Neuroscience 126 (2004) 807–819

REVIEW

FOOD FOR THOUGHT: HEDONIC EXPERIENCE BEYOND HOMEOSTASIS IN THE HUMAN BRAIN

M. L. KRINGELBACH[a,b]*

[a]*University of Oxford, University Laboratory of Physiology, Parks Road, Oxford OX1 2PT, UK*

[b]*FMRIB, Oxford Centre for Functional Magnetic Resonance Imaging, John Radcliffe Hospital, Headley Way, Oxford OX3 9DU, UK*

Abstract—Food intake is an essential human activity regulated by homeostatic and hedonic systems in the brain which has mostly been ignored by the cognitive neurosciences. Yet, the study of food intake integrates fundamental cognitive and emotional processes in the human brain, and can in particular provide evidence on the neural correlates of the hedonic experience central to guiding behaviour. Neuroimaging experiments provide a novel basis for the further exploration of the brain systems involved in the conscious experience of pleasure and reward, and thus provide a unique method for studying the hedonic quality of human experience. Recent neuroimaging experiments have identified some of the regions involved in the cortical networks mediating hedonic experience in the human brain, with the evidence suggesting that the orbitofrontal cortex is the perhaps strongest candidate for linking food and other kinds of reward to hedonic experience. Based on the reviewed literature, a model is proposed to account for the roles of the different parts of the orbitofrontal cortex in this hedonic network.

Key words: taste, smell, pleasantness, insula/operculum, anterior cingulate cortex, motivation.

Contents

*Correspondence to: M. L. Kringelbach, University of Oxford, University Laboratory of Physiology, Parks Road, Oxford OX1 2PT, UK. Tel: +44-1865-282271; fax: +44-1865-272469.
E-mail address: morten.kringelbach@physiol.ox.ac.uk (M. L. Kringelbach).

Abbreviations: VNO, vomeronasal olfactory system.

The essential energy to sustain life is obtained from food intake and so is much of the pleasure of life (especially on an empty stomach). Although the necessary homeostatic regulation and consummatory behaviour is hard-wired in even brain-less species, the challenges of regulating feeding are much greater for mammals who must maintain a stable body temperature in a wide variety of hostile climates, which in turn requires intricate neural circuits. The relative sophistication of foraging in higher primates compared with other mammals indicates that significant parts of our large brains are dedicated to the required motivational, emotional and cognitive processing, and that mental processes related to food intake may indeed underlie other higher functions. 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 non-food 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).

Food intake relies on our brain to obtain sensory information about a food, to evaluate for desirability and to choose the appropriate behaviour. Part of this process is closely linked to homeostatic regulation, which has been elucidated in great details in animal models, with mammals including humans sharing many sub-cortical circuits and molecules (such as leptin and ghrelin) as e.g. outlined in an excellent recent review (Saper et al., 2002). However, food intake in humans is not only regulated by homeostatic processes as is illustrated by our easy overindulgence on sweet foods beyond homeostatic needs and the rising obesity levels. Instead, food intake relies on the interaction between homeostatic regulation and hedonic pleasure. This complex sub-cortical and cortical processing involves higher order processes such as 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 contents and viscosity) but also the valence elicited by the food (including, most importantly, the hedonic pleasure obtained).

This paper reviews the evidence from recent neuroimaging studies linking regions of the human brain (and in

0306-4522/04$30.00+0.00
doi:10.1016/j.neuroscience.2004.04.035

particular the orbitofrontal cortex) to various aspects of food intake and especially to the representation of the subjective pleasantness of foods. These findings appear for the first time to provide a solid basis for the further exploration of the brain systems involved in the conscious experience of pleasure and reward, and provide a unique method for studying the hedonic quality of human experience. This hedonic experience is related to *qualia*, which has been described as 'the hard problem of consciousness' (Chalmers, 1995) and which some philosophers believe will never become amenable to scientific analysis. Yet as demonstrated below, recent neuroimaging of the neural mechanisms behind various aspects of food intake suggest that this line of scientific inquiry may still yield important insights into the core of subjective experience.

Food intake

Food intake is a precisely controlled act that can potentially be fatal if the wrong decision is taken to swallow toxins, microorganisms or non-food objects on the basis of erroneously determining the sensory properties of the food. Humans have therefore developed elaborate food behaviours which are aimed at balancing conservative risk-minimising 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 the 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 (Le-Magnen, 1985; Woods and Stricker, 1999). Simple behaviours linked to food intake are controlled by homeostatic systems in the brainstem, as shown by the fact that even decerebrate animals are able to survive (Grill and Norgren, 1978).

However, most of this research has been carried out in other animals which has not helped to inform about the strong hedonic component of human food intake. It is clear that much of complex human behaviour 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 behaviour include the decrease of the rated pleasantness of sweet tastes when subjects are sated relative to when they are hungry (negative gustatory allesthesia; Cabanac, 1971) and satiation signals that selectively suppress further food intake of previously ingested foods whilst other foods can still be readily ingested (sensory-specific satiety; Rolls et al., 1981).

Motivation and emotion

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; Rolls, 1999; Weiskrantz, 1968). One often used functional distinction between motivation and emotion is that motivated behaviours are elicited by rewards (and punishers) related to internal homeostatic states associated with, say, hunger and thirst, whilst emotional states and behaviours are elicited by the great majority of rewards and punishers that are external stimuli and not associated with these internal need states. The field of emotion research has advanced tremendously in recent years (Kringelbach, 2004), 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.

Neuroimaging can be used to research these complex behaviours and their underlying neural substrate as discussed below. However, first it is important to understand the basic primate anatomy of the main sensory systems involved in taste and smell.

Human sensory systems and food intake

Most of our sensory systems are involved in the regulation of food intake. Whilst Aristotle and other ancient philosophers proposed only five senses (sight, hearing, smell, taste, and touch), it is clear that many other senses exist such as e.g. the sensory receptors in the digestive tract which are sensitive to e.g. gastric distension, and those in the circulatory system that are sensitive to changes in blood pressure or carbon dioxide gas in the blood.

