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Plenary Lecture

Sensory processing in the brain related to the control of food intake

Edmund T. Rolls
University of Oxford, Department of Experimental Psychology, South Parks Road, Oxford OX1 3UD, UK

Complementary neurophysiological recordings in rhesus macaques (*Macaca mulatta*) and functional neuroimaging in human subjects show that the primary taste cortex in the rostral insula and adjoining frontal operculum provides separate and combined representations of the taste, temperature and texture (including viscosity and fat texture) of food in the mouth independently of hunger and thus of reward value and pleasantness. One synapse on, in the orbitofrontal cortex, these sensory inputs are for some neurons combined by learning with olfactory and visual inputs. Different neurons respond to different combinations, providing a rich representation of the sensory properties of food. In the orbitofrontal cortex feeding to satiety with one food decreases the responses of these neurons to that food, but not to other foods, showing that sensory-specific satiety is computed in the primate (including the human) orbitofrontal cortex. Consistently, activation of parts of the human orbitofrontal cortex correlates with subjective ratings of the pleasantness of the taste and smell of food. Cognitive factors, such as a word label presented with an odour, influence the pleasantness of the odour, and the activation produced by the odour in the orbitofrontal cortex. Food intake is thus controlled by building a multimodal representation of the sensory properties of food in the orbitofrontal cortex and gating this representation by satiety signals to produce a representation of the pleasantness or reward value of food that drives food intake. Factors that lead this system to become unbalanced and contribute to overeating and obesity are described.

Sensory-specific satiety: Fat: Food texture: Taste: Olfaction

The aims of the present paper are to describe the rules of the cortical processing of taste and smell, how the pleasantness or affective value of taste and smell are represented in the brain, and to relate this information to the brain mechanisms underlying the control of appetite, food intake and obesity. To make the results relevant to understanding the control of human food intake, complementary evidence is provided by neurophysiological studies in non-human primates and by functional neuroimaging studies in human subjects. A broad perspective on brain processing involved in emotion and in hedonic aspects of the control of food intake is provided by Rolls (2005*a*).

Taste processing in the primate brain

Pathways

A diagram of the taste and related olfactory, somatosensory and visual pathways in primates is shown in Fig. 1. The multimodal convergence that enables single neurons to respond to different combinations of taste, olfactory,

Abbreviation: fMRI, functional magnetic resonance imaging.

Corresponding author: Professor E. T. Rolls, fax +44 1865 310447, email Edmund.Rolls@psy.ox.ac.uk, website http://www.cns.ox.ac.uk

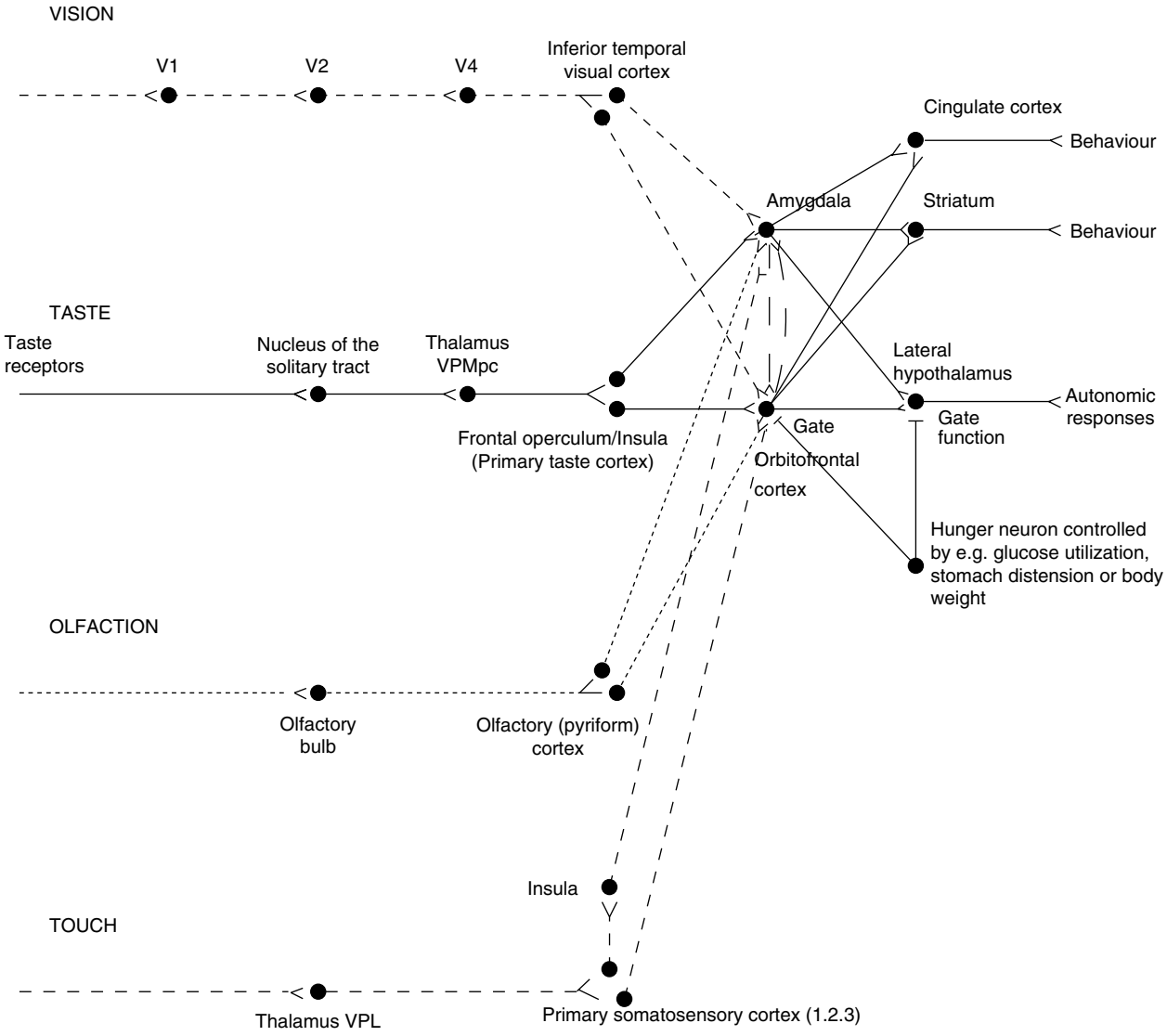

Fig. 1. A schematic diagram of the taste and olfactory pathways in primates, including man, showing how they converge with each other and with visual pathways. Hunger modulates the responsiveness of the representations in the orbitofrontal cortex of the taste, smell, texture and sight of food (indicated by the gate function), and the orbitofrontal cortex is where the palatability and pleasantness of food is represented. V1, V2, V4, visual cortical areas; VPMpc, ventral posteromedial nucleus pars parvicellularis; VPL, ventral posterolateral nucleus.

texture, temperature and visual inputs to represent different flavours produced often by new combinations of sensory input is a theme of recent research that will be described.

The primary taste cortex

The primary taste cortex in the primate anterior insula and adjoining frontal operculum contains not only taste neurons tuned to sweet, salt, bitter, sour (Scott *et al*. 1986; Yaxley *et al*. 1990; Rolls & Scott, 2003) and umami, as exemplified by monosodium glutamate (Baylis & Rolls, 1991; Rolls *et al*. 1996*a*), but also other neurons that encode oral somatosensory stimuli including viscosity, fat texture, temperature and capsaicin (Verhagen *et al*. 2004). Some neurons in the primary taste cortex respond to particular combinations of taste and oral texture stimuli, but do not respond to olfactory stimuli or visual stimuli such as the sight of food (Verhagen *et al*. 2004). Neurons in the primary taste cortex do not represent the reward value of taste, i.e. the appetite for a food, in that their firing is not decreased to zero by feeding the taste to satiety (Rolls *et al*. 1988; Yaxley *et al*. 1988).

The secondary taste cortex

There is a secondary cortical taste area in primates (Rolls *et al*. 1990) in the caudolateral orbitofrontal cortex, extending several millimetres in front of the primary taste cortex. One principle of taste processing is that by the secondary taste cortex, the tuning of neurons can become quite specific, with some neurons responding, for example, only to sweet taste. This specific tuning (especially when

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combined with olfactory inputs) helps to provide a basis for changes in appetite for some, but not other, foods eaten during a meal.

