including learning, memory, planning, and prediction, and gives rise to conscious experience of not only the sensory properties of the food (such as the identity, intensity, temperature, fat content, and viscosity) but also the valence elicited by the food (including, most importantly, the pleasure experienced) (Kringelbach, 2005).

This chapter reviews the evidence linking cortical regions of the human brain to aspects of human food intake including appetite and food consumption. This evidence was obtained through neurophysiological findings in other primates and then further elaborated in human neuroimaging and neuropsychology studies.

The emphasis on cortical processing in humans and other primates relies on the direct projection from the rostral part of the nucleus of the solitary tract, which is different from the pontine taste area and associated subcortical projections found in rodents (Norgren, 1984; Pritchard et al., 1986). It is proposed here that the human brain utilizes at least four main computational principles underlying food intake. First, the identity of a food is established in primary cortical areas which contain neural activity that encode the sensory (taste, smell, somatosensory, auditory, and visual) aspects of the food. These cortical representations are to a large extent invariant and thus independent of current motivational

state (such as hunger or thirst). Second, this multitude of unimodal sensory information is subsequently combined to form multimodal representations in polysensory cortical regions (including the orbitofrontal cortex). These multimodal representations use slowly acting learning mechanisms to associate taste, smell, and other sensory food information. Third, reward representations are computed in further cortical regions by taking into account the desirability of a food, the current motivational state, and previous learned associations. These reward representations include selective satiation mechanisms that selectively suppress further food intake of previously ingested foods while other foods can still be readily ingested. Fourth, these reward representations may either result directly in behavioral change or in stable monitoring, learning, and memory processing. This cortical processing may also lead to subjective hedonic experience of the food, which is correlated with neural activity in circumscribed regions of the orbitofrontal cortex. This link between food intake and hedonic experience may still yield important insights into the core of subjective experience and is thus a promising avenue for further research with wide-ranging consequences.

## II. FOOD MOTIVATION

Food motivation (and motivation in general) is closely related to emotion and is generally defined in opposition to cognition as that which moves us in some way, as implied by the common Latin root of both words (*movere*, to move). It is only recently that the fields of motivation and emotion have tended to go different ways, and have in the past been considered together (Gray, 1975; Papez, 1937; Weiskrantz, 1968). One often-used functional distinction between motivation and emotion is that motivated behaviors are elicited by rewards (and punishers) related to internal homeostatic states

associated with, say, hunger and thirst, while emotional states and behaviors are elicited by the great majority of rewards and punishers that are external stimuli and not associated with these internal need states (Rolls, 1999).

The field of emotion research has advanced tremendously (Kringelbach, 2004a), and may provide conceptualizations that could benefit the field of motivation and motivational hedonics. One important insight from emotion research is to divide the concept of emotion into two parts: the *emotional state* that can be measured through physiological changes such as autonomic and endocrine responses, and *feelings*, seen as the subjective experience of emotion. The emotional state relies on basic implicit brain mechanisms, which are rarely available for immediate conscious introspection. We do, however, appraise our emotional state on a regular basis and this conscious appraisal must partly rely on interfacing our language system with some introspection of our current emotional state. One could argue that a very similar division could be made for motivational processes, where the motivational state relies on basic brain mechanisms that can subsequently be appraised or evaluated as hedonic experience.

Historically, early drive theories of motivation proposed that hedonic behavior is controlled by need states (Hull, 1951). But these theories do not, for example, explain why people still continue to eat when sated. This led to theories of incentive motivation where hedonic behavior is mostly determined by the incentive value of a stimulus or its capacity to function as a reward (Bindra, 1978). Need states such as hunger are still important but only work indirectly on the stimulus' incentive value. The principle of modulation of the hedonic value of a consummatory sensory stimulus by homeostatic factors was labeled *alliesthesia* (from *allios*, changed, and *esthesia*, sensation) (Cabanac, 1971). A useful distinction has been proposed between two aspects of reward: hedonic impact and incentive

salience, where the former refers to the liking or pleasure related to the reward, and the latter to the wanting or desire for the reward (Berridge, 1996; Berridge and Robinson, 1998).

Food intake is a precisely controlled act that can potentially be fatal if the wrong decision is taken to swallow toxins, microorganisms, or nonfood objects on the basis of erroneously determining the sensory properties of the food. Humans have therefore developed elaborate food behaviors which are aimed at balancing conservative risk-minimizing and life-preserving strategies, with occasional novelty seeking in the hope of discovering new sources of nutrients (Rozin, 2001).

Food intake must provide the right balance of carbohydrates, fats, amino acids, vitamins, and minerals (apart from sodium) to sustain life. The neural mechanisms regulating food intake are complicated and must like any regulatory system include at least four features: system variables, detectors for the system variables, set points for these system variables, and correctional mechanisms. A simple regulatory feedback system operates best with immediate changes, and it becomes significantly more complex when the feedback is not immediate. In the case of controlling food intake, there are significant delays in system changes caused by relatively slow metabolic processes, and therefore the regulatory neural systems controlling food intake must include sophisticated mechanisms to learn to predict in advance when a meal should be initiated and terminated. Many of the basic components and principles of food intake have been elucidated in great detail and have been described in reviews elsewhere (LeMagnen, 1985; Woods and Stricker, 1999).

Most research in this area has been carried out in nonhuman animals, which has not helped us understand the strong hedonic component of human food intake which is directly linked to appetite. It is clear that much of complex human

behavior related to food intake must be linked to neural activity in the cerebral cortex integrating the complex multitude of stimuli and situational variables. Important examples of such complex behavior include the decrease of the rated pleasantness of sweet tastes when subjects are sated relative to when they are hungry (negative gustatory alliesthesia) (Cabanac, 1971) and satiation signals that selectively suppress further food intake of previously ingested foods while other foods can still be readily ingested (sensory-specific satiety) (Rolls et al., 1981).

### III. CORTICAL REPRESENTATIONS OF SENSORY INPUTS

All of the classic five senses (vision, hearing, smell, taste, and touch) are involved in the regulation of food intake. However, in addition to these sensory systems there are also other sensory receptors such as those in the digestive tract which are sensitive to gastric distension, or those in the circulatory system that are sensitive to changes in blood pressure or carbon dioxide gas in the blood.