Potential food sources can be evaluated 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

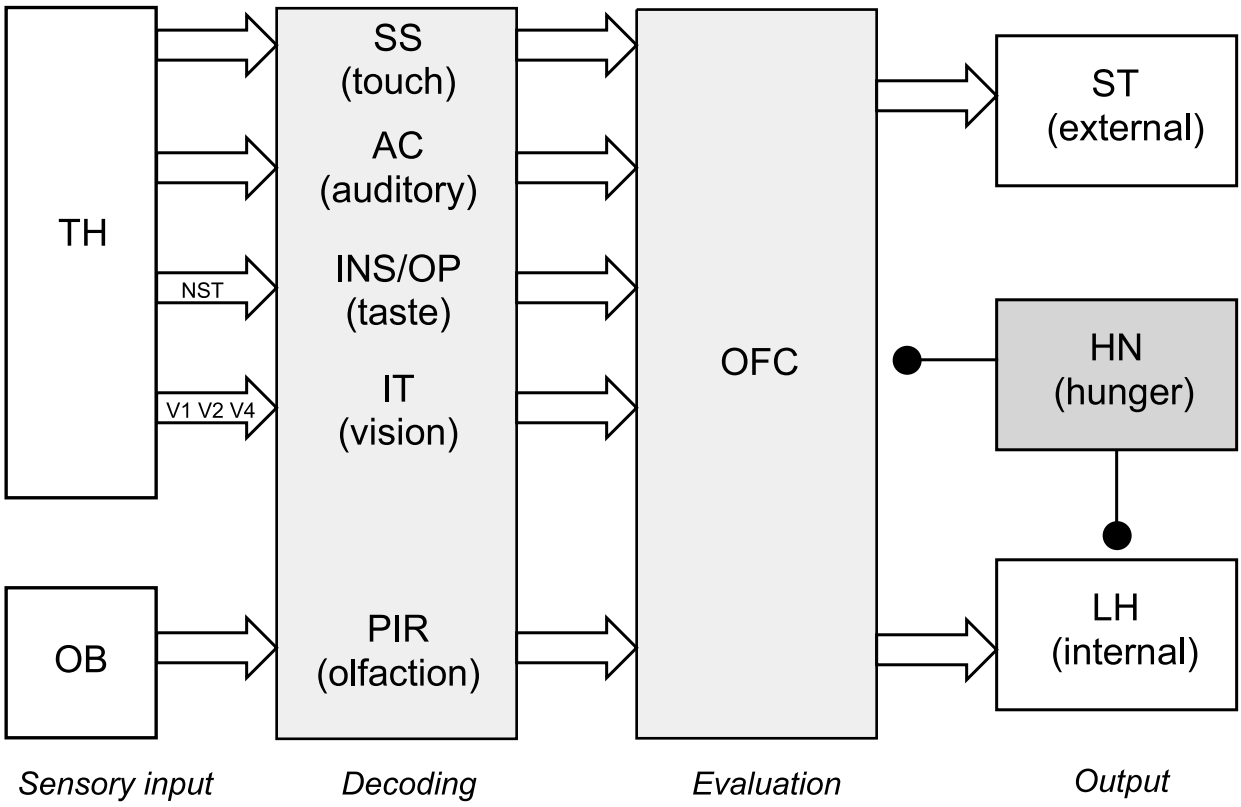

Fig. 1. Schematic diagram of information flow linked to the non-human primate orbitofrontal cortex. The orbitofrontal cortex receives input from all the sensory modalities: gustatory, olfactory, somatosensory, auditory and visual. This information is then represented and available for pattern-association 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 behaviour. AC, auditory cortex; HN, hunger neurons; INS/OP, insula cortex/frontal operculum; IT, inferior temporal visual cortex; LH, lateral hypothalamus; NST, nucleus of the solitary tract; OB, olfactory bulb; OFC, orbitofrontal cortex; PIR, piriform cortex; SS, somatosensory cortex (3, 1, 2); ST, striatum; TH, thalamus; V1, V2, V4, primary and secondary visual areas (figure modified from Rolls, 1999).

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 colouring a white wine red (Morrot et al., 2001).

Foremost, of course, the sensing of food occurs when a food is grasped and delivered to the mouth. This evaluation depends in the first instance on the integration of 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 multi-modal sensory integration is essential in making the vital decision of whether to swallow or reject a potentially poisonous food. Yet, such decisions are so important that there are 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). Further cortical processing to regulate food intake depends on additional sensory information from the autonomic system including information about hunger, thirst and gastric distension but also on learned associations with pleasure states.

It is an important principle of sensory processing in the brain 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 non-human 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, and in this way shape behaviour both internally (via the hypothalamus and brainstem structures) and externally (via the motor systems; Rolls, 1999).

The following is a brief outline of the anatomical pathways in primates and especially humans for establishing brain representations of taste and smell, as well as their multimodal integration.

Taste

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 (Scott and Plata-Salaman, 1999). Taste receptor cells are constantly being renewed and have a turnover period of between 7 and 10 days. As a convenient way of organising 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).

Taste is mediated by several cranial nerves that also carry information about touch, temperature and pain sensitivity on the tongue. In primates including humans the taste information then converges on the nucleus of the solitary tract in the brainstem from where it is relayed via the thalamus (in the parvocellular part of the ventroposterior medial nucleus; Pritchard et al., 1989) to the primary taste cortex in the frontal operculum and the dorsal part of the anterior insula (Pritchard et al., 1986; Scott et al., 1986; Sudakov et al., 1971) and to a smaller area of the anterior primary somatosensory cortex (area 3b; Norgren, 1990a). This is consistent with patients suffering from ageusia from bullet wounds to the parietal operculum (Bornstein, 1940a,b) and with the original observations by Penfield and Faulk (1955) on a patient with an aura of unpleasant taste stemming from a tumour in the insula. Taste information is relayed slightly differently in other mammals such as rats where a further relay station is found in the gustatory parabrachial nuclei in the pons before projecting directly to the amygdala and the hypothalamus (Norgren, 1984; Norgren and Leonard, 1973).

Neurophysiological investigations in primates found that roughly 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 taste neurons in the brainstem (Scott et al., 1986; Ogawa et al., 1989). 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, 1990b).

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 posterior orbitofrontal cortex which does not receive projections from the thalamus and is therefore defined as the secondary taste cortex (Baylis et al., 1994). There are also projections to the lateral hypothalamus where neurons have been 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 further neural system (in addition to the system in the orbitofrontal cortex) involved in learning associations between primary taste reinforcers and other arbitrary stimuli, and in particular learned taste aversion (Sanghera et al., 1979).

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). There is also recent evidence from neuroimaging that the human dorsolateral prefrontal cortex has representations of taste, which could aid higher cognitive processes in guiding complex motivational and emotional behaviour (Kringelbach et al., 2004). This is consistent with neurophysiological recordings in the dorsolateral prefrontal and orbitofrontal cortices in non-human 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, whilst 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 behaviour.

Smell

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 10 min 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 (although smell in other animals including rodents is probably significantly more important relative to other senses). The resulting number of unique odours which can be discriminated is likely to be on the order of around half a million odours (Mori et al., 1998).