Five prototypical tastes, including umami

In the primary and secondary taste cortex there are many neurons that respond best to each of the four classical prototypical tastes (sweet, salt, bitter and sour; Rolls, 1997; Rolls & Scott, 2003), but also there are many neurons that respond best to umami tastants such as glutamate (which is present in many natural foods such as tomatoes, mushrooms and milk; Baylis & Rolls, 1991) and inosine monophosphate (which is present in meat and some fish such as tuna; Rolls *et al*. 1996*a*). This evidence, taken together with the identification of a glutamate taste receptor (Zhao *et al*. 2003), leads to the view that there are five prototypical types of taste information channels, with umami contributing, often in combination with corresponding olfactory inputs (Rolls *et al*. 1998; ET Rolls and C McCabe, unpublished results), to the flavour of protein. In addition, other neurons respond to water and others to somatosensory stimuli including astringency, as exemplified by tannic acid (Critchley & Rolls, 1996*a*) and capsaicin (Rolls *et al*. 2003*b*; Kadohisa *et al*. 2004).

The pleasantness of the taste of food

The modulation of the reward value of a sensory stimulus such as the taste of food by motivational state, e.g. hunger, is one important way in which motivational behaviour is controlled (Rolls, 1999, 2005*a*). The subjective correlate of this modulation is that food tastes pleasant when hungry and tastes hedonically neutral when it has been eaten to satiety. It has been found that the modulation of taste-evoked signals by motivation is not a property found in the early stages of the primate gustatory system. The responsiveness of taste neurons in the nucleus of the solitary tract (Yaxley *et al*. 1985) and in the primary taste cortex (frontal opercular, Rolls *et al*. 1988; insular, Yaxley *et al*. 1988) is not attenuated by feeding to satiety. In contrast, in the secondary taste cortex, located in the caudolateral part of the orbitofrontal cortex, it has been shown that the responses of the neurons to the taste of glucose decrease to zero while a monkey eats it to satiety, during the course of which the behaviour turns from avid acceptance to active rejection (Rolls *et al*. 1989). This modulation of responsiveness of the gustatory responses of the orbitofrontal cortex neurons by satiety could not have been a result of peripheral adaptation in the gustatory system or to altered efficacy of gustatory stimulation after satiety is reached, because modulation of neuronal responsiveness by satiety is not seen at the earlier stages of the gustatory system, including the nucleus of the solitary tract, the frontal opercular taste cortex and the insular taste cortex.

Sensory-specific satiety

In the secondary taste cortex it has also been found that the decreases in the responsiveness of the neurons are relatively specific to the food with which the monkey has been fed to satiety. An example for a neuron that has taste, olfactory and visual responses to food is shown in Fig. 2. Feeding to satiety with blackcurrant juice produces a larger decrease in the neuron's response to the blackcurrant juice than to most of the other stimuli in all three sensory modalities (Rolls *et al*. 1989; Critchley & Rolls, 1996*b*).

This evidence shows that the reduced acceptance of food that occurs when food is eaten to satiety, and the reduction in the pleasantness of its taste (Cabanac, 1971; Rolls & Rolls, 1977, 1982; Rolls *et al*. 1981*a*,*b*, 1982, 1983*a*), are not produced by a reduction in the responses of neurons in the nucleus of the solitary tract or frontal opercular or insular gustatory cortices to gustatory stimuli. Indeed, after feeding to satiety, human subjects report that the taste of the food on which they have been satiated tastes almost as intense as when they are hungry, although much less pleasant (Rolls ET *et al*. 1983). This comparison is consistent with the possibility that activity in the frontal opercular and insular taste cortices as well as the nucleus of the solitary tract does not reflect the pleasantness of the taste of a food, but rather its sensory qualities independently of motivational state. On the other hand, the responses of the neurons in the caudolateral orbitofrontal cortex taste area and in the lateral hypothalamus (Rolls *et al*. 1986) are modulated by satiety, and it is presumably in areas such as these that neuronal activity may be related to whether a food tastes pleasant, and to whether the food should be eaten (for further information, see Scott *et al*. 1995; Critchley & Rolls, 1996*c*; Rolls, 1996, 1999, 2000*a*,*b*; Rolls & Scott, 2003). In addition to providing an implementation of sensory-specific satiety (probably by habituation of the synaptic afferents to orbitofrontal neurons with a time-course of the order of the length of a course of a meal), it is likely that visceral and other satiety-related signals reach the orbitofrontal cortex (as indicated in Fig. 1; from the nucleus of the solitary tract, via thalamic nuclei) and there modulate the representation of food, resulting in an output that reflects the reward (or appetitive) value of each food (Rolls, 2005*a*).

It is an important principle that the identity of a taste, and its intensity, are represented separately from its pleasantness. Thus, it is possible to represent what a taste is, and to learn about it, even when not hungry.

The representation of flavour: convergence of olfactory and taste inputs

At some stage in taste processing it is likely that taste representations are brought together with inputs from different modalities, e.g. with olfactory inputs to form a representation of flavour (see Fig. 1). It has been found (Rolls & Baylis, 1994) that in the orbitofrontal cortex taste areas, of 112 single neurons that respond to any of these modalities, many are unimodal (taste 34%, olfactory 13%, visual 21%), but are found in close proximity to each other. Some single neurons show convergence, responding for example to taste and visual inputs (13%), taste and olfactory inputs (13%) and olfactory and visual inputs (5%). Some of these multimodal single neurons have corresponding sensitivities in the two modalities, in that they

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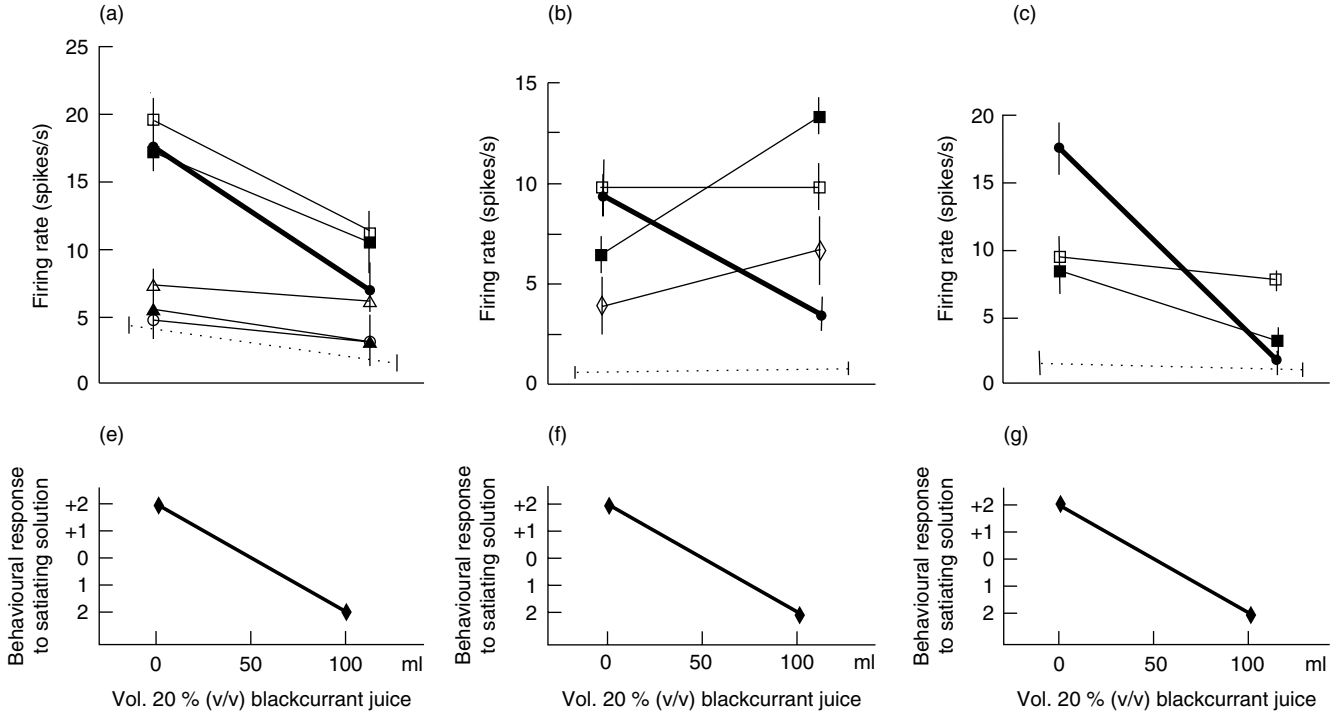

Fig. 2. Orbitofrontal cortex neuron with olfactory (a), taste (b) and visual (c) responses, showing the responses before and after feeding to satiety with blackcurrant juice (●—●). The olfactory stimuli included apple (□—□), banana (■—■), citral (△—△), phenylethanol (▲—▲) and caprylic acid (○—○). (◇—◇), Glucose; (- - - -), the spontaneous firing rate of the neuron. The taste data are for the flavour of food in the mouth. (◆—◆), The neuronal response data for each experiment (e, f and g respectively); the behavioural measure of the acceptance or rejection of the solution on a scale from +2 to −2 is shown. The values are the mean firing rates with their standard errors represented by vertical bars. (After Critchley & Rolls, 1996*b*.)

respond best to sweet tastes (e.g. 1 M-glucose) and respond more in a visual discrimination task to the visual stimulus that signifies sweet fruit juice than to that that signifies saline (NaCl solution), or respond to sweet taste and in an olfactory discrimination task to fruit odour. The different types of neurons (unimodal in different modalities, and multimodal) are frequently found close to one another in tracks made into this region, consistent with the hypothesis that the multimodal representations are actually being formed from unimodal inputs to this region.