Our sensory systems help identify and evaluate potential food sources. This can happen even from a distance using olfactory, visual, and (to some extent) auditory systems. Olfactory evaluation relies on receptors in the nose that are used to identify volatile airborne molecules. The sense of smell has limited use at longer distances and has to be aided by other more precise distance and directional senses such as the visual system (Gottfried and Dolan, 2003). Even at close range visual influences can override the olfactory system, such as demonstrated by experiments manipulating the olfactory perception of wine by artificially coloring a white wine red (Morrot et al., 2001).

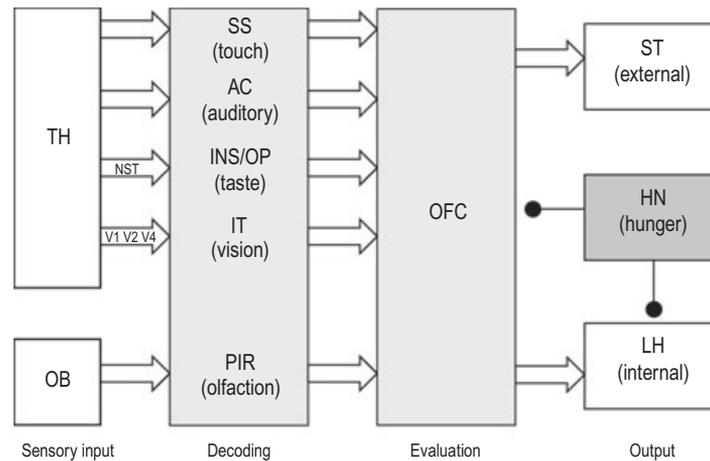
Foremost, of course, the sensing of food occurs when a food is grasped and deliv-

ered to the mouth. This includes taste, smell, and somatosensory (such as temperature, viscosity, pungency, and irritation) input primarily from our oral and nasal cavity (but also in rare cases from the eyes, such as in the case of irritation excreted from, e.g., onions). This sensory input is essential in making the vital decision of whether to swallow or reject a potentially poisonous food. 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, 1978).

An important computational principle of sensory processing in the brain is that the primary sensory cortices receive sensory information from receptor cells and process this information to form neural representations of the identity of the stimulus (see Fig. 1). It has been shown in other primates that this representation of stimulus identity remains to a large degree constant and is not modulated by motivational state (Rolls, 1999). This principle is important in forming stable and accurate representations of the world, and this unimodal information is then integrated further on in the hierarchy of cortical processing in the secondary and tertiary sensory cortices. Some of these multimodal representations can be modulated by motivational state which depends on hunger, thirst, and gastric distension but also on learned associations with pleasure states. This can then influence behavior both internally (via the hypothalamus and brainstem structures) and externally (via the motor systems).

#### A. The Taste System

Taste is sensed by taste receptor cells arranged in taste buds which are primarily found on the tongue but also on other areas in the oral cavity such as the soft palate, the pharynx, the larynx, and the epiglottis



**FIGURE 1** Schematic diagram of information flow linked to the orbitofrontal cortex. The orbitofrontal cortex receives input from all the sensory modalities: gustatory, olfactory, somatosensory, auditory, and visual. This information is then represented and made available for pattern association between primary (e.g., taste) and secondary (e.g., visual) reinforcers. The reward value of this representation can be modulated by hunger neurons (HN). The output from the orbitofrontal cortex to both striatum (external) and lateral hypothalamus (internal) can then lead to behavior. Abbreviations utilized: TH, thalamus; OB, olfactory bulb; NST, nucleus of the solitary tract; V1, V2, V4, primary and secondary visual areas; SS, somatosensory cortex (3,1,2); AC, auditory cortex; INS/OP, insula cortex/frontal operculum; IT, inferior temporal visual cortex; PIR, piriform cortex; OFC, orbitofrontal cortex; HN, hunger neurons; ST, striatum; LH, lateral hypothalamus.

(Scott and Plata-Salaman, 1999). Taste receptor cells are constantly being renewed and have a turnover period of between 7 to 10 days. As a convenient way of organizing the taste system, most researchers agree that there are four different taste qualities with specific receptor types: sweet (glucose, sucrose), salty (NaCl), sour (HCl, citric acid), and bitter (quinine). Some have also argued for the inclusion of the amino acid taste *umami* (of which an exemplar is monosodium glutamate) that corresponds to what is sometimes described as the taste of protein. The argument for including umami as a basic taste has received support from the recent discovery of specific receptors for glutamate in lingual tissue with taste buds (Chaudhari et al., 2000).

### 1. Central Taste Pathways

The taste information is relayed from the taste buds to the cortex by way of the nucleus of the solitary tract of the medulla and the parvocellular part of the ventral

posterior medial (VPMpc) nucleus of the thalamus. The three cranial nerves involved are the facial nerve (VII) which conveys information from the anterior two thirds of the tongue, the glossopharyngeal nerve (IX) which innervates the posterior third of the tongue, and the vagus nerve (X) which conveys information from the remaining taste buds from other areas in the mouth (Norgren, 1990). It should be noted that these cranial nerves also carry information about touch, temperature, and pain sensitivity on the tongue. These projections are primarily ipsilateral in higher primates (Pritchard et al., 1989) but other evidence suggests that crossed and bilateral projections may exist (Norgren, 1984, 1990).

In primates gustatory information is relayed to cortical areas via the VPMpc nucleus in the thalamus. In rats a further nonthalamic gustatory system synapses on the parabrachial taste nuclei before projecting directly to the amygdala and the hypothalamus (Norgren, 1984; Norgren and

Leonard, 1973), but this pathway has not been found in primates (Pritchard, 1991).

### 2. Primary Taste Cortex

The primary taste cortex is the next gustatory relay station from the VPMpc and is found in the frontal operculum and the dorsal part of the anterior insula (Bornstein, 1940a,b; Pritchard et al., 1986; Scott et al., 1986; Sudakov et al., 1971). Another smaller area of the anterior primary somatosensory cortex (area 3b) also receives taste information from the VPMpc (Norgren, 1990). Neurophysiological investigations in primates found that 4% of neurons in the primary taste cortex showed broadly tuned responses to different tastes and that responses of these neurons were more specific than neurons in the nucleus of the solitary tract (Ogawa et al., 1989; Scott et al., 1986). Other sensory information related to feeding such as temperature and somatosensory input from the mouth is processed by other neurons in the primary taste cortex (Norgren, 1990).