The main olfactory system relies on these receptors for the conscious perception of odours but also relies on the trigeminal system mediating somatosensory information such as irritation, tickling, burning and cooling of odours. 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 behaviour 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 synchronising 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 non-functioning unit (Bhatnagar and Meisami, 1998).

In the main olfactory system smell is mediated by the first cranial nerve which runs through the bony cribriform plate to the ipsilateral olfactory bulb. 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, where the axons in the lateral olfactory tract run ipsilateral through the olfactory peduncle synapsing on primary olfactory cortices: 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. Olfaction is thus unique amongst the senses in that the sensory information is not relayed via the thalamus (Carmichael et al., 1994). In primates (including humans) the piriform cortex is located anatomically at the junction of the temporal and frontal lobes (Eslinger et al., 1982).

Numerous secondary brain regions receive projections from the primary olfactory cortex including the orbitofrontal cortex, medial thalamus, ventral striatum and pallidum, agranular insular cortex, hippocampus, medial and lateral hypothalamus. One of the most important olfactory pathways converges on the orbitofrontal cortex and experiments in non-human primates have shown secondary olfactory areas in the posterior orbitofrontal cortex (Takagi, 1986; Tanabe et al., 1975a,b) and in the medial central posterior orbitofrontal cortex (Carmichael et al., 1994; Takagi, 1986; Yarita et al., 1980).

Multimodal integration

In addition to multimodal information from taste and smell, decisions about food intake also integrate e.g. somatosensory information, which is sensed by receptors in the oral and nasal cavity. This sensory information includes temperature, viscosity, fat contents, 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 above, simple brainstem mechanisms also exist). Ingestion 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 non-invasive 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 e.g. 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 be 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 be 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).

An important principle of cross-modal integration between taste and smell is the formation of odour–taste associations, which are required to be more stable than, say, visual-taste associations to facilitate the formation and perception of flavours 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 odour–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).

Reward in the human brain

Multiple reward systems have been demonstrated in the mammalian brain (Rolls, 1999; Panksepp, 1998; Robbins et al., 1989; Wise, 1996). Many successful animal models have explored reward-learning mechanisms related to various forms of classical and instrumental conditioning. Until recently, however, not much was known about hedonic processes in the human brain. These hedonic systems are now being explored using novel neuroimaging experiments that provide evidence of activity in brain regions directly correlating with subjective pleasantness ratings of not only primary reinforcers such as taste, smell and touch but also with secondary and higher order reinforcers such as music, facial attractiveness and monetary reward.

Hedonics

Historically, the research on reward and motivation was initially focussed on intra-cranial self-stimulation (Liebman, 1983; Milner, 1991; Olds and Olds, 1963) and drug addiction (Wise, 1996; Berke and Hyman, 2000), which has led to the identification of brain reward systems that allow reinforcement of responses without homeostatic value. Some studies have, however, suggested that food and drug rewards may share common neural circuits and neurotransmitters which include opioid receptors (Hayward et al., 2002; Kelley et al., 2002; Kelley and Berridge, 2002).

Reward-related learning has been shown to involve many different brain areas and pathways such as the extended amygdala (Amaral et al., 1992; Swanson and Petrovich, 1998), the ventral striatal loops (Alexander et al., 1986), and the lateral hypothalamus (Williams et al., 1993; Grossman, 1975). The reward-related role of these sub-cortical structures has already been outlined in a number of excellent reviews (Robbins et al., 1989; Cardinal et al., 2002). Here the role of just one of the important neurotransmitters in these pathways is therefore considered: the dopaminergic system including the ventral striatum and the tegmental midbrain. The precise role of dopamine in reward is not yet evidently but is clearly involved in the responses to rewarding stimuli. Lesions to the ventral striatum failed to reduce food intake in rats (Ikemoto and Panksepp, 1996; Koob et al., 1978), and did not impair operant responding for food (Balleine and Killcross, 1994). Instead, dopamine has been proposed to play a role in the incentive motivational state (Berridge and Robinson, 1998) and in the prediction error in reward learning (Schultz and Dickinson, 2000), rather than being related to the hedonic value of the reward itself. Neuroimaging studies in humans have confirmed the role of dopamine in reward learning with indications of dopamine release in the ventral striatum following unpredictable monetary reward (Pappata et al., 2002). The ventral striatum has also been shown to be active in the human brain in the prediction of taste reward (Berns et al., 2001) and in the expectation of taste (O'Doherty et al., 2002) and olfaction reward (Gottfried et al., 2002b).

It has been proposed that food reward can usefully be split into the two components of appetite/incentive motivation and pleasure/palatability with dissociable neural substrates (Berridge, 1996). Dopamine has been shown to be related more to the neural mechanisms of incentive motivation than hedonics (Berridge and Robinson, 1998). Furthermore, in order to provide hedonic evaluation of stimuli it is also clear that the brain regions implicated in hedonic assessment must receive salient information about stimulus identity from the primary and secondary sensory cortices.

Neuroimaging offers a powerful way to investigate the 'liking' component in the human brain. One way is for instance to take subjective hedonic ratings throughout a human neuroimaging experiment and then correlate these ratings with changes in activity in the human brain. This allows for a unique window on the hedonic processes evaluating the pleasantness of salient stimuli. Recently, and as reviewed in the following, a string of neuroimaging experiments have investigated these hedonic processes for many different kinds of reinforcers.

Taste

The results of investigating the hedonic processes associated with pure taste in the human brain confirm that dissociable brain areas are involved in the representation of the identity and the hedonics of the stimulus. The primary gustatory areas have been investigated using neuroimaging with pure sweet, salt, sour, bitter and umami stimuli, and consistent with neurophysiological studies in non-human primates found to be located in the anterior insula/frontal operculum and caudal orbitofrontal cortex (O'Doherty et al., 2002; De Araujo et al., 2003a,b; Frey and Petrides, 1999; Kinomura et al., 1994; O'Doherty et al., 2001b, 2003b; Small et al., 1997, 1999, 2003). In addition, there is emerging evidence that regions of both the anterior cingulate cortex (Kringelbach et al., 2004; De Araujo et al., 2003c; Small et al., 2003) and dorsolateral prefrontal cortex (Kringelbach et al., 2004) are consistently activated by taste stimuli compared with tasteless (which provided a rinse for the taste and was also used to control for non-taste including somatosensory effects of placing solutions in the mouth).

In contrast to these motivation-independent representations of reinforcer identity, one recent neuroimaging study has dissociated 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, whilst valence-specific responses were observed in the orbitofrontal cortex with the right caudolateral orbitofrontal cortex responding preferentially to pleasant compared with unpleasant taste, irrespective of intensity.