It thus appears to be in these orbitofrontal cortex areas that flavour representations are built, where flavour is taken to mean a representation that is evoked best by a combination of gustatory and olfactory input. This orbitofrontal region does appear to be an important region for convergence, for there is only a low proportion of bimodal taste and olfactory neurons in the primary taste cortex (Rolls & Baylis, 1994; Verhagen *et al*. 2004).

The rules underlying the formation of olfactory representations in the primate cortex

Critchley & Rolls (1996*c*) have shown that 35% of orbitofrontal cortex olfactory neurons categorise odours based on their taste association in an olfactory-to-taste discrimination task. Rolls *et al*. (1996*a*) have found that 68% of orbitofrontal cortex odour-responsive neurons modify their responses in some way following changes in the taste–reward associations of the odourants during olfactory–taste discrimination learning and its reversal. (In an olfactory discrimination experiment, if a lick response to one odour S+) is made one drop of glucose taste reward is obtained; if incorrectly a lick response is made to another odour (S−), one drop of aversive saline is obtained. At some time in the experiment the contingency between the odour and the taste is reversed, and when the 'meaning' of the two odours alters, so does the behaviour. It is of interest to investigate in which parts of the olfactory system the neurons show reversal, for where they do it can be concluded that the neuronal response to the odour depends on the taste with which it is associated, and does not depend primarily on the physico-chemical structure of the odour.) These findings demonstrate directly a coding principle in primate olfaction whereby the responses of some orbitofrontal cortex olfactory neurons are modified by, and depend on, the taste with which the odour is associated (Rolls, 2001, 2002*a*,*b*).

It is of interest, however, that this modification is less complete, and much slower, than the modifications found for orbitofrontal visual neurons during visual–taste reversal (Rolls *et al*. 1996*c*). This relative inflexibility of olfactory responses is consistent with the need for some stability in odour–taste associations to facilitate the formation and perception of flavours. In addition, some orbitofrontal cortex olfactory neurons do not encode information in

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relation to the taste with which the odour is associated (Critchley & Rolls, 1996*c*), showing that there is also a taste-independent representation of odour in this region.

The representation of the pleasantness of odour in the brain: olfactory and visual sensory-specific satiety, their representation in the primate orbitofrontal cortex and the role of sensory-specific satiety in appetite

It has also been possible to investigate whether the olfactory representation in the orbitofrontal cortex is affected by hunger, and thus whether the pleasantness of odour is represented in the orbitofrontal cortex. In satiety experiments Critchley & Rolls (1996*b*) have shown that the responses of some olfactory neurons to a food odour are decreased during feeding to satiety with a food (e.g. fruit juice) containing that odour. In particular, seven of nine olfactory neurons that were responsive to the odours of foods, such as blackcurrant juice, were found to decrease their responses to the odour of the satiating food. The decrease was typically found to be at least partly specific to the odour of the food that had been eaten to satiety, potentially providing part of the basis for sensory-specific satiety. It was also found for eight of nine neurons that had selective responses to the sight of food that they demonstrated a sensory-specific reduction in their visual responses to foods following satiation (see Fig. 2). These findings show that the olfactory and visual representations of food, as well as the taste representation of food, in the primate orbitofrontal cortex are modulated by hunger. Usually, a component related to sensory-specific satiety can be demonstrated.

These findings link at least part of the processing of olfactory and visual information in this brain region to the control of feeding-related behaviour. They are further evidence that part of the olfactory representation in this region is related to the hedonic value of the olfactory stimulus, and in particular that at this level of the olfactory system in primates, the pleasure elicited by the food odour is at least part of what is represented.

As a result of the neurophysiological and behavioural observations showing the specificity of satiety in the monkey (originally made by ET Rolls in 1974 and illustrated, for example, in Rolls, 1981), experiments have been performed to determine whether in human subjects satiety is specific to foods eaten. It was found that the pleasantness of the taste of food eaten to satiety decreases more than for foods that have not been eaten (Rolls *et al*. 1981*a*). One consequence of this finding is that if one food is eaten to satiety, appetite reduction for other foods is often incomplete, and this effect will lead to enhanced eating when a variety of foods is offered (Rolls *et al*. 1981*a*,*b*, 1984). Since sensory factors such as similarity of colour, shape, flavour and texture are usually more important than metabolic equivalence in terms of protein, carbohydrate and fat content in influencing how foods interact in this type of satiety, it has been termed 'sensory-specific satiety' (Rolls & Rolls, 1977, 1982; Rolls *et al*. 1981*a*,*b*, 1982; Rolls, 1990). It should be noted that this effect is distinct from alliesthesia, in that alliesthesia is a change in the pleasantness of sensory inputs produced by internal signals (such as glucose in the gut; see Cabanac & Duclaux, 1970; Cabanac, 1971; Cabanac & Fantino, 1977), whereas sensory-specific satiety is a change in the pleasantness of sensory inputs that is accounted for, at least partly, by the external sensory stimulation received (such as the taste of a particular food), in that, as shown earlier, it is at least partly specific to the external sensory stimulation received.

To investigate whether the sensory-specific reduction in the responsiveness of the orbitofrontal olfactory neurons might be related to a sensory-specific reduction in the pleasure produced by the odour of a food when it is eaten to satiety, Rolls & Rolls (1997) have measured the responses of human subjects to the smell of a food that is eaten to satiety. It was found that the pleasantness of the odour of a food, but much less markedly its intensity, is decreased when the subjects eat it to satiety. It was also found that the pleasantness of the smell of other foods (i.e. foods not eaten in the meal) shows much less decrease. This finding has clear implications for: the control of food intake; ways to keep foods presented in a meal appetitive and effects on odour pleasantness ratings that could occur following meals. In their investigation of the mechanisms of this odour-specific sensory-specific satiety Rolls & Rolls (1997) also allowed human subjects to chew a food, without swallowing, for approximately as long as the food is normally in the mouth during eating. They demonstrated some sensory-specific satiety with this procedure, showing that partial sensory-specific satiety can occur without food reaching the stomach. Thus, at least part of the mechanism is likely to be produced by a change in processing in the olfactory pathways. The earliest stage of olfactory processing at which this modulation occurs is not yet known. It is unlikely to be in the receptors, because the change in pleasantness found is much more important than the change in the intensity (Rolls & Rolls, 1997).

The increase of food intake that can occur when a variety of foods is available, as a result of the operation of sensory-specific satiety, may have been advantageous in evolution in ensuring that different foods with important different nutrients were consumed. However, in the present day in human subjects, when a wide variety of foods is readily available, this response may be a factor that can lead to overeating and obesity. In a test of this potential outcome in the rat it has been found that variety itself can lead to obesity (Rolls *et al*. 1983*b*; Rolls & Hetherington, 1989).