### 3. Higher Order Taste Cortices

Following the general principle of sensory processing, the responses of neurons in the primary taste cortex in primates are not influenced by motivational state and thus maintain stable neural properties for correctly decoding taste input (Yaxley et al., 1988). The primary taste cortex projects to the secondary taste cortex found in the adjoining caudolateral orbitofrontal cortex which does not receive projections from the VPMpc of the thalamus and is therefore defined as the secondary taste cortex (Baylis et al., 1994). Neurons in this region are more finely tuned than those found in the primary taste cortex and respond to single taste, whereas other neurons in more anterior and medial orbitofrontal cortex are more broadly tuned and some neurons have multimodal responses to both gustatory and olfactory (Rolls and Baylis, 1994). It has been pro-

posed that these multimodal neurons may encode the flavor of food.

Furthermore, it has been shown that the taste representation carried by neurons in the orbitofrontal cortex can be influenced by motivational states such that neurons will decrease their response to a taste when a food with this taste is being eaten to satiety but still respond to other foods not eaten to satiety—an effect known as sensory-specific satiety (Rolls, 1999).

Another important brain area receiving gustatory information is the lateral hypothalamus, where neurons were found to be modulated by hunger (Burton et al., 1976). Neurons responding to tastes have also been found in the amygdala, which may be part of a system involved in learning associations between primary taste reinforcers and other arbitrary stimuli (Sanghera et al., 1979). Such a system would be important for reliably selecting food for ingestion.

Further brain areas receiving taste information include the ventral striatum (including the nucleus accumbens and the olfactory tubercle), which could interface reward signals with initiation of action in output motor systems (Williams et al., 1993).

### 4. Human Lesion Studies

The literature on patients with gustatory symptoms is rather sparse. One of the first studies found ageusia in patients with bullet wounds to the parietal operculum and thus established this site as the most probable for the human primary taste cortex (Bornstein, 1940a,b). This was extended to the insula following the observations by Penfield and Faulk (1955) of a patient with an aura of unpleasant taste stemming from a tumor in the insula. Further support came from cortical stimulation of the insula in epileptics, which was found to elicit taste perception. In a more recent study, gustatory auras were found in three patients with magnetic resonance imaging evidence of lesions to the insula (Cascino and Karnes, 1990).

Published case studies of gustation in patients with surgical lesions are even more rare. Only two studies have been published to date and both studies concern detection and recognition thresholds in patients with resection of the temporal lobe for intractable epilepsy (Henkin et al., 1977; Small et al., 1997b). Both studies found normal detection thresholds in the patients but differed in their results on how recognition thresholds were affected by the lesions. Small and colleagues (1997b) found a general impairment in recognizing citric acid in their group of patients with right surgical resection of the temporal lobe, while Henkin and colleagues (1977) found a deficit for recognizing citric acid in their patient group with *left* resection. This discrepancy is not easily resolved and more data are clearly needed. Yet, these experiments show that the anterior temporal lobe is involved in the recognition of taste quality. The observed deficits in patients in recognizing taste are likely to be due to the disconnection of the amygdala, orbitofrontal cortex, and interacting brain areas in temporal lobectomy.

### 5. Neuroimaging Studies of Taste

The functional neuroimaging of taste in humans has been delayed due to a number of methodological challenges. Taste experiments naturally involve some tongue, mouth, and swallowing related movement, which have been seen as problematic by some investigators. Early investigators used manual application and removal of taste stimuli from the tongue of the subject, which created more problems than it solved, given that it still involved mouth movement and would not necessarily elicit the best taste response.

Most investigators are therefore using tubes that deliver the taste directly to the oral cavity and the taste is subsequently swallowed. A control stimulus applied in exactly the same fashion can then serve to act as control for movement. It is important that the control stimulus is not water

because water is a primary reinforcer that animals will work for. Thus neurons in primary and secondary gustatory cortex have been found to respond to water when thirsty (Rolls et al., 1990). Instead, the best option currently available is to use a tasteless control substance containing the main ionic components of saliva.

*i. Motivation-Independent Taste Representations* The early neuroimaging studies were affected by the methodological challenges mentioned but have in general corroborated the findings from human lesions studies and the neurophysiological findings in primates. The primary gustatory area in humans has been found to be located in the anterior insula/frontal operculum (Frey and Petrides, 1999; Kinomura et al., 1994; O'Doherty et al., 2001b; Small et al., 1997a, 1999).

The largest functional magnetic resonance imaging (fMRI) study of taste processing to date used 40 data sets from 38 right-handed subjects (13 women and 25 men, of which two subjects participated in two experiments) in four taste investigations that used (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 taste, olfactory, and somatosensory stimulation) ranging from pleasant to unpleasant were used in the four experiments. The main analysis included both unimodal and multimodal taste stimuli, which was then confirmed in a separate analysis using only unimodal taste stimuli.

Stringent random effects analysis of taste activation across the 40 data sets revealed three cortical activation foci to the main effects of taste in the human brain (which were corrected for multiple comparisons). Bilateral activation of the anterior insular/frontal opercular cortex was found with a

slightly stronger response on the right side. The locations in standard brain space in Montreal Neurological Institute (MNI) coordinates:  $[x,y,z: 38,20,-4]$  and  $[x,y,z: -32,22,0]$  are the likely bilateral sites of the primary taste cortices. 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 peak to taste fall in the right hemisphere (Small et al., 1999).

Taste stimuli also produced activation in the medial caudal orbitofrontal cortex. The location in MNI coordinates:  $[x,y,z: 6,22,-16]$  is likely to coincide with the secondary taste cortex, which fits well with neurophysiological recordings in medial parts of the macaque orbitofrontal cortex (Pritchard et al., 2005).

In addition, activation was also found in the left dorsolateral prefrontal cortex in the posterior part of the middle frontal gyrus (Brodmann Area 46):  $[x,y,z: -42,26,36]$ . This could aid higher cognitive processes in guiding complex motivational and emotional behavior. The finding is consistent with neurophysiological recordings in the dorsolateral prefrontal and orbitofrontal cortices in nonhuman primates in a reward preference task (Wallis and Miller, 2003). This experiment demonstrated that neurons in the dorsolateral prefrontal cortex encode both the reward amount and the monkeys' forthcoming response, while neurons in the orbitofrontal cortex more often encode the reward amount alone. Furthermore, the reward selectivity arose more rapidly in the orbitofrontal cortex than the dorsolateral prefrontal cortex, which is consistent with the idea that reward information enters the prefrontal cortex via the orbitofrontal cortex, where it is passed to the dorsolateral prefrontal cortex and used to control behavior. The finding is also consistent with a monkey PET (positron emission tomography) study on olfactory and gustatory processing that found activation of the inferior frontal gyrus (Kobayashi et al., 2002).