Another recent 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 0.005 M inosine 5′-monophosphate is added to 0.5 M monosodium glutamate (compared with both delivered separately) was correlated with increased activity in an anterior part of the orbitofrontal cortex (De Araujo et al., 2003a).

Olfaction

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.

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., 2002a; 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 odours 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 odour in a paired discrimination task activate the orbitofrontal cortex (Zatorre et al., 2000).

Multimodal stimuli

The evidence from neuroimaging studies of pure taste and smell thus 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 multi-modal 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. 2; Kringelbach et al., 2003). This result strongly indicates that the reward value of the taste, olfactory, and somatosensory components of a whole food is represented in the orbitofrontal cortex, and that the subjective pleasantness of food thus might be represented here.

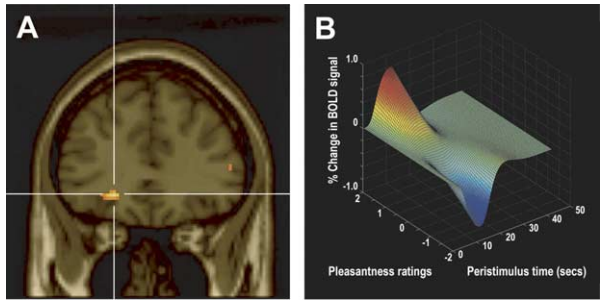

Fig. 2. Regions of the human orbitofrontal cortex that correlate with pleasantness ratings. (A) Coronal section through the region of the orbitofrontal cortex from the random effects group analysis showing the peak in the left orbitofrontal cortex (MNI co-ordinates X, Y, Z = −22, 34, −8; Z-score = 4.06), in which the BOLD signal in the voxels shown in yellow was significantly correlated with the subjects' subjective pleasantness ratings of the foods throughout the experiment. (B) Plot of the magnitude of the fitted haemodynamic response from a representative single subject against the subjective pleasantness ratings (on a scale from −2 to +2) and peristimulus time in seconds (figure modified from Kringelbach et al., 2003).

Further evidence 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).

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., 1997). 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 (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).

Other sensory modalities

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 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). There is also evidence to suggest that facial attractiveness is correlated with activity in the orbitofrontal cortex (Aharon et al., 2001; O'Doherty et al., 2003a). 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 recently found between a reliable index of the rush of i.v. methamphetamine in drug-naive subjects (mind-racing) and activity in the orbitofrontal cortex (Völlm et al., 2004).

The above evidence implicates the orbitofrontal cortex in a wide variety of tasks, and it is important to try to understand the functional neuroanatomy of this rather large brain structure. Some progress has already been made from a large meta-analysis demonstrating mediolateral 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 behaviour. It should be noted that other authors have proposed that response inhibition might be another explanation for the role of the lateral orbitofrontal cortex (Elliott et al., 2000). 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).

Lesion studies

Neuroimaging studies are essentially only correlative measures of behaviour, 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, behaviour, 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 was changed completely (although care should be taken since our amount of information is rather 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., 2003; Hornak et al., 1996). 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 impairments 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) produces not only major and pervasive behavioural changes in personality and social conduct resembling those produced by orbitofrontal lesions but also 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 non-human primates support the hypothesis that reward value is represented in the orbitofrontal cortex. In devaluation paradigms monkeys with lesions to the orbitofrontal cortex are able to respond normally to associations between food and conditioners but fail to modify their behaviour 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), whilst 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 block the ability to adapt behaviour 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. The elaboration of some of these brain areas has been so extensive in primates that even evolutionary old systems such as the taste system appear to have been rewired (see the section on Taste above) to place more emphasis on cortical processing in areas such as the orbitofrontal cortex.

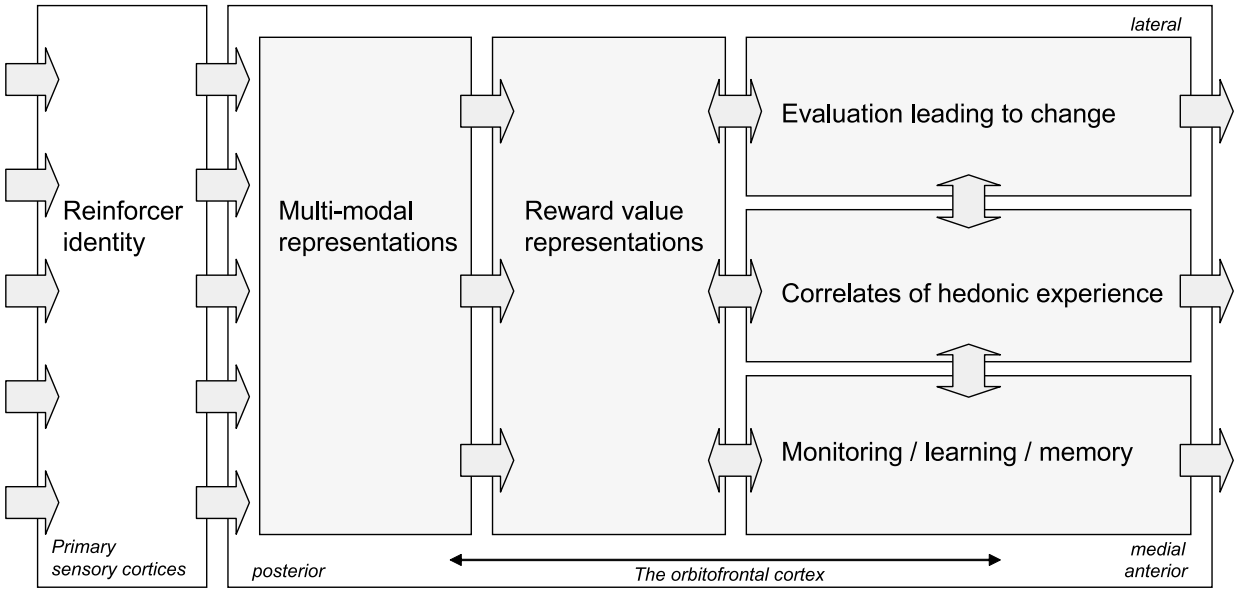

Fig. 3. Proposed model for the interaction between sensory and hedonic systems in the human brain using as an example one hemisphere of the orbitofrontal cortex. Information is flowing from left to right on the figure. Sensory information about primary (e.g. taste, smell, touch and pain) and secondary (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 behaviour (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, whilst 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.