The responses of orbitofrontal cortex taste and olfactory neurons to the sight, texture and temperature of food

Many of the neurons with visual responses in this region also show olfactory or taste responses (Rolls & Baylis, 1994), reverse rapidly in visual discrimination reversal (see earlier and Rolls *et al*. 1996*b*) and only respond to the sight of food if hunger is present (Critchley & Rolls, 1996*b*). This part of the orbitofrontal cortex thus seems to implement a mechanism that can flexibly alter the responses to

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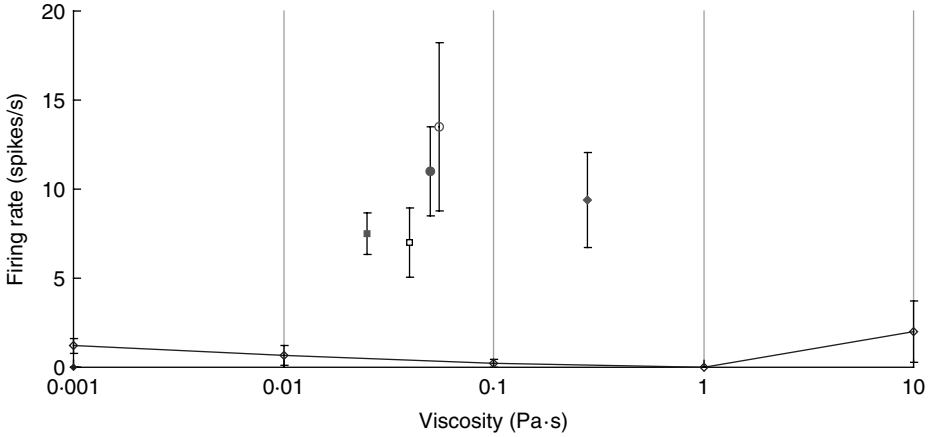

Fig. 3. A neuron in the primate orbitofrontal cortex responding to the texture of fat in the mouth independently of viscosity. In response to a range of fats and oils, the viscosities (Pa·s) of which were: paraffin (mineral) oil, 0·025 (■); coconut oil, 0·040 (□); safflower oil, 0·050 (●); vegetable oil, 0·055 (○); silicone oil, 0·28 (◆), the cell (bk265) increased its firing rate. Values are means with their standard errors represented by vertical bars. The neuron did not respond to the methyl cellulose (◇) viscosity series, indicating that the information that reaches this type of neuron is independent of a viscosity-sensing channel. Furthermore, the response to silicone oil $(Si(CH_3)_2O)_n$ and paraffin oil (hydrocarbon) indicates that the neuron responded to the texture of the fat rather than its chemical structure. Some of these neurons have taste inputs. (After Verhagen *et al.* 2003.)

visual stimuli depending on the reinforcement (e.g. the taste) associated with the visual stimulus (see Thorpe *et al.* 1983; Rolls, 1996). This process enables prediction of the taste associated with ingestion of what is seen, and thus enables the visual selection of foods (see Rolls, 1999, 2000*b*, 2005*a*). It also provides a mechanism for the sight of a food to influence its flavour.

The orbitofrontal cortex of primates is also important as an area of convergence for somatosensory inputs related, for example, to the texture of food, including fat in the mouth. It has been shown that single neurons influenced by taste in this region can in some cases have their responses modulated by the texture of the food; for example, in experiments in which the texture of food is manipulated by the addition of methyl cellulose or gelatine, or by puréeing a semi-solid food (Rolls, 1998, 1999). Furthermore, some of these neurons with texture-related responses encode parametrically the viscosity of food in the mouth (investigated using a methyl cellulose series in the range 0·001–10 Pa·s), and other neurons independently encode the particulate quality of food in the mouth, which can be produced quantitatively by adding 20–100 μm microspheres to methyl cellulose (Rolls *et al.* 2003*b*).

In addition, recent findings (Kadohisa *et al.* 2004) have revealed that some neurons in the orbitofrontal cortex reflect the temperature of substances in the mouth, and that this temperature information is represented independently of other sensory inputs by some neurons, and in combination with taste or texture by other neurons.

The mouth feel of fat: orbitofrontal cortex, primary taste cortex and amygdala

Texture in the mouth is an important indicator of whether fat is present in a food, which is important not only as a high-value energy source, but also as a potential source of essential fatty acids. Rolls *et al.* (1999) have found a population of neurons in the orbitofrontal cortex that responds when fat is in the mouth. An example of such a neuron is shown in Fig. 3. The fat–related responses of these neurons are produced, at least in part, by the texture of the food rather than by chemical receptors sensitive to certain chemicals, as such neurons typically respond not only to foods such as cream and milk containing fat, but also to paraffin oil (which is a pure hydrocarbon) and silicone oil $(Si(CH_3)_2O)_n$). Moreover, the texture channel through which these fat-sensitive neurons are activated are separate from viscosity-sensitive channels, as the responses of these neurons cannot be predicted by the viscosity of the oral stimuli (Verhagen *et al.* 2003; illustrated in Fig. 3). Some of the fat–related neurons do, however, have convergent inputs from the chemical senses, because in addition to taste inputs some of these neurons respond to the odour associated with a fat, such as the odour of cream (Rolls *et al.* 1999). Feeding to satiety with fat (e.g. cream) decreases the responses of these neurons to zero on the food eaten to satiety, but if the neuron receives a taste input from, for example, glucose taste, that response is not decreased by feeding to satiety with cream (Rolls *et al.* 1999). Thus, there is a representation of the macronutrient fat in this brain area, and the activation produced by fat is reduced by eating fat to satiety.

Fat texture, oral viscosity and temperature, for some neurons in combination with taste, are represented in the rhesus macaque (*Macaca mulatta*) primary taste cortex in the rostral insula and adjoining frontal operculum (Verhagen *et al.* 2004).

These oral sensory properties of food, and also the sight and smell of food, are also represented in the primate amygdala (Rolls, 2000*c*; Rolls & Scott, 2003; Kadohisa

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et al. 2005*a*,*b*). Interestingly, the responses of these amygdala neurons do not correlate well with the preferences of the macaques for the oral stimuli (Kadohisa *et al*. 2005*a*), and feeding to satiety does not produce the large reduction in the responses of amygdala neurons to food (Rolls, 2000*c*; Rolls & Scott, 2003) that is typical of orbitofrontal cortex neurons.

Learning about the sight of food: orbitofrontal cortex *v*. amygdala

There are also differences between the primate orbitofrontal cortex and amygdala in the way that they learn about stimuli associated with the flavour of food. Neurons in the orbitofrontal cortex reverse their responses very rapidly, often in one trial, to a visual stimulus when it no longer signifies food (Thorpe *et al*. 1983; Rolls *et al*. 1996*b*), whereas such rapid visual–taste discrimination reversal in the same task is not a general property of primate amygdala neurons that respond to the sight of food (Sanghera *et al*. 1979; Rolls, 2000*c*). Thus, the primate orbitofrontal cortex appears to be more closely related to hedonic aspects of stimuli relevant to the control of food intake than does the primate amygdala (Rolls, 2000*c*, 2005*a*; Rolls & Scott, 2003). Part of the underlying basis for at least the rapid reward reversal learning shown by primate orbitofrontal cortex neurons but not amygdala neurons may be that the orbitofrontal cortex as a cortical structure has well-developed recurrent collateral axon systems that enable the network to operate as a short-term memory. A short-term memory would then enable a rule to be kept active about which stimulus is currently rewarded, and cortical connectivity would allow this rule network to influence visual neurons in the orbitofrontal cortex using biased competition mechanisms (Deco & Rolls, 2005*a*,*b*). This process provides a computational basis for understanding the special role of the orbitofrontal cortex in the rapid re-evaluation of the responses to be made to food (Deco & Rolls, 2005*b*; Rolls, 2005*a*). In addition, habituation of the afferent synapses to the orbitofrontal cortex with a time-course of several minutes provides a probable neurophysiological basis for sensory-specific satiety (Rolls, 2005*a*).

Imaging studies in human subjects

Taste

In human subjects it has been shown in neuroimaging studies using functional magnetic resonance imaging (fMRI) that taste activates an area of the anterior insula/frontal operculum, which is probably the primary taste cortex, and part of the orbitofrontal cortex, which is probably the secondary taste cortex (Francis *et al*. 1999; O'Doherty *et al*. 2001; de Araujo *et al*. 2003*b*). Furthermore, it has been shown that within individual subjects separate areas of the orbitofrontal cortex are activated by sweet (pleasant) and by salt (unpleasant) taste (O'Doherty *et al*. 2001).

It has also been reported (Francis *et al*. 1999) that the human amygdala is activated by the taste of glucose. Furthermore, in an extension of this study (O'Doherty *et al*. 2001) it has been shown that the human amygdala is as much activated by the affectively pleasant taste of glucose as by the affectively negative taste of NaCl (O'Doherty *et al*. 2001), thus providing evidence that the human amygdala is not especially involved in processing aversive stimuli as compared with rewarding stimuli. While it had earlier been shown (Zald *et al*. 1998) that the amygdala, as well as the orbitofrontal cortex, responds to aversive (saline) taste stimuli, this study (O'Doherty *et al*. 2001) shows that there is nothing special about aversive taste stimuli in relation to the brain areas activated, as pleasant stimuli also activate the amygdala and orbitofrontal cortex.