Furthermore, at a lower statistical threshold, taste-related activity was found in the anterior cingulate cortex:  $[x,y,z: 8,18,50]$ ;  $p < 0.001$ , uncorrected for multiple comparisons]. Quite a few other studies have found taste-related activations in the cingulate cortex (De Araujo et al., 2003a,b,c; Francis et al., 1999; Kringelbach et al., 2003; O'Doherty et al., 2001b, 2002; Small et al., 2003; Zald et al., 1998, 2002). Regions of the anterior cingulate cortex thus may contain taste-related activity which can help the role of this region in executive control.

*ii. Reward-Dependent Taste Representations* In contrast to these motivation-independent representations of reinforcer identity, one neuroimaging study was able to dissociate the brain regions responding to taste intensity and taste affective valence (Small et al., 2003). It was found that the cerebellum, pons, middle insula, and amygdala responded to intensity regardless of valence, while 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 study used neuroimaging to show that subjective ratings of taste pleasantness (but not intensity) correlate with activity in the orbitofrontal cortex and in the anterior cingulate cortex (De Araujo et al., 2003b). Moreover, in this study investigating the effects of thirst and subsequent replenishment, it was found that the orbitofrontal cortex and a region of mid-insula was correlated with subjective pleasantness ratings of water across the whole experiment (De Araujo et al., 2003b).

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 umami taste that occurs when 0.005M inosine 5'-monophosphate is added to 0.5M monosodium glutamate (compared to both delivered separately) was correlated with increased activity in an anterior part of the orbitofrontal cortex (see Fig. 2b) (De Araujo et al., 2003a).

## B. The Olfactory System

Smell is sensed by olfactory receptors placed in the upper part of the nasal cavity. There are about 100 million bipolar olfactory cells in humans with lifelong continuous replacement every 4–8 weeks from stem cells in the sensory epithelium. Each bipolar olfactory cell bears up to a thousand hairs (cilia), which are the points of contact for aromatic molecules. The cilia must be moistened continuously by mucous glands roughly every 10min to avoid desiccation. The mucus consists of a water base with dissolved mucopolysaccharides, salts, and proteins, including odorant binding proteins, enzymes, and antibodies (which help protect the brain from odorant-borne illnesses).

The specific olfactory receptor proteins are genetically specified by about 1000 different genes (Buck and Axel, 1991), which correspond to the largest family of genes found in humans and underlie the profound importance of smell in humans. The resulting number of unique odors which can be discriminated is likely to be on the order of around half a million odors (Mori et al., 1998).

The main olfactory system relies on these receptors for the conscious perception of odors but also relies on the trigeminal system mediating somatosensory information such as irritation, tickling, burning, and cooling of odors. In addition, other animals have a vomeronasal system which plays a major role in the perception of pheromones that are extremely important in controlling reproduction and related sexual behavior including aggression. It

remains highly controversial whether humans have a vomeronasal olfactory system (VNO, also called Jacobson's organ) (Monti-Bloch et al., 1998), although the presence of such a system (operating non-consciously) has been proposed to mediate pheromones synchronizing the menstrual cycle of cohabiting women (Stern and McClintock, 1998). Although nearly all humans have paired VNO-like structures at the base of the septum and paired VNO ducts near the posterior aspect of the external nares, the human VNO appears to lose receptor cells and associated neural elements in the second trimester of pregnancy (Smith and Bhatnagar, 2000). The human VNO thus appears to lack basic elements needed for a functioning VNO and is therefore most likely a nonfunctioning unit (Bhatnagar and Meisami, 1998).

### 1. Primary Olfactory Cortex

Olfactory receptor neurons run through the bony cribriform plate to the ipsilateral olfactory bulb forming the first cranial nerve. The input layer in each olfactory bulb contains several thousand glomeruli (Royet et al., 1988). Within a glomerulus, several thousand primary olfactory axons converge and terminate on the dendrites of a few hundred second-order olfactory relay neurons. The projections of these neurons form the olfactory tract.

The axons in the lateral olfactory tract run ipsilateral through the olfactory peduncle synapsing on the anterior olfactory nucleus, the piriform cortex, the periamygdaloid cortex, the anterior cortical nucleus of the amygdala, and the anteromedial part of the entorhinal cortex. These cortical areas receiving direct projections from the lateral olfactory tract by definition constitute the primary olfactory cortices. Olfaction is unique among the senses in that the sensory information is not relayed via the thalamus (Carmichael et al., 1994). In higher primates (including humans) the primary olfactory cortex is situated near the border of the dorsomedial anterior temporal lobes and the

caudolateral part of orbitofrontal cortex. In the human brain the piriform cortex is also located anatomically at this junction of the temporal and frontal lobes based on its cytoarchitectonic definition (Eslinger et al., 1982).

The projections from the olfactory bulb are all primarily ipsilateral although there are contralateral connections running through the anterior commissure via the anterior olfactory nucleus and the anterior piriform cortex.

## 2. Higher Order Olfactory Cortices

Numerous brain regions receive projections from the primary olfactory cortex including the orbitofrontal cortex, medial thalamus, ventral striatum and pallidum, agranular insular cortex, hippocampus, and medial and lateral hypothalamus. One of the most important olfactory pathways converges on the orbitofrontal cortex, and experiments in nonhuman primates have shown olfactory areas in the posterior orbitofrontal cortex (Takagi, 1986; Tanabe et al., 1975a,b) and in the medial central posterior orbitofrontal cortex (part of area 13) (Carmichael et al., 1994; Takagi, 1986; Yarita et al., 1980). These regions of the orbitofrontal cortex then, by definition, constitute the secondary olfactory cortices (Rolls and Baylis, 1994) and have onward connections to the secondary taste cortex (Carmichael et al., 1994; Carmichael and Price, 1994).

Single-neuron activity in the orbitofrontal cortex was recorded during an olfactory discrimination task, where behavioral responses following eight odors were rewarded with sucrose while responses following two other odors were punished with saline (Rolls and Baylis, 1994). It was found that 3.1% of the 1580 neurons recorded had olfactory responses and that 2.2% responded differentially to the different odors in the task. The findings showed that a 65% subset of olfactory representation within the orbitofrontal cortex reflects the odor irrespective of its reward

association and that the remaining 35% reflects the taste associations of the odor.