CONCLUSIONS

Food intake is essential to sustain life, and the sensory systems of taste and smell are amongst the most fundamental building blocks of the brain's natural reward systems (Kelley and Berridge, 2002). Humans' large so-called higher cognitive functions have evolved to support the required cognitive processing involved in the sophisticated foraging needed for the sustained food intake needed for omnivores such as humans. However, with the current state of overabundance of food in the developed world these cognitive requirements have been overlooked and the study of food intake has been sidelined from the cognitive neurosciences. In this review it has been shown that the study of food intake, and in particular the study of subjective hedonic experience, is central to understanding human behaviour, and as such should be re-integrated in the mainstream of the cognitive neurosciences.

The evidence reviewed here from recent neuroimaging experiments suggests that the orbitofrontal cortex is a strong candidate for mediating hedonic experience, but that there are also other candidate brain regions such as the anterior cingulate, the insular cortex and ventral striatum which could be part of hedonic networks in the human brain. Based on the recent neuroimaging reviewed above and using the orbitofrontal cortex as an example system, a possible model for the interaction between sensory and hedonic systems in the human brain can now be proposed (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., 1997). The reward value of the reinforcer is assigned (e.g. in more anterior parts of the orbitofrontal cortex; Small et al., 2003; Gottfried et al., 2003) from where it can then be used for influencing subsequent behaviour (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; Gottfried and Dolan, 2003; De Araujo et al., 2003b) 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 (O'Doherty et al., 2000; Gottfried et al., 2003; Kringelbach et al., 2003), whilst the identity representation is remarkably stable and not subjected to modulation (De Araujo et al., 2003b; Rolls et al., 2003a). This model of only one of the nodes (the orbitofrontal cortex) is of course relatively simple compared with what has to be a much more complex hedonic network, but it offers some important insights that future

research may help refine. In addition, 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 important to larger questions such as the neural correlates of subjective experience.

Acknowledgements—This research is supported by the Wellcome Trust and the MRC (to FMRIB). 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 work reviewed here. Furthermore, the helpful points raised by the two anonymous reviewers are gratefully acknowledged.

REFERENCES

Aharon I, Etcoff N, Ariely D, Chabris CF, O'Connor E, Breiter HC (2001) Beautiful faces have variable reward value: fMRI and behavioral evidence. Neuron 32:537–551.

Alexander GE, DeLong MR, Strick PL (1986) Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci 9:357–381.

Amaral DG, Price JL, Pitkanen A, Carmichael ST (1992) Anatomical organization of the primate amygdaloid complex. In: The Amygdala (Aggleton JP, ed), pp 1–66. New York: Wiley-Liss.

Anderson AK, Christoff K, Stappen I, Panitz D, Ghahremani DG, Glover G, Gabrieli JD, Sobel N (2003) Dissociated neural representations of intensity and valence in human olfaction. Nat Neurosci 6:196–202.

Anderson SW, Bechara A, Damasio H, Tranel D, Damasio AR (1999) Impairment of social and moral behavior related to early damage in human prefrontal cortex. Nat Neurosci 2:1032–1037.

Balleine B, Killcross S (1994) Effects of ibotenic acid lesions of the nucleus accumbens on instrumental action. Behav Brain Res 65: 181–193.

Barer DH (1989) The natural history and functional consequences of dysphagia after hemispheric stroke. J Neurol Neurosurg Psychiatry 52:236–241.

Baxter MG, Parker A, Lindner CC, Izquierdo AD, Murray EA (2000) Control of response selection by reinforcer value requires interaction of amygdala and orbital prefrontal cortex. J Neurosci 20:4311–4319.

Baylis LL, Gaffan D (1991) Amygdalctomy and ventromedial prefrontal ablation produce similar deficits in food choice and in simple object discrimination learning for an unseen reward. Exp Brain Res 86: 617–622.

Baylis LL, Rolls ET, Baylis GC (1994) Afferent connections of the orbitofrontal cortex taste area of the primate. Neuroscience 64: 801–812.

Berke JD, Hyman SE (2000) Addiction, dopamine, and the molecular mechanisms of memory. Neuron 25:515–532.

Berns GS, McClure SM, Pagnoni G, Montague PR (2001) Predictability modulates human brain response to reward. J Neurosci 21: 2793–2798.

Berridge KC (1996) Food reward: brain substrates of wanting and liking. Neurosci Biobehav Rev 20:1–25.

Berridge KC, Robinson TE (1998) What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? Brain Res Brain Res Rev 28:309–369.

Bhatnagar KP, Meisami E (1998) Vomeronasal organ in bats and primates: extremes of structural variability and its phylogenetic implications. Microsc Res Tech 43:465–475.

Blood AJ, Zatorre RJ (2001) Intensely pleasurable responses to music correlate with activity in brain regions implicated in reward and emotion. Proc Natl Acad Sci USA 98:11818–11823.

Blood AJ, Zatorre RJ, Bermudez P, Evans AC (1999) Emotional responses to pleasant and unpleasant music correlate with activity in paralimbic brain regions. Nat Neurosci 2:382–387.

Bornstein WS (1940a) Cortical representation of taste in man and monkey: I. Functional and anatomical relations of taste, olfaction and somatic sensibility. Yale J Biol Med 12:719–736.

Bornstein WS (1940b) Cortical representation of taste in man and monkey: II. The localization of the cortical taste area in man, a method of measuring impairment of taste in man. Yale J Biol Med 13:133–156.

Breiter HC, Gollub RL, Weisskoff RM, Kennedy DN, Makris N, Berke JD, Goodman JM, Kantor HL, Gastfriend DR, Riorden JP, Mathew RT, Rosen BR, Hyman SE (1997) Acute effects of cocaine on human brain activity and emotion. Neuron 19:591–611.

Buck L, Axel R (1991) A novel multigene family may encode odorant receptors: a molecular basis for odor recognition. Cell 65:175–187.

Burton MJ, Rolls ET, Mora F (1976) Effects of hunger on the responses of neurones in the lateral hypothalamus to the sight and taste of food. Exp Neurol 51:668–677.

Butter CM, Mishkin M, Rosvold HE (1963) Conditioning and extinction of a food-rewarded response after selective ablations of frontal cortex in rhesus monkeys. Exp Neurol 7:65–75.

Cabanac M (1971) Physiological role of pleasure. Science 173:1103–1107.

Cardinal RN, Parkinson JA, Hall J, Everitt BJ (2002) Emotion and motivation: the role of the amygdala, ventral striatum, and prefrontal cortex. Neurosci Biobehav Rev 26:321–352.

Carmichael ST, Clugnet M-C, Price JL (1994) Central olfactory connections in the macaque monkey. J Comp Neurol 346:403–434.