Another study (de Araujo *et al*. 2003*a*) has shown that umami taste stimuli, exemplified by monosodium glutamate and capturing what is described as the taste of protein, activate similar cortical regions of the human taste system to those activated by a prototypical taste stimulus, glucose. A part of the rostral anterior cingulate cortex was also shown to be activated. When the nucleotide 0·005 M-inosine 5′-monophosphate was added to monosodium glutamate (0·05 M), the blood oxygenation level-dependent signal in an anterior part of the orbitofrontal cortex was found to show supralinear additivity, and this finding may reflect the subjective enhancement of umami taste that has been described (Rifkin & Bartoshuk, 1980) when inosine 5′-monophosphate is added to monosodium glutamate. Overall, these results illustrate that the responses of the brain can reflect inputs produced by particular combinations of sensory stimuli with supralinear activations, and that the combination of sensory stimuli may be especially represented in particular brain regions.

Odour

In human subjects, in addition to activation of the pyriform (olfactory) cortex (Zald & Pardo, 1997; Sobel *et al*. 2000; Poellinger *et al*. 2001), there is strong and consistent activation of the orbitofrontal cortex by olfactory stimuli (Zatorre *et al*. 1992; Francis *et al*. 1999). In an investigation into where the pleasantness of olfactory stimuli might be represented in human subjects, O'Doherty *et al*. (2000) have shown that the activation of an area of the orbitofrontal cortex to banana odour is decreased (relative to a control vanilla odour) after bananas are eaten to satiety. Thus, activity in a part of the human orbitofrontal cortex olfactory area is related to sensory-specific satiety, and the orbitofrontal cortex is one brain region where the pleasantness of odour is represented.

An important issue is whether there are separate regions of the brain that can be discriminated using fMRI that represent pleasant and unpleasant odours. To investigate this issue, the brain activations produced by three pleasant and three unpleasant odours have been measured. The pleasant odours chosen were linalyl acetate (floral, sweet), geranyl acetate (floral) and α-ionone (woody, slightly food-related); chiral substances were used as racemates. The unpleasant odours chosen were hexanoic acid, octanol and isovaleric acid. It was found that they activate dissociable parts of the human brain (Rolls *et al*. 2003*a*). Pleasant odours, but not unpleasant odours, were found to activate a medial region of the rostral orbitofrontal cortex

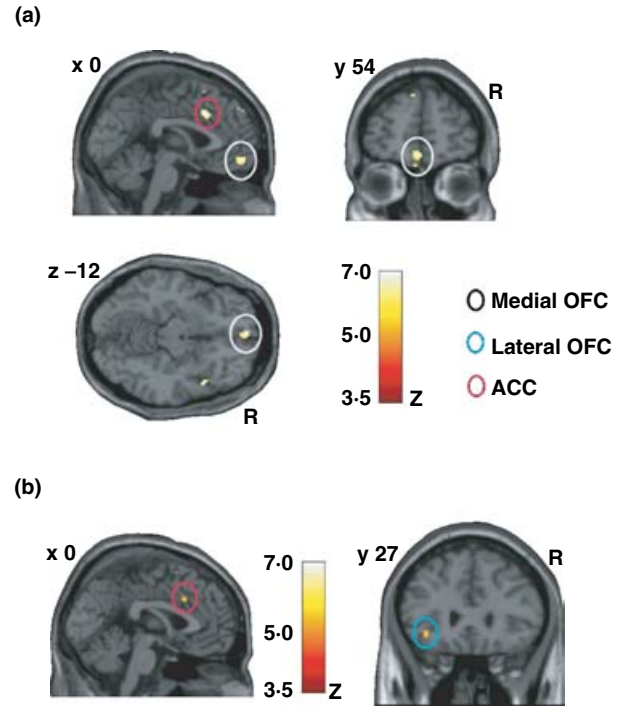

Fig. 4. The representation of pleasant (a) and unpleasant (b) odours in the human brain. (a) Group conjunction results for the three pleasant odours. Saggital and horizontal (left) and coronal (right) views are shown at the levels indicated, all including the same activation in the medial orbitofrontal cortex (OFC; x, y, z, 0, 54, −12; Z score 5·23). Also shown is activation for the three pleasant odours in the anterior cingulate cortex (ACC; x, y, z, 2, 20, 32; Z score 5·44). These activations were significant ($P<0·05$; fully corrected for multiple comparisons). (b) Group conjunction results for the three unpleasant odours. The saggital view (left) shows an activated region of the ACC (x, y, z, 0, 18, 36; Z score 4·42; $P<0·05$; small volume correction (SVC)). The coronal view (right) shows an activated region of the lateral OFC (x, y, z, −36, 27, −8; Z score 4·23; $P<0·05$; SVC). All the activations were thresholded at $P<0·00001$ to show the extent of the activations. R, right side of the brain. (After Rolls *et al.* 2003*a*.)

(see Fig. 4). Further, a correlation was found between the subjective pleasantness ratings of the six odours given during the investigation and activation of a medial region of the rostral orbitofrontal cortex (see Fig. 5). In contrast, a correlation between the subjective unpleasantness ratings of the six odours was found in regions of the left and more lateral orbitofrontal cortex. Activation was also found in the anterior cingulate cortex, with a middle part of the anterior cingulate activated by both pleasant and unpleasant odours, and a more anterior part of the anterior cingulate cortex showing a correlation with the subjective pleasantness ratings of the odours (Rolls *et al.* 2003*a*). These results provide evidence that there is a hedonic map of the sense of smell in brain regions such as the orbitofrontal cortex and cingulate cortex.

Olfactory–taste convergence to represent flavour, and the influence of satiety

To investigate where in the human brain interactions between taste and odour stimuli may be realised to implement flavour, an event-related fMRI study (de Araujo *et al.* 2003*c*) has been performed with sucrose and monosodium glutamate taste, and strawberry and methional (chicken) odours, delivered unimodally or in different combinations. The brain regions that were shown to be activated by both taste and smell include parts of the caudal orbitofrontal cortex, amygdala, insular cortex and adjoining areas, and anterior cingulate cortex. It was shown that a small part of the anterior (putatively agranular) insula responds to unimodal taste and to unimodal olfactory stimuli, and that a part of the anterior frontal operculum is a unimodal taste area (putatively primary taste cortex) not activated by olfactory stimuli. Activations to combined olfactory and taste stimuli where there is little or no activation to either alone (providing positive evidence for interactions between the olfactory and taste inputs) were found in a lateral anterior part of the orbitofrontal cortex. Correlations with consonance ratings for the smell and taste combinations, and for their pleasantness, were found in a medial anterior part of the orbitofrontal cortex (see Fig. 6). Similarly, Small *et al.* (2004) have also found supradditive interactions between congruent taste and smell stimuli in areas including the caudal orbitofrontal cortex and anterior cingulate cortex (see also Small & Prescott, 2005). These results provide evidence on the neural substrate for the convergence of taste and olfactory stimuli to produce flavour in human subjects, and where the pleasantness of flavour is represented in the human brain.

It has been shown (ET Rolls & C McCabe, unpublished results) that the convergence of taste and olfactory information appears to be important for the delicious flavour of umami. When glutamate is given in combination with a consonant savoury odour (vegetable), the resulting flavour can be much more pleasant than the glutamate taste or vegetable odour alone. Moreover, it was found using functional brain imaging with fMRI that the glutamate and savoury odour combination produces much greater activation of the pregenual cingulate cortex and medial orbitofrontal cortex than the sum of the activations by the taste and olfactory components presented separately. Further, activations in these brain regions were shown to be correlated with the pleasantness and consonance of the taste and olfactory components, and the fullness of the flavour, of the stimuli. Similar non-linear effects were not found for NaCl and vegetable odour. It has thus been proposed (ET Rolls & C McCabe, unpublished results) that glutamate acts by the non-linear effects it can produce when combined with a consonant odour. Also, the concept of umami can be thought of as a rich and delicious flavour that is produced by a combination of glutamate taste and a consonant savoury odour. Glutamate is thus a flavour enhancer because of the way that it can combine non-linearly with consonant odours.