Further neurophysiological investigations of orbitofrontal cortex neurons with olfactory responses were carried out in a series of experiments using an olfactory discrimination task where the taste reward contingencies of two odors were reversed once they had been successfully acquired (Rolls et al., 1996). Of the 28 odor-responsive neurons analyzed it was found that 68% of these neurons modified their responses following changes in taste reward associations, with 25% of the neurons reversing their responses and task-reversal extinction of differential neuronal responses seen in 43% of the neurons. The remaining 32% of the neurons did not change their responses. This modification of odor-taste reward associations was found to be much slower and inflexible than visual-taste associations which usually take place with one-trial learning (Thorpe et al., 1983). This relative inflexibility of olfactory responses could be important for forming stable odor-taste associations needed for the formation and perception of flavors.

## 3. Human Lesion Studies

The bulk of patients studied for olfactory processing are patients who have undergone surgery for intractable epilepsy. Almost all patients therefore have unilateral selective surgical excisions to the temporal lobes, while only a few cases have lesions in the frontal lobes. Most olfactory studies have investigated detection thresholds, odor identification, quality discrimination, and odor memory in such patients. Across these studies there is great variation with regards to stimulation type (mono- or binhinal), stimuli type (e.g., odors are presented from bottles, on cotton wands, or on paper labels) and number of stimuli. With such variation it is hard to draw firm conclusions but all studies have shown that detection thresholds have been shown to be unimpaired following lesions of the

anterior temporal lobe (Henkin et al., 1977; Jones-Gotman and Zatorre, 1988). This would suggest that odor detection is computed earlier in the olfactory pathways or perhaps in a parallel pathway (Zatorre et al., 2000). Mild deficits with discrimination of odor quality have been found in patients with temporal lobe excision although they appear to be confined to the ipsilateral nostril (Zatorre and Jones-Gotman, 1991). The temporal lobes also appear to be involved in odor memory, odor identification (Jones-Gotman et al., 1994, 1997), and affective responses and intensity judgments (Rouby et al., 1997). The relatively mild deficits following temporal lobe excisions should be contrasted with the odor deficits in patients with lesions to the orbitofrontal cortex, which cause severe impairments to all aspects of odor processing except odor detection (Jones-Gotman and Zatorre, 1993). This fits well with the neurophysiological data from primates where the frontal and in particular the orbitofrontal cortex appear to play a more important role in olfactory processing (Rolls and Baylis, 1994).

The evidence for hemispheric specialization in odor processing in patients is not very clear. Some studies find a right hemispheric dominance in patients with right-sided lesions (Eskenazi et al., 1983; Jones-Gotman and Zatorre, 1993), whereas other studies find olfactory deficits following left hemisphere lesions (Henkin et al., 1977; Jones-Gotman et al., 1994). There does, however, seem to be more patient studies implicating the right hemisphere in olfaction although the numbers are too small to be significant. It would also be interesting to look at the performance of patients with bilateral surgical lesions.

#### 4. Neuroimaging Studies of Olfaction

Relatively few neuroimaging studies have investigated olfaction. Most of those have dealt with the identification of the human brain areas involved in odor processing in general. Specifically brain activ-

ity in the piriform cortex, which is part of the primary olfactory cortices, has proven quite difficult to detect. Lately neuroimaging studies have started to explore brain activity related to hedonic processes.

Some of the main difficulties with imaging olfactory processes are that they involve brain structures from which it is quite hard to get a good signal with fMRI because their proximity to air- and bone-tissue gives rise to susceptibility artefacts and geometric distortion (Wilson et al., 2002). Such problems are virtually absent when using PET, but instead other problems arise with imaging brain regions such as the piriform cortex exhibiting fast habituation, which is problematic given the temporal resolution of PET.

*i. Motivation-Independent Odor Representations* Similar to taste stimuli, pure olfactory stimuli activate dissociable brain areas for motivation-independent representations of reinforcer identity and hedonic representations. Neuroimaging studies have found representations of olfactory identity in primary olfactory cortices (Anderson et al., 2003; Gottfried et al., 2002a; O'Doherty et al., 2000; Rolls et al., 2003a; Royet et al., 2000, 2001; Zald and Pardo, 1997), which are distinct from hedonic representations in other brain areas.

Zatorre and colleagues (1992) were among the first to present PET data of odor processing in normal volunteer subjects. Two conditions were used which both involved birhinally sniffing for seven seconds from a cotton wand which was either odorless in the control condition or one of eight different odorants. Activation was seen bilaterally in a region at the junction of the temporal and frontal lobes in what probably corresponds to primary olfactory cortex. Further activation was also seen in the right orbitofrontal cortex, prompting the authors to claim a hemispheric asymmetry in olfactory processing. It is interesting to note, however, that activity just below the chosen threshold was

also seen in left orbitofrontal cortex (Zatorre et al., 2000). The asymmetry argument for olfactory is weak as demonstrated in a large meta-analysis of neuroimaging studies (Kringelbach and Rolls, 2004). While some studies found similar asymmetric activations in the orbitofrontal cortex (Dade et al., 1998; Small et al., 1997a; Sobel et al., 1998), other studies have found activation exclusively in the left orbitofrontal cortex (Francis et al., 1999; Gottfried et al., 2002a; Rolls et al., 2003a; Yousem et al., 1997; Zald and Pardo, 1997).

*ii. Reward-Dependent Odor Representations* Several neuroimaging studies have found dissociable encoding of olfactory stimuli with the intensity encoded in the amygdala and nearby regions, and the pleasantness correlated with activity in the orbitofrontal cortex and anterior cingulate cortex (Anderson et al., 2003; Gottfried et al., 2002b; Rolls et al., 2003a). This is consistent with studies that have found that hedonic judgments activate the orbitofrontal cortex (Royet et al., 2001) and that the unpleasantness of aversive odors correlates with activity in the 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 recent 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 which measured the brain activity related to two arbitrary visual stimuli both before and after olfactory devaluation (Gottfried et al., 2003). In the amygdala and the orbitofrontal cortex, responses evoked by a predictive target stimulus were decreased after devaluation, whereas responses to the non-devalued stimulus were maintained. 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. It should also be noted that the affect and intensity judgments of odor in a paired discrimination task activates the orbitofrontal cortex (Zatorre et al., 2000).

### C. Multimodal Integration

In addition to multimodal information from taste and smell, decisions about food intake also integrate, for example, somatosensory information, which is sensed by receptors in the oral and nasal cavity. This sensory information includes temperature, viscosity, fat content, pungency, and irritation and is mediated by a large variety of neural systems. This integrated information is processed and made available for the crucial decision of ingestion or rejection of a potentially poisonous food (although, as mentioned before, simple brainstem mechanisms also exist).