Carmichael ST, Price JL (1994) Architectonic subdivision of the orbital and medial prefrontal cortex in the macaque monkey. J Comp Neurol 346:366–402.

Cerf-Ducastel B, Murphy C (2001) fMRI activation in response to odorants orally delivered in aqueous solutions. Chem Senses 26: 625–637.

Chalmers D (1995) Facing up to the problem of consciousness. J Conscious Studies 2:200–219.

Chaudhari N, Landin AM, Roper SD (2000) A metabotropic glutamate receptor variant functions as a taste receptor. Nat Neurosci 3:113–119.

Craig AD (2002) Opinion: how do you feel? Interoception: the sense of the physiological condition of the body. Nat Rev Neurosci 3:655–666.

Craig AD, Chen K, Bandy D, Reiman EM (2000) Thermosensory activation of insular cortex. Nat Neurosci 3:184–190.

De Araujo IET, Kringelbach ML, Rolls ET, Hobden P (2003a) The representation of umami taste in the human brain. J Neurophysiol 90:313–319.

De Araujo IET, Kringelbach ML, Rolls ET, McGlone F (2003b) Human cortical responses to water in the mouth, and the effects of thirst. J Neurophysiol 90:1865–1876.

De Araujo IET, Rolls ET, Kringelbach ML, McGlone F, Phillips N (2003c) Taste-olfactory convergence, and the representation of the pleasantness of flavour, in the human brain. Eur J Neurosci 18: 2059–2068.

Diamond JM (1999) Guns, germs, and steel: the fates of human societies. New York: Norton.

Douglas M (1966) Purity and danger: an analysis of concepts of pollution and taboo. London: Routledge & Kegan Paul.

Elliott R, Dolan RJ, Frith CD (2000) Dissociable functions in the medial and lateral orbitofrontal cortex: evidence from human neuroimaging studies. Cereb Cortex 10:308–317.

Eslinger PJ, Damasio AD, Van Hoesen GW (1982) Olfactory dysfunction in man: anatomical and behavioural aspects. Brain Cogn 1:259–285.

Frey S, Petrides M (1999) Re-examination of the human taste region: a positron emission tomography study. Eur J Neurosci 11:2985–2988.

Gallagher M, McMahan RW, Schoenbaum G (1999) Orbitofrontal cor-

tex and representation of incentive value in associative learning. J Neurosci 19:6610–6614.
Gordon C, Hewer RL, Wade DT (1987) Dysphagia in acute stroke. BMJ (Clin Res Ed) 295:411–414.
Gottfried JA, Deichmann R, Winston JS, Dolan RJ (2002a) Functional heterogeneity in human olfactory cortex: an event-related functional magnetic resonance imaging study. J Neurosci 22:10819–10828.
Gottfried JA, Dolan RJ (2003) The nose smells what the eye sees: crossmodal visual facilitation of human olfactory perception. Neuron 39:375–386.
Gottfried JA, O'Doherty J, Dolan RJ (2002b) Appetitive and aversive olfactory learning in humans studied using event-related functional magnetic resonance imaging. J Neurosci 22:10829–10837.
Gottfried JA, O'Doherty J, Dolan RJ (2003) Encoding predictive reward value in human amygdala and orbitofrontal cortex. Science 301: 1104–1107.
Gray JA (1975) Elements of a two-process theory of learning. London: Academic Press.
Grill HJ, Norgren R (1978) The taste reactivity test: II. Mimetic responses to gustatory stimuli in chronic thalamic and chronic decerebrate rats. Brain Res 143:281–297.
Grossman S-P (1975) Role of the hypothalamus in the regulation of food and water intake. Psychol Rev 82:200–224.
Hamdy S, Mikulis DJ, Crawley A, Xue S, Lau H, Henry S, Diamant NE (1999a) Cortical activation during human volitional swallowing: an event-related fMRI study. Am J Physiol 277:G219–225.
Hamdy S, Rothwell JC, Brooks DJ, Bailey D, Aziz Q, Thompson DG (1999b) Identification of the cerebral loci processing human swallowing with H2(15)O PET activation. J Neurophysiol 81:1917–1926.
Harlow JM (1848) Passage of an iron rod through the head. Boston Med Surg J 39:389–393.
Hayward MD, Pintar JE, Low MJ (2002) Selective reward deficit in mice lacking beta-endorphin and enkephalin. J Neurosci 22:8251–8258.
Hornak J, Bramham J, Rolls ET, Morris RG, O'Doherty J, Bullock PR, Polkey CE (2003) Changes in emotion after circumscribed surgical lesions of the orbitofrontal and cingulate cortices. Brain 126:1671–1712.
Hornak, J, O'Doherty, J, Bramham, J, Rolls, ET, Morris, RG, Bullock, PR, Polkey, CE (2004) Reward-related reversal learning after surgical excisions in orbitofrontal and dorsolateral prefrontal cortex in humans. J Cogn Neurosci 16:463–478.
Hornak J, Rolls ET, Wade D (1996) Face and voice expression identification in patients with emotional and behavioural changes following ventral frontal lobe damage. Neuropsychologia 34:247–261.
Ikemoto S, Panksepp J (1996) Dissociations between appetitive and consummatory responses by pharmacological manipulations of reward-relevant brain regions. Behav Neurosci 110:331–345.