To assess how satiety influences the brain activations to a whole food that produces taste, olfactory and texture stimulation, brain activation by whole foods before and after the food is eaten to satiety has been measured (de Araujo *et al.* 2003*a*). The aim was to show, using a food that has olfactory, taste and texture components, the extent of the region that shows decreases when the food becomes less pleasant, in order to identify the different

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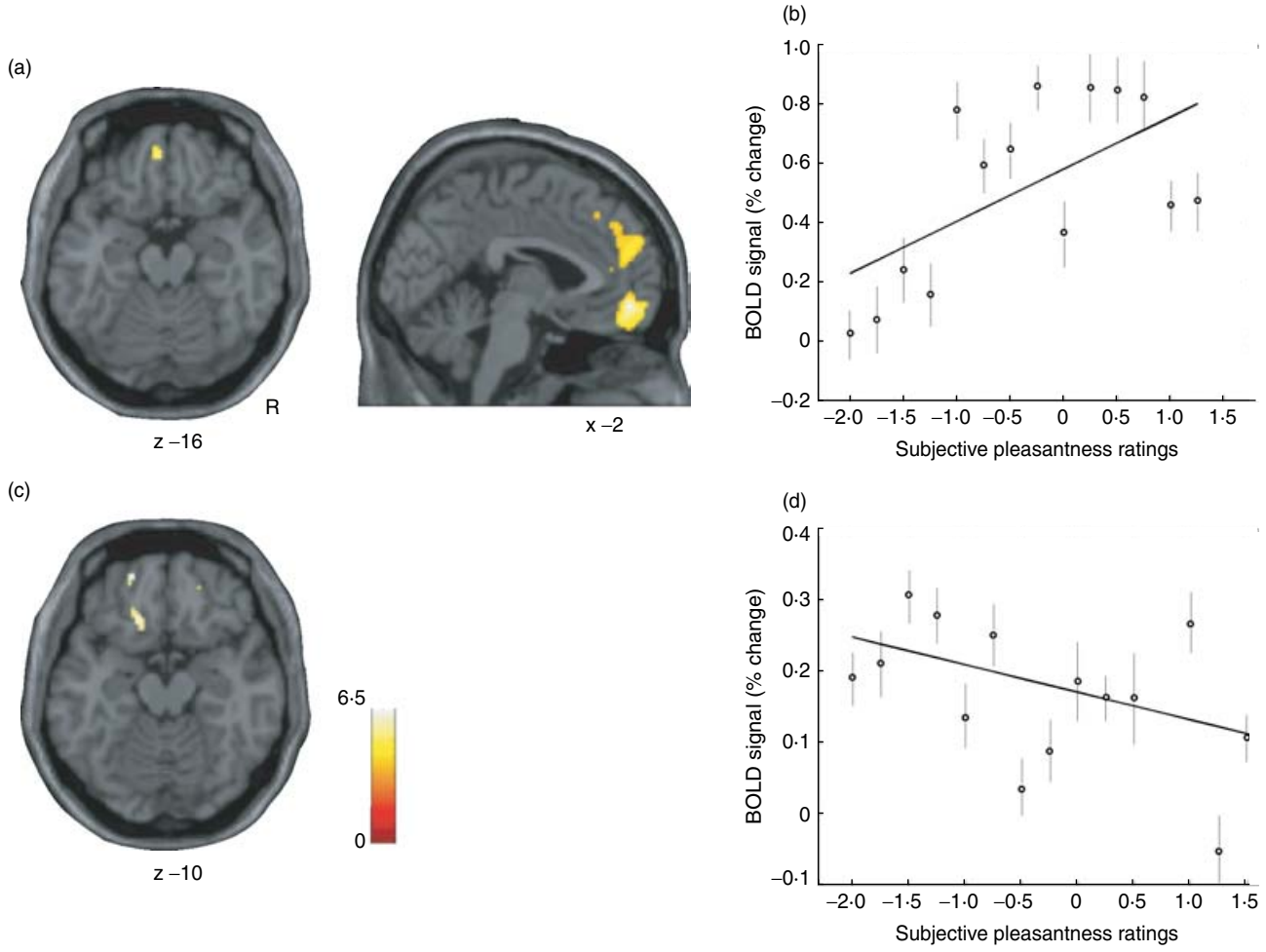

Fig. 5. The representation of pleasant (a, b) and unpleasant (c, d) odours in the human brain. Random-effects group analysis showing the correlation between the blood oxygenation level-dependent (BOLD) signal and the subjective pleasantness ratings in regions of the brain. (a) The region of the medio-rostral orbitofrontal (left; peak at x, y, z, −2, 52, −10; Z score 4·28) correlating positively with pleasantness ratings, as well as the region of the anterior cingulate cortex (right). (b) The relationship between the subjective pleasantness ratings and the BOLD signal from this cluster (in the medial orbitofrontal cortex at y 52), together with the regression line. Values are means with their standard errors across subjects. (c) The regions of the left and more lateral orbitofrontal cortex (peaks at x, y, z, −20, 54, −14; Z score 4·26 and x, y, z, −16, 28, −18; Z score 4·08) correlating negatively with pleasantness ratings. (d) The relationship between the subjective pleasantness ratings and the BOLD signal from the first cluster (in the lateral orbitofrontal cortex at y 54), together with the regression line. Values are means with their standard errors across subjects. R, right side of the brain. The activations were thresholded at $P<0·0001$ for extent. (After Rolls *et al.* 2003*a*.)

brain areas where the pleasantness of the odour, taste and texture of food are represented. The foods eaten to satiety were either chocolate milk or tomato juice. A decrease in activation by the food eaten to satiety relative to the other food was found in the orbitofrontal cortex (Kringelbach *et al.* 2003) but not in the primary taste cortex (see Fig. 7). This study provides evidence that the pleasantness of the flavour of food, and sensory-specific satiety, are represented in the orbitofrontal cortex.

Oral viscosity and fat texture

The viscosity of food in the mouth is represented in the human primary taste cortex (in the anterior insula), and also in a mid-insular area that is not taste cortex but which represents oral somatosensory stimuli (de Araujo & Rolls, 2004). In these regions the fMRI blood oxygenation level-dependent activations are proportional to log viscosity of carboxymethyl cellulose in the mouth. Oral viscosity is also represented in the human orbitofrontal and perigenual cingulate cortices, and it is notable that the perigenual cingulate cortex, an area in which many pleasant stimuli are represented, is strongly activated by the texture of fat in the mouth and also by oral sucrose (de Araujo & Rolls, 2004).

The sight of food

O'Doherty *et al.* (2002) have shown that visual stimuli associated with the taste of glucose activate the orbitofrontal cortex and some connected areas, consistent with the primate neurophysiology. Simmons *et al.* (2005) have

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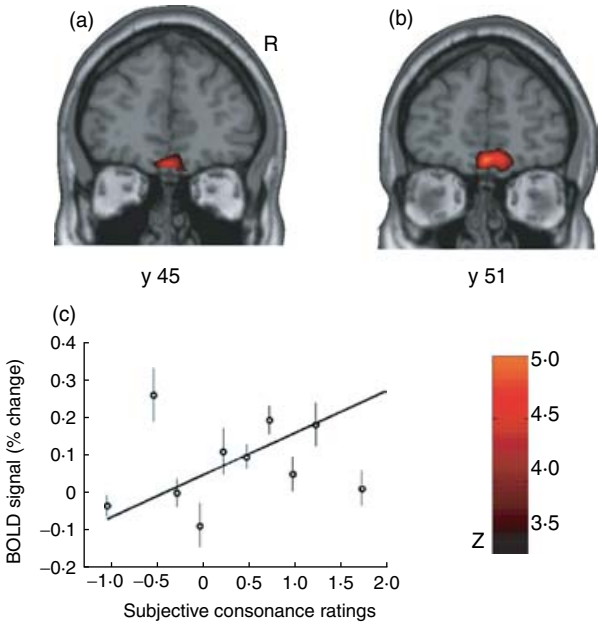

Fig. 6. Flavour formation in the human brain, shown by cross-modal olfactory–taste convergence. Brain areas where activations were correlated with the subjective ratings for stimulus (taste–odour) consonance and pleasantness are shown. (a) A second-level random-effects analysis based on individual contrasts (the consonance ratings being the only effect of interest) revealed a significant activation in a medial part of the anterior orbitofrontal cortex. (b) Random-effects analysis based on the pleasantness ratings showed a significant cluster of activation located in a (nearby) medial part of the anterior orbitofrontal cortex. The images were thresholded at $P<0{\cdot}0001$ for illustration. (c) The relationship between the blood oxygenation level-dependent (BOLD) signal from the cluster of voxels in the medial orbitofrontal (shown in a) and the subjective consonance ratings. The analyses shown included all the stimuli included in this investigation. Values are means with their standard errors across subjects. r 0·52. R, right side of the brain. (After de Araujo *et al.* 2003*c*.)

found that showing pictures of foods, compared with pictures of locations, can also activate the orbitofrontal cortex and some connected areas. However, taste stimuli were not used in this study, so the extent to which the activations to the sight and taste of food overlap cannot be defined. Consistent with these findings, Pelchat *et al.* (2004) have found that after consuming a monotonous diet subjects who are instructed to imagine foods that they crave show more activation in some brain areas, including part of the insula, than subjects who consume a normal diet. Similarly, the orbitofrontal cortex and connected areas have also been found to be activated after presentation of food stimuli to food-deprived subjects (Wang *et al.* 2004).