Food consumption relies on swallowing, which in itself is a complex physiological process that involves numerous central processes including sensorimotor integration, reflexive and voluntary motor activity, autonomic regulation, and salivatory processes. Emphasis has been placed on the brainstem control of swallowing (Jean, 1984, 2001) but recently noninvasive neuroimaging techniques has revealed some of the cortical areas involved in reflexive and voluntary swallowing (Hamdy et al., 1999a,b; Martin et al., 2001; Martin and Sessle, 1993; Zald and Pardo, 1999). Dysphagia is caused by a variety of neurological disorders with, for example, up to one-third of patients suffering unilateral hemispheric stroke (Barer, 1989; Gordon et al., 1987), which may reflect the widespread network involved in swallowing.

Furthermore, once a decision regarding ingestion or rejection has been taken it is important that this choice is integrated in the cortical processes governing learning, memory, planning, and prediction. It is

also important that further information from the autonomic system about internal states such as hunger, thirst, nausea, and gastric distension are integrated in these processes.

Differences have been reported in olfactory experience depending on whether a smell reaches the nasal cavity through the nose (orthonasal) or mouth via the posterior nares of the nasopharynx (retronasal) (Pierce and Halpern, 1996), which is likely to be related to differences in somatosensory influences (e.g., mastication). Consequently, several neuroimaging studies have found differences in cortical activation patterns between ortho- and retronasal olfaction (Cerf-Ducastel and Murphy, 2001; De Araujo et al., 2003c; Small et al., 2005).

As mentioned previously, an important principle of cross-modal integration between taste and smell is the formation of odor-taste associations, which are required to be more stable than, say, visual-taste associations to facilitate the formation and perception of flavors which guide food intake (Rolls et al., 1996). Within the orbitofrontal cortex there are direct projections from secondary olfactory cortices to the secondary taste cortices (Carmichael et al., 1994; Carmichael and Price, 1994). Neurophysiological recordings have found that odor-taste reward associations are much slower and inflexible (Rolls et al., 1996) than visual-taste associations which usually take place with one-trial learning (Thorpe et al., 1983).

#### D. Hedonic Representations

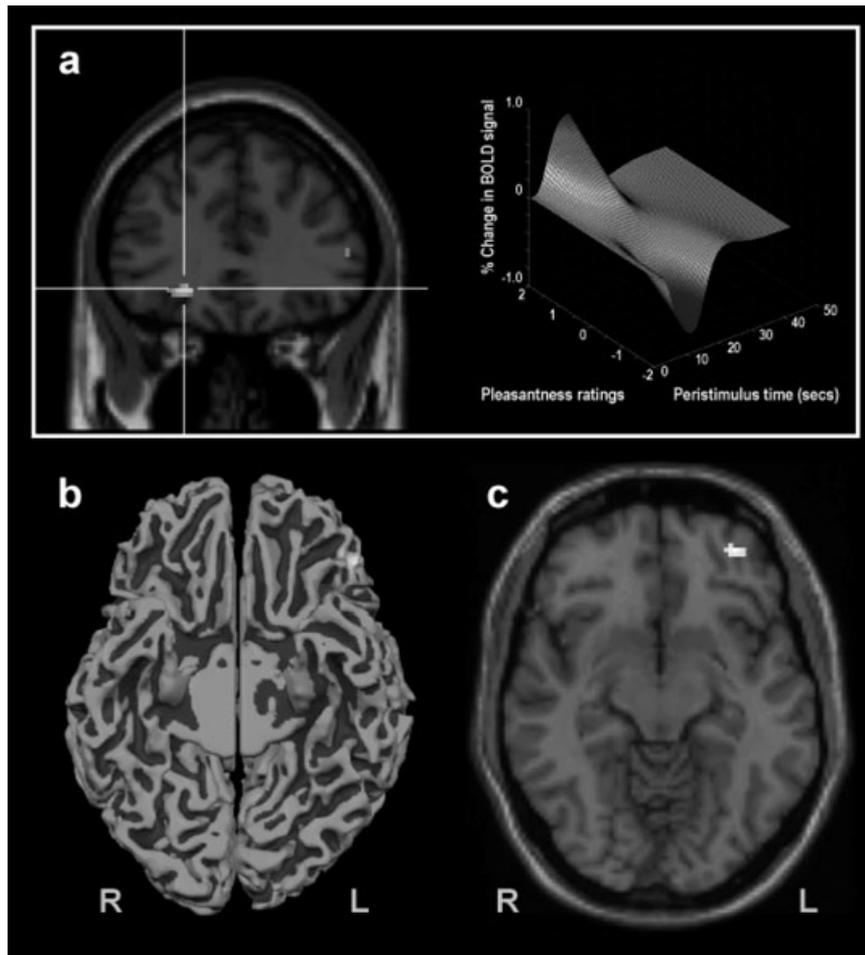
The evidence from neuroimaging studies of pure taste and smell cited previously shows that the orbitofrontal cortex is consistently correlated with the subjective pleasantness ratings of the stimuli. Therefore, it is to be expected that studies using multimodal combinations of taste and smell should find correlations between pleasantness and activity in these brain regions.

Compelling evidence that this is indeed the case comes from a sensory-specific satiety neuroimaging study which has shown that a region of the left orbitofrontal cortex showed not only a sensory-specific decrease in the reward value to the whole food eaten to satiety (and not to the whole food not eaten), but also a correlation with pleasantness ratings (see Fig. 2a) (Kringelbach et al., 2003). This result strongly indicates that the reward value of the taste, olfactory, and somatosensory components of a whole food are represented in the orbitofrontal cortex, and that the subjective pleasantness of food thus might be represented here.

Further evidence comes from a study investigating the nonspecific 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).

Other multimodal neuroimaging studies have investigated the interaction between taste and smell, and found significant activity in more posterior parts of the orbitofrontal cortex and nearby agranular insula for the combination of taste and smell (De Araujo et al., 2003c; Small et al., 1997a). 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 activated (see Fig. 2c) (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 (De Araujo et al., 2003a).