Jean A (1984) Brainstem organization of the swallowing network. Brain Behav Evol 25:109–116.
Jean A (2001) Brain stem control of swallowing: neuronal network and cellular mechanisms. Physiol Rev 81:929–969.
Kelley AE, Bakshi VP, Haber SN, Steininger TL, Will MJ, Zhang M (2002) Opioid modulation of taste hedonics within the ventral striatum. Physiol Behav 76:365–377.
Kelley AE, Berridge KC (2002) The neuroscience of natural rewards: relevance to addictive drugs. J Neurosci 22:3306–3311.
Kinomura S, Kawashima R, Yamada K, Ono S, Itoh M, Yoshioka S, Yamaguchi T, Matsui H, Miyazawa H, Itoh H, Goto R, Fujiwara T, Satoh K, Fukuda H (1994) Functional anatomy of taste perception in the human brain studied with positron emission tomography. Brain Res 659:263–266.
Koob GF, Riley SJ, Smith SC, Robbins TW (1978) Effects of 6-hydroxydopamine lesions of the nucleus accumbens septi and olfactory tubercle on feeding, locomotor activity, and amphetamine anorexia in the rat. J Comp Physiol Psychol 92:917–927.
Kringelbach, ML (2002) D. Phil. thesis: The functional neuroanatomy of emotion. Department of Experimental Psychology. Oxford: University of Oxford.
Kringelbach ML (2004) Emotion. In: The Oxford companion to the mind 2nd edition (Gregory RL, ed). Oxford: Oxford University Press, in press.
Kringelbach ML, de Araujo IET, Rolls ET (2004) Taste-related activity in the human dorsolateral prefrontal cortex. Neuroimage 21:781–788.
Kringelbach ML, O'Doherty J, Rolls ET, Andrews C (2003) Activation of the human orbitofrontal cortex to a liquid food stimulus is correlated with its subjective pleasantness. Cereb Cortex 13:1064–1071.
Kringelbach ML, Rolls ET (2003) Neural correlates of rapid context-dependent reversal learning in a simple model of human social interaction. Neuroimage 20:1371–1383.
Kringelbach, ML, Rolls, ET (2004) The functional neuroanatomy of the human orbitofrontal cortex: evidence from neuroimaging and neuropsychology. Prog Neurobiol 72:341–372.
LeMagnen J (1985) Hunger. London: Cambridge University Press.
Lévi-Strauss C (1964) Le cru et le cuit. [The raw and the cooked: introduction to a science of mythology.] London: Jonathan Cape.
Liebman JM (1983) Discriminating between reward and performance: a critical review of intracranial self-stimulation methodology. Neurosci Biobehav Rev 7:45–72.
Macmillan M (2000) An odd kind of fame: stories of Phineas Gage. Cambridge, Mass: MIT Press.
Martin RE, Goodyear BG, Gati JS, Menon RS (2001) Cerebral cortical representation of automatic and volitional swallowing in humans. J Neurophysiol 85:938–950.
Martin RE, Sessle BJ (1993) The role of the cerebral cortex in swallowing. Dysphagia 8:195–202.
Milner PM (1991) Brain-stimulation reward: a review. Can J Psychol 45:1–36.
Monti-Bloch L, Jennings-White C, Berliner DL (1998) The human vomeronasal system: a review. Ann NY Acad Sci 855:373–389.
Mori K, Nagao H, Sasaki YF (1998) Computation of molecular information in mammalian olfactory systems. Network 9:R79–102.
Morrot G, Brochet F, Dubourdieu D (2001) The color of odors. Brain Lang 79:309–320.
Norgren R (1984) Central neural mechanisms of taste. In: Handbook of physiology: the nervous system III: sensory processes 1 (Brookhart JM, Mountcastle VB, Darien-Smith I, eds), pp 1087–1128. Washington, DC: American Physiological Society.
Norgren R (1990a) The central gustatory system in humans. In: The Human Nervous System (Paxinos G, ed), New York: Academic.
Norgren R (1990b) Gustatory system. In: The Human Nervous System (Paxinos G, ed), pp 845–861. New York: Academic Press.
Norgren R, Leonard CM (1973) Ascending central gustatory pathways. J Comp Neurol 150:217–237.
O'Doherty J, Kringelbach ML, Rolls ET, Hornak J, Andrews C (2001a) Abstract reward and punishment representations in the human orbitofrontal cortex. Nat Neurosci 4:95–102.
O'Doherty J, Rolls ET, Francis S, Bowtell R, McGlone F (2001b) Representation of pleasant and aversive taste in the human brain. J Neurophysiol 85:1315–1321.
O'Doherty J, Rolls ET, Francis S, Bowtell R, McGlone F, Kobal G, Renner B, Ahne G (2000) Sensory-specific satiety-related olfactory activation of the human orbitofrontal cortex. Neuroreport 11:893–897.
O'Doherty J, Winston J, Critchley H, Perrett D, Burt DM, Dolan RJ (2003a) Beauty in a smile: the role of medial orbitofrontal cortex in facial attractiveness. Neuropsychologia 41:147–155.
O'Doherty JP, Dayan P, Friston K, Critchley H, Dolan RJ (2003b) Temporal difference models and reward-related learning in the human brain. Neuron 38:329–337.
O'Doherty JP, Deichmann R, Critchley HD, Dolan RJ (2002) Neural responses during anticipation of a primary taste reward. Neuron 33:815–826.