Cognitive effects on representations of food

Brie cheese can smell pleasant. However, the same odour taken out of the context of cheese might be unpleasant. There is evidence that the sight (including colour) of a food or wine can influence its flavour. However, what about a more cognitive influence, such as a word? Can it influence the perception and hedonics of food-related stimuli? If so, how far back down into the sensory system does the cognitive influence reach? To address this issue, an fMRI investigation (de Araujo *et al.* 2005) has been performed in which the delivery of a standard test odour (isovaleric acid combined with cheddar cheese flavour, presented orthonasally using an olfactometer) was paired with a descriptor word on a screen, which in different trials was 'Cheddar cheese' or 'body odour'. The subjects rated the pleasantness and the intensity of the odour in every trial. α-Ionone (pleasant, labelled 'flowers') and octanol (unpleasant, labelled 'burned plastic') were used as reference pleasant and unpleasant stimuli for the psychophysics and neuroimaging. Subjects were found to rate the affective value of the test odour as more unpleasant when labelled 'body odour' than when labelled 'Cheddar cheese'. Furthermore, the medial orbitofrontal cortex/rostral anterior cingulate cortex (anterior cingulate cortex) was more activated by the test stimulus labelled 'Cheddar cheese' than when labelled 'body odour', and these activations were correlated with the pleasantness ratings (see Fig. 8). This cognitive modulation was also found in the medial amygdala olfactory area, and extended towards the olfactory tubercle. Thus, cognitive modulation extends in the olfactory system as far down as the secondary olfactory cortex, in the orbitofrontal cortex, and may even influence some parts of the primary olfactory areas such as the olfactory tubercle. The implication is that cognitive factors can have profound effects on the responses to the hedonic and sensory properties of food, in that these effects are manifest quite far back into sensory processing, so that at least hedonic representations of odours are affected, and even perceptual representations may be modulated (de Araujo *et al.* 2005).

Implications for understanding, preventing and treating obesity

Understanding the mechanisms that control appetite is becoming an increasingly important issue, given the increasing incidence of obesity (a threefold increase in the UK since 1980 to 20%, defined by BMI >30 kg/m^2) and the realisation that it is associated with major health risks (with 1000 deaths each week in the UK attributable to obesity). It is important to understand and thereby be able to minimise and treat obesity, because many diseases are associated with a body weight that is much above normal. These diseases include hypertension, CVD, hypercholesterolaemia and gall bladder disease; in addition, obesity is associated with some deficits in reproductive function (e.g. ovulatory failure) and with an excess mortality from certain types of cancer (Garrow, 1988; Barsh & Schwartz, 2002; Cummings & Schwartz, 2003; Schwartz & Porte, 2005).

There are many factors that can cause or contribute to obesity in man (Brownell & Fairburn, 1995) that are investigated using approaches within or related to neuroscience and psychology (Rolls, 2005*a*,*b*, 2006). Rapid progress is being made at present in understanding many of these factors, with the aim of leading to better ways to minimise and treat obesity. These factors include the following.

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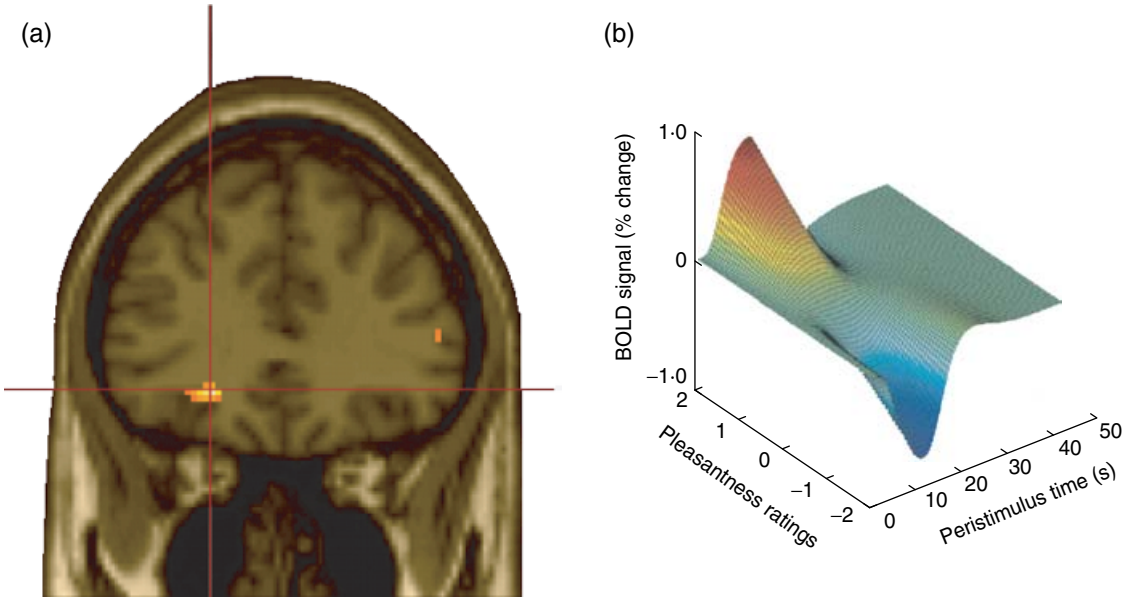

Fig. 7. Areas of the human orbitofrontal cortex with activations correlating with pleasantness ratings for food in the mouth. (a) Coronal section through the region of the orbitofrontal cortex from the random-effects group analysis showing the peak in the left orbitofrontal cortex (Talairach coordinates x, y, z, −22, 34, −8, Z score 4·06), in which the blood oxygenation level-dependent (BOLD) signal in the voxels (shown in yellow) was significantly correlated with the subjects' subjective pleasantness ratings of the foods throughout an experiment in which the subjects were hungry and found the food pleasant, and were then fed to satiety with the food, after which the pleasantness of the food decreased to neutral or slightly unpleasant. The design was a sensory-specific satiety design, and the pleasantness of the food not eaten in the meal, and the BOLD activation in the orbitofrontal cortex, were not altered by eating the other food to satiety. The two foods were tomato juice and chocolate milk. (b) Plot of the magnitude of the fitted haemodynamic response from a representative single subject *v.* the subjective pleasantness ratings (on a scale from −2 to +2) and peristimulus time (s). (After Kringelbach *et al.* 2003.)

Genetic factors

Genetic factors are of some importance; for example, 11% of the variance in RMR in a human population is attributable to inheritance (Garrow, 1988; Barsh & Schwartz, 2002; Cummings & Schwartz, 2003). However, the 'obesity epidemic' that has occurred since 1990 cannot be attributed to genetic changes, for which the time scale is far too short, but instead to factors such as the increased palatability, variety and availability of food (as well as less exercise), which are some of the crucial drivers of food intake and the amount of food that is eaten (Rolls, 2005*a*,*b*, 2006) and will be described later.

Endocrine factors and their interaction with brain systems

A small proportion of cases of obesity can be related to gene-related dysfunctions of the peptide systems in the hypothalamus; for example, 4% of obese individuals have deficient receptors (melanocortin 4 receptor) for melanocyte-stimulating hormone (Barsh & Schwartz, 2002; Cummings & Schwartz, 2003; Horvath, 2005). Cases of obesity that can be related to changes in the leptin hormone satiety system are very rare (Farooqi *et al.* 2001). Further, obese individuals generally have high levels of leptin, so leptin production is not the problem; instead, leptin resistance (i.e. insensitivity) may be somewhat related to obesity, with the resistance perhaps related in part to smaller effects of leptin on arcuate nucleus neuropeptide Y/agouti-related protein neurons (Munzberg & Myers, 2005). However, although there are similarities in fatness within families, these similarities are as strong between spouses as they are between parents and children, so that these similarities cannot be attributed to genetic influences, but presumably reflect the effect of family attitudes to food and weight.