Further neuroimaging studies have investigated the hedonic systems involved in other sensory modalities and, consistent with the results obtained with food relevant stimuli, activations were found that link



**FIGURE 2** Hedonic experience. (a) A neuroimaging study using selective satiation found that mid-anterior parts of the orbitofrontal cortex are correlated with the subjects' subjective pleasantness ratings of the foods throughout the experiment (Kringelbach et al., 2003). On the right is shown a plot of the magnitude of the fitted hemodynamic response from a representative single subject against the subjective pleasantness ratings (on a scale from -2 to +2) and peristimulus time in seconds. (b) Additional evidence for the role of the orbitofrontal cortex in subjective experience comes from another neuroimaging experiment investigating the supra-additive effects of combining the umami tastants monosodium glutamate and inosine monophosphate (De Araujo et al., 2003a). The figure shows the region of mid-anterior orbitofrontal cortex showing synergistic effects (rendered on the ventral surface of human cortical areas with the cerebellum removed). The perceived synergy is unlikely to be expressed in the taste receptors themselves and the activity in the orbitofrontal cortex may thus reflect the subjective enhancement of umami taste which must be closely linked to subjective experience. (c) Adding strawberry odor to a sucrose taste solution makes the combination significantly more pleasant than the sum of each of the individual components. The supralinear effects reflecting the subjective enhancement were found to significantly activate a lateral region of the left anterior orbitofrontal cortex, which is remarkably similar to that found in the other experiments (De Araujo et al., 2003c).

hedonic processing to activity in the orbitofrontal cortex. In a study of thermal stimulation it was found that the perceived thermal intensity was correlated with activity in the insula and orbitofrontal cortices

(Craig, 2002; Craig et al., 2000). In another study investigating the effects of touch to the hand it was found that dissociable regions of the anterior cingulate and orbitofrontal cortex were activated by

painful and pleasant (but not neutral) touch (Rolls et al., 2003b). Another pain study found that the lateral orbitofrontal cortex and the anterior cingulate cortex are mediating the placebo effect in placebo responders (Petrovic et al., 2002). Studies investigating the effects of auditory stimulation and music have found that activation of the orbitofrontal cortex correlates with the negative dissonance (pleasantness) of musical chords (Blood et al., 1999) and that intensely pleasurable responses (chills) elicited by music are correlated with activity in the orbitofrontal cortex, ventral striatum, cingulate, and insula cortex (Blood and Zatorre, 2001).

Even more abstract reinforcers such as monetary reward (O'Doherty et al., 2001a; Thut et al., 1997) and punishment (O'Doherty et al., 2001a) have been found to activate the orbitofrontal cortex, and there is evidence to suggest that dissociable regions of the medial and lateral orbitofrontal cortex correlate with the amount of monetary gain and loss, respectively (O'Doherty et al., 2001a). More generally, it has been demonstrated by another neuroimaging study that the lateral orbitofrontal cortex and a region of the anterior cingulate cortex are together responsible for supporting general reversal learning in the human brain (Kringelbach and Rolls, 2003). Further compelling evidence from drug studies have found responses to cocaine in the orbitofrontal cortex, ventral striatum, and other reward-related brain structures (e.g., Breiter et al., 1997). A correlation was also found between a reliable index of the rush of i.v. methamphetamine in drug-naïve subjects (mind-racing) and activity in the orbitofrontal cortex (Völlm et al., 2004).

The preceding evidence implicates the orbitofrontal cortex in a wide variety of tasks. A large meta-analysis has demonstrated medio-lateral and anterior-posterior functional distinctions in the orbitofrontal cortex (Kringelbach, 2002; Kringelbach and Rolls, 2004). Activity in the medial orbitofrontal cortex has been shown to

relate to the monitoring of the reward value of many different reinforcers (involving, of course, mechanisms for learning and memory), whereas lateral orbitofrontal cortex activity has been proposed to be related to the evaluation of reinforcers which leads to a change in ongoing behavior. Furthermore, it has also been demonstrated that there is a posterior-anterior distinction with more complex or abstract reinforcers (such as monetary gain and loss) being represented more anteriorly in the orbitofrontal cortex than simpler reinforcers such as taste or pain (Kringelbach, 2002; Kringelbach and Rolls, 2004).

### 1. *Lesion Studies and Reward*

Neuroimaging studies are essentially only correlative measures of behavior, and it is therefore important to briefly consider the evidence from lesions in both humans and higher primates to assess the validity of the findings. In humans, damage to the orbitofrontal cortex causes major changes in motivation, emotion, personality, behavior, and social conduct. A classic case of orbitofrontal damage is that of Phineas Gage, whose medial frontal lobes were penetrated by a metal rod (Harlow, 1848). Miraculously Gage survived but his personality and emotional processing were changed completely (although care should be taken since our sources are severely limited) (Macmillan, 2000). In more recent cases of orbitofrontal cortex damage, patients often show lack of affect, social inappropriateness, and irresponsibility (Anderson et al., 1999; Hornak et al., 2003; Rolls et al., 1994). It has been shown that patients are impaired at correctly identifying social signals including, for example, face and voice expressions (Hornak et al., 1996,2003). Interestingly, the recent experiments on human patients with surgical lesions to the orbitofrontal cortex have found functional heterogeneity in that bilateral lesions to the lateral orbitofrontal cortex—but not unilateral or lesions to medial parts of the orbitofrontal cortex—produce significant impair-

ments in reversal learning (Hornak et al., 2004).

Furthermore, in the context of the evidence for a role of the orbitofrontal cortex in motivational hedonics, it is interesting to note that frontotemporal dementia (a progressive neurodegenerative disorder attacking the frontal lobes) does not only produce major and pervasive behavioral changes in personality and social conduct resembling those produced by orbitofrontal lesions. The condition is also associated with profound changes in eating habits with escalating desire for sweet food coupled with reduced satiety, which is often followed by enormous weight gain (Rahman et al., 1999).

Lesion studies in nonhuman primates support the hypothesis that reward value is represented in the orbitofrontal cortex. In devaluation paradigms monkeys with lesions to the orbitofrontal cortex were able to respond normally to associations between food and conditioners but fail to modify their behavior to the cues when probing these representations by reducing the incentive value of the food (Butter et al., 1963). Other studies found that lesions to the orbitofrontal cortex alter food preferences in monkeys (Baylis and Gaffan, 1991), while another lesion study used unilateral crossed lesions to show that the orbitofrontal cortex and the amygdala are important for the alteration of stimulus-reward associations (Baxter et al., 2000). Even in rats, it has been demonstrated that lesions to the orbitofrontal cortex blocks the ability to adapt behavior by accessing representational information about the incentive value of the associated food reinforcement (Gallagher et al., 1999). When making comparisons between rats and higher primates it is important to note that many brain areas have undergone considerable development. As mentioned previously, the elaboration of some of these brain areas has been so extensive in primates that even ancient systems such as the taste system appear to have been rewired to

place more emphasis on cortical processing in areas such as the orbitofrontal cortex.