Ogawa H, Ito SL, Nomura T (1989) Oral cavity representation at the frontal operculum of macaque monkeys. Neurosci Res 6:283–298.
Olds ME, Olds J (1963) Approach avoidance analysis of rat diencephalon. J Comp Neurol 120:259–295.
Panksepp J (1998) Affective neuroscience: the foundations of human and animal emotions. Oxford: Oxford University Press.
Papez JW (1937) A proposed mechanism for emotion. Arch Neurol Psychiatry 38:725–743.
Pappata S, Dehaene S, Poline JB, Gregoire MC, Jobert A, Delforge J, Frouin V, Bottlaender M, Dolle F, Di Giamberardino L, Syrota A (2002) In vivo detection of striatal dopamine release during reward: a PET study with [(11)C]raclopride and a single dynamic scan approach. Neuroimage 16:1015–1027.
Penfield W, Faulk ME (1955) The insula: further observations on its function. Brain 78:445–470.
Petrovic P, Kalso E, Petersson KM, Ingvar M (2002) Placebo and opioid analgesia: imaging a shared neuronal network. Science 295:1737–1740.
Pierce J, Halpern BP (1996) Orthonasal and retronasal odorant identification based upon vapor phase input from common substances. Chem Senses 21:529–543.
Pritchard TC, Hamilton RB, Morse JR, Norgren R (1986) Projections of thalamic gustatory and lingual areas in the monkey, *Macaca fascicularis*. J Comp Neurol 244:213–228.
Pritchard TC, Hamilton RB, Norgren R (1989) Neural coding of gustatory information in the thalamus of *Macaca mulatta*. J Neurophysiol 61:1–14.
Rahman S, Sahakian BJ, Hodges JR, Rogers RD, Robbins TW (1999) Specific cognitive deficits in mild frontal variant frontotemporal dementia. Brain 122:1469–1493.
Robbins TW, Cador M, Taylor JR, Everitt BJ (1989) Limbic-striatal interactions in reward-related processes. Neurosci Biobehav Rev 13:155–162.
Rolls BJ, Rolls ET, Rowe EA, Sweeney K (1981) Sensory specific satiety in man. Physiol Behav 27:137–142.
Rolls ET (1999) The brain and emotion. Oxford: Oxford University Press.
Rolls ET, Critchley HD, Mason R, Wakeman EA (1996) Orbitofrontal cortex neurons: role in olfactory and visual association learning. J Neurophysiol 75:1970–1981.
Rolls ET, Hornak J, Wade D, McGrath J (1994) Emotion-related learning in patients with social and emotional changes associated with frontal lobe damage. J Neurol Neurosurg Psychiatry 57:1518–1524.
Rolls ET, Kringelbach ML, de Araujo IET (2003a) Different representations of pleasant and unpleasant odours in the human brain. Eur J Neurosci 18:695–703.
Rolls ET, O'Doherty J, Kringelbach ML, Francis S, Bowtell R, McGlone F (2003b) Representations of pleasant and painful touch in the human orbitofrontal and cingulate cortices. Cereb Cortex 13:308–317.
Royet JP, Hudry J, Zald DH, Godinot D, Gregoire MC, Lavenne F, Costes N, Holley A (2001) Functional neuroanatomy of different olfactory judgments. Neuroimage 13:506–519.
Royet JP, Souchier C, Jourdan F, Ploye H (1988) Morphometric study of the glomerular population in the mouse olfactory bulb: numerical density and size distribution along the rostrocaudal axis. J Comp Neurol 270:559–568.
Royet JP, Zald D, Versace R, Costes N, Lavenne F, Koenig O, Gervais R (2000) Emotional responses to pleasant and unpleasant olfactory, visual, and auditory stimuli: a positron emission tomography study. J Neurosci 20:7752–7759.
Rozin P (2001) Food Preference. In: International encyclopedia of the social and behavioral sciences (Smelser NJ, Baltes PB, eds), pp 5719–5722. Amsterdam: Elsevier.
Sanghera MK, Rolls ET, Roper-Hall A (1979) Visual responses of neurons in the dorsolateral amygdala of the alert monkey. Exp Neurol 63:610–626.
Saper CB, Chou TC, Elmquist JK (2002) The need to feed: homeostatic and hedonic control of eating. Neuron 36:199–211.
Schultz W, Dickinson A (2000) Neuronal coding of prediction errors. Ann Rev Neurosci 23:473–500.
Scott TR, Plata-Salaman CR (1999) Taste in the monkey cortex. Physiol Behav 67:489–511.
Scott TR, Yaxley S, Sienkiewicz ZJ, Rolls ET (1986) Gustatory responses in the frontal opercular cortex of the alert cynomolgus monkey. J Neurophysiol 56:876–890.
Small DM, Gregory MD, Mak YE, Gitelman D, Mesulam MM, Parrish T (2003) Dissociation of neural representation of intensity and affective valuation in human gustation. Neuron 39:701–711.
Small DM, Jones-Gotman M, Zatorre RJ, Petrides M, Evans AC (1997) Flavor processing: more than the sum of its parts. Neuroreport 8:3913–3917.
Small DM, Zald DH, Jones-Gotman M, Zatorre RJ, Pardo JV, Frey S, Petrides M (1999) Human cortical gustatory areas: a review of functional neuroimaging data. Neuroreport 10:7–14.
Small DM, Zatorre RJ, Dagher A, Evans AC, Jones-Gotman M (2001) Changes in brain activity related to eating chocolate: from pleasure to aversion. Brain 124:1720–1733.
Smith TD, Bhatnagar KP (2000) The human vomeronasal organ: Part II. Prenatal development. J Anat 197:421–436.
Stern K, McClintock MK (1998) Regulation of ovulation by human pheromones. Nature 392:177–179.
Sudakov K, MacLean PD, Reeves A, Marino R (1971) Unit study of exteroceptive inputs to claustrocortex in awake, sitting, squirrel monkey. Brain Res 28:19–34.
Swanson LW, Petrovich GD (1998) What is the amygdala? Trends Neurosci 21:323–331.
Takagi SF (1986) Studies on the olfactory nervous system of the old world monkey. Prog Neurobiol 27:195–250.
Tanabe T, Iino M, Takagi SF (1975a) Discrimination of odors in olfactory bulb, pyriform-amygdaloid areas, and orbitofrontal cortex of the monkey. J Neurophysiol 38:1284–1296.
Tanabe T, Yarita H, Iino M, Ooshima Y, Takagi SF (1975b) An olfactory projection area in orbitofrontal cortex of the monkey. J Neurophysiol 38:1269–1283.
Thorpe SJ, Rolls ET, Maddison S (1983) The orbitofrontal cortex: neuronal activity in the behaving monkey. Exp Brain Res 49:93–115.
Thut G, Schultz W, Roelcke U, Nienhusmeier M, Missimer J, Maguire RP, Leenders KL (1997) Activation of the human brain by monetary reward. Neuroreport 8:1225–1228.
Völlm, BA, de Araujo, IET, Cowen, PJ, Rolls, ET, Kringelbach, ML, Smith, KA, Jezzard, P, Heal, RJ, Matthews, PM (2004) Methamphetamine activates reward circuitry in drug naïve human subjects. Neuropsychopharmacology, in press.
Wallis JD, Miller EK (2003) Neuronal activity in primate dorsolateral and orbital prefrontal cortex during performance of a reward preference task. Eur J Neurosci 18:2069–2081.
Weiskrantz L (1968) Emotion. In: Analysis of behavioural change (Weiskrantz L, ed), pp 50–90. New York: Harper and Row.
Williams GV, Rolls ET, Leonard CM, Stern C (1993) Neuronal responses in the ventral striatum of the behaving macaque. Behav Brain Res 55:243–252.
Wise RA (1996) Addictive drugs and brain stimulation reward. Ann Rev Neurosci 19:319–340.
Woods SC, Stricker EM (1999) Central control of food intake. In: Fundamental neuroscience (Zigmond MJ, Bloom FE, Landis SC, Roberts JL, Squire LR, eds), pp 1091–1109. San Diego, CA: Academic Press.
Yarita H, Iino M, Tanabe T, Kogure S, Takagi SF (1980) A transthalamic olfactory pathway to the orbitofrontal cortex in the monkey. J Neurophysiol 43:69–85.
Yaxley S, Rolls ET, Sienkiewicz ZJ (1988) The responsiveness of neurons in the insular gustatory cortex of the macaque monkey is independent of hunger. Physiol Behav 42:223–229.
Zald DH, Pardo JV (1997) Emotion, olfaction, and the human

amygdala: amygdala activation during aversive olfactory stimulation. Proc Natl Acad Sci USA 94:4119–4124.
Zald DH, Pardo JV (1999) The functional neuroanatomy of voluntary swallowing. Ann Neurol 46:281–286.
Zatorre RJ, Jones-Gotman M, Evans AC, Meyer E (1992) Functional localization and lateralization of human olfactory cortex. Nature 360:339–340.
Zatorre RJ, Jones-Gotman M, Rouby C (2000) Neural mechanisms involved in odor pleasantness and intensity judgments. Neuroreport 11:2711–2716.

(Accepted 14 April 2004)
(Available online 8 June 2004)