#### IV. CONCLUSION

Food intake is essential to sustain life, and the sensory systems of taste and smell are among the most fundamental building blocks of the brain's natural reward systems (Kelley and Berridge, 2002). The special importance of food in human life is underlined by the predominance of food symbols and metaphors in human expressions across cultures (Lévi-Strauss, 1964) and the elaborate social constructions regarding purity and taboo of foods (Douglas, 1966). Food intake and food choice constitute a fundamental and frequent part of human life and have played a major role in the cultural evolution of nonfood systems such as ritual, religion, and social exchange as well as in the advancement of technology, development of cities, illnesses, and warfare through agriculture and domestication (Diamond, 1999).

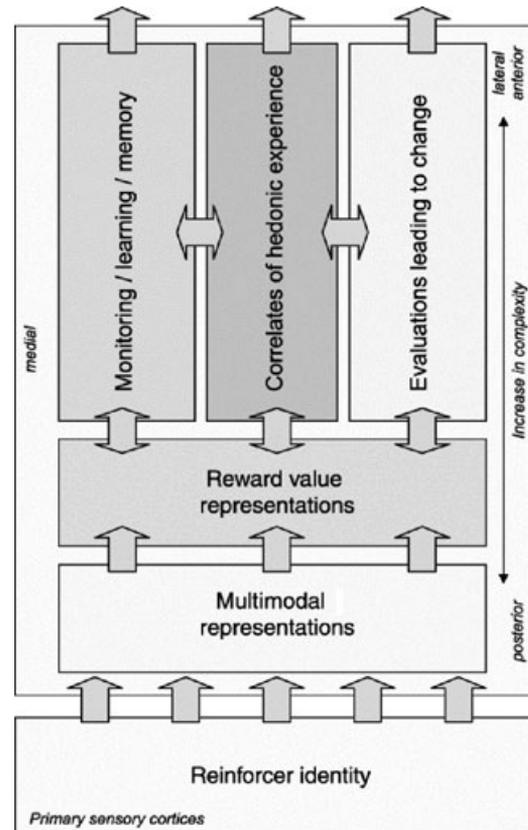
It has been proposed that humans' higher cognitive functions may have evolved to support the required cognitive processing involved in the sophisticated foraging necessary for the sustained food intake needed for omnivores such as humans (Kringelbach, 2004b).

The evidence reviewed here suggests that food consumption and the control of appetite rely on cortical processing in humans and other primates. Four main computational principles have been proposed: (1) motivation-independent processing of identity and intensity; (2) formation of learning-dependent multimodal sensory representations; (3) reward representations using mechanisms including selective satiation, and (4) representations of hedonic experience, monitoring/learning, or direct behavioral change.

This processing relies to a large extent on the orbitofrontal cortex. In line with earlier proposals (Kringelbach, 2004b, 2005) a

possible model is proposed which implements these computational principles for the interaction between sensory and hedonic systems in the human brain (see Fig. 3). Sensory information about primary (e.g., taste and smell) and secondary (e.g., visual) reinforcers is carried from the periphery to the primary sensory cortices (e.g., anterior insula/frontal operculum for taste and pyriform cortex for smell), where stimulus identity is decoded into stable representations (Small et al., 1999; Zatorre et al., 1992). This information is then conveyed for further multimodal integration in brain structures such as the posterior parts of the orbitofrontal cortex (De Araujo et al., 2003c; Small et al., 1997a). The reward value of the reinforcer is assigned (e.g., in more anterior parts of the orbitofrontal cortex) (Gottfried et al., 2003; Small et al., 2003) from where it can then be used for influencing subsequent behavior (e.g., lateral parts of the anterior orbitofrontal cortex, anterior cingulate cortex (Kringelbach and Rolls, 2003), and dorsolateral prefrontal cortex (Kringelbach et al., 2004; Wallis and Miller, 2003)), monitored as part of learning and memory mechanisms (e.g., in medial parts of the anterior orbitofrontal cortex) (De Araujo et al., 2003b; Gottfried and Dolan, 2003), and made available for subjective hedonic experience (e.g., mid-anterior orbitofrontal cortex) (Kringelbach et al., 2003). The reward value, and thus also the subjective hedonic experience of a reinforcer, can be modulated by hunger and other internal states (Gottfried et al., 2003; Kringelbach et al., 2003; O'Doherty et al., 2000), while the identity representation is remarkably stable and not subject to modulation (De Araujo et al., 2003b; Rolls et al., 2003a).

This model of the orbitofrontal cortex is obviously simplified but begins to address the basic principles of how food consumption and appetite are controlled in the human brain. More research into the cortical mechanisms of food intake is likely not only to further elucidate the workings of this network but may perhaps also prove



**FIGURE 3** Proposed model for the interaction between sensory and hedonic systems in the human brain using as an example one hemisphere of the orbitofrontal cortex. Information is flowing from the bottom to the top of the figure. Sensory information about primary (e.g., taste, smell, touch, and pain) and secondary (e.g., visual) reinforcers is sent from the periphery to the primary sensory cortices (e.g., anterior insula/frontal operculum for taste), where the stimulus identity is decoded into stable cortical representations. This information is then conveyed for further multimodal integration in brain structures in the posterior parts of the orbitofrontal cortex. The reward value of the reinforcer is assigned in more anterior parts of the orbitofrontal cortex from where it can then be used for influencing subsequent behavior (in lateral parts of the anterior orbitofrontal cortex from where it is sent to anterior cingulate cortex and dorsolateral prefrontal cortex), stored for learning (medial parts of the anterior orbitofrontal cortex), and made available for subjective hedonic experience (mid-anterior orbitofrontal cortex). The reward value and thus also the subjective hedonic experience of a reinforcer can be modulated by hunger and other internal states, while the identity representations in primary sensory cortices are remarkably stable and not subjected to modulation. It should be noted that there is, of course, important reciprocal information flowing between the higher level regions of the orbitofrontal cortex.

important to larger questions such as the neural correlates of subjective experience.

### Acknowledgments

This research has been supported by the Danish Research Agency, the Wellcome Trust, and the MRC (to FMRI, where most of the neuroimaging was carried out). The author would like to thank Caroline Andrews, Annie Cattrell, Phil Cowen, Ivan De Araujo, Peter Hobden, Julia Hornak, John O'Doherty, Edmund Rolls, Birgit Völlm, and James Wilson for their collaboration on some of the research reviewed here.

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