Brain processing of the sensory properties and pleasantness of food

The way in which the sensory factors produced by the taste, smell, texture and sight of food interact in the brain with satiety signals (such as gastric distension and satiety-related hormones) to determine the pleasantness and palatability of food, and therefore whether and how much food will be eaten, has been described earlier (see above) and is shown in Fig. 1. The concept is that convergence of sensory inputs produced by the taste, smell, texture and sight of food occurs in the orbitofrontal cortex to build a representation of food flavour. The orbitofrontal cortex is where the pleasantness and palatability of food are represented, on the basis that these representations of food are only activated if hunger is present and correlate with the subjective pleasantness of the food flavour (Rolls, 2005*a*,*b*, 2006). The orbitofrontal cortex representation of whether food is pleasant (given any satiety signals present) then

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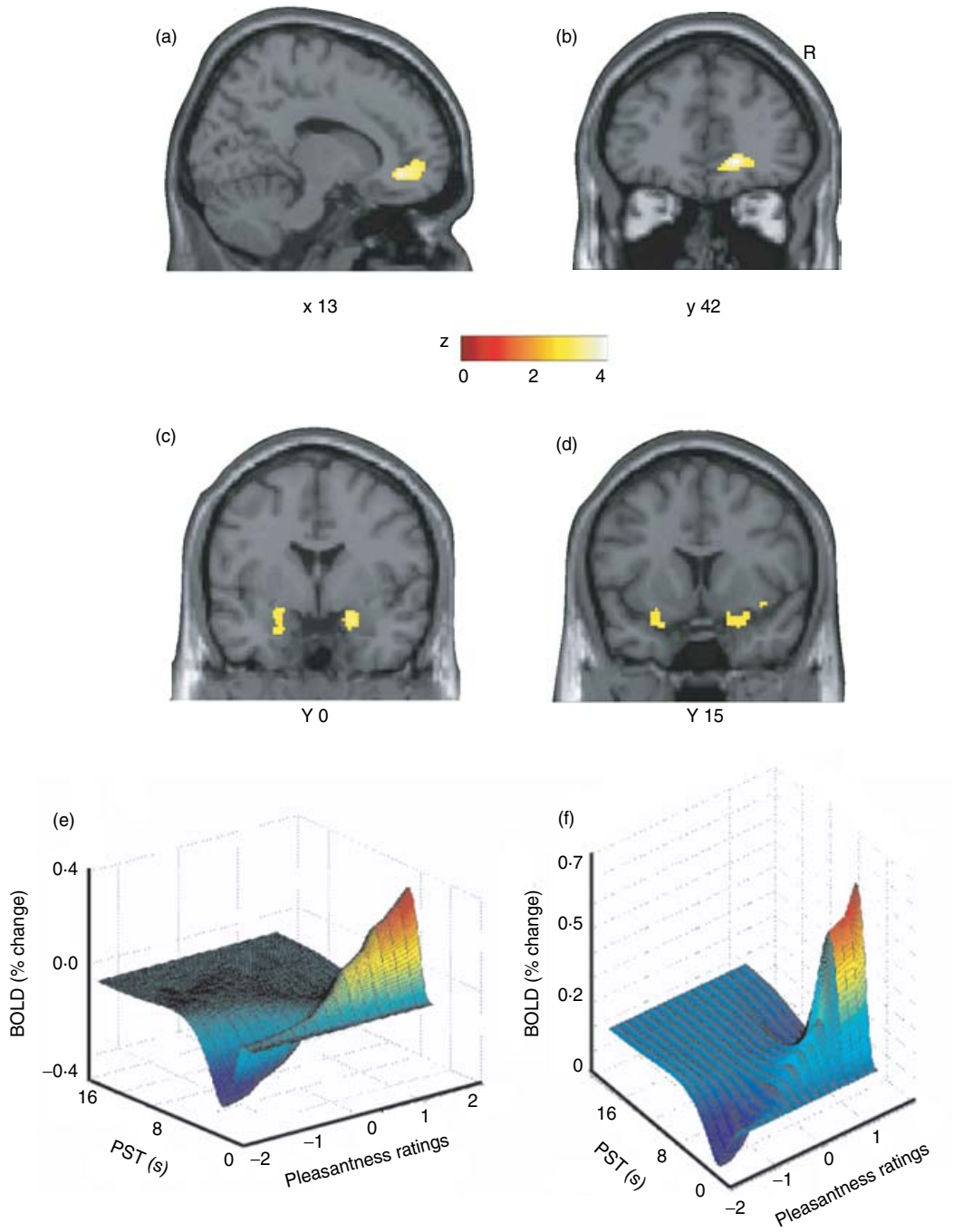

Fig. 8. Cognitive influences (word labels) on olfactory representations in the human brain. Group (random) effects analysis showing the brain regions where the blood oxygenation level-dependent (BOLD) signal was correlated with pleasantness ratings given to the test odour. The pleasantness ratings were being modulated by the word labels (for details, see p. 105). Activations in the rostral anterior cingulate cortex, in the region adjoining the medial orbitofrontal cortex, shown in a saggital slice (a) and coronally (b). Bilateral activations in the amygdala (c) and extended anteriorly to the primary olfactory cortex (d). The image was thresholded at $P<0{\cdot}0001$ uncorrected in order to show the extent of the activation. (e) Parametric plots of the data averaged across all subjects showing that the percentage BOLD change (fitted) correlates with the pleasantness ratings in the region shown in a and b. The parametric plots were very similar for the primary olfactory region shown in d. PST, post-stimulus time (s). (f) Parametric plots for the amygdala region shown in c. R, right side of the brain. (After de Araujo *et al.* 2005.)

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drives brain areas such as the striatum and cingulate cortex that then lead to eating behaviour.

The fundamental concept about some of the major causes of obesity that this information leads to is that sensory stimulation produced by the taste, smell, texture and appearance of food, as well as its availability, has increased dramatically over the last 30 years, yet the satiety signals produced by stomach distension, satiety hormones etc. have remained essentially unchanged. Consequently, the effect on the brain's control system for appetite (shown in Fig. 1) is to lead to a net average increase in the reward value and palatability of food that over-rides the satiety signals and contributes to the tendency to be overstimulated by food and to overeat.

In this scenario it is important to reach a much better understanding of the rules used by the brain to produce the representation of the pleasantness of food and how the system is modulated by eating and satiety. The attainment of this understanding and knowing how the sensory factors can be designed and controlled so that satiety signals are not overridden are important research areas in the understanding, prevention and treatment of obesity. Advances in understanding the receptors that encode the taste and olfactory properties of food (Buck, 2000; Zhao *et al*. 2003) and the processing in the brain of these properties (Rolls, 2004, 2005*a*,*b*) are also important in providing the potential to produce highly-palatable food that is at the same time nutritious and healthy.

Food palatability

A factor in obesity (as mentioned earlier) is food palatability, which with modern methods of food production can now be greater than would have been the case during the evolution of man's feeding control systems. These brain systems evolved so that internal signals from, for example, gastric distension and glucose utilisation could act to decrease the pleasantness of the sensory sensations produced by feeding sufficiently by the end of a meal to stop further eating (Rolls, 2004, 2005*a*,*b*). However, the greater palatability of modern food may mean that this balance is altered, so that there is a tendency for the greater palatability of food to be insufficiently decreased by a standard amount of food eaten, and extra food is eaten in a meal (see Fig. 1).

Sensory-specific satiety and the effects of variety on food intake

Sensory-specific satiety is the decrease in the appetite for a particular food as it is eaten in a meal, without a decrease in the appetite for different foods (Rolls, 2004, 2005*a*,*b*), as shown earlier. It is an important factor influencing how much of each food is eaten in a meal, and its evolutionary importance may be to encourage eating of a range of different foods, thus obtaining a range of nutrients. As a result of sensory-specific satiety, if a wide variety of foods is available overeating in a meal can occur. Given that it is now possible to make available a very wide range of food flavours, textures and appearances, and such foods are readily available, this variety effect may be a factor in promoting excess food intake.

Fixed meal times and the availability of food

Another factor that could contribute to obesity is fixed meal times, in that the normal control of food intake by alterations in inter-meal interval is not readily available in human subjects, and food may be eaten at a meal time even if hunger is not present (Rolls, 2005*a*). Furthermore, because of the high and easy availability of food (in the home and workplace) and stimulation by advertising, there is a tendency to start eating again when satiety signals after a previous meal have decreased only a little, and the consequence is that the system again becomes overloaded.

Food saliency and portion size

Making food salient, for example by placing it on display, may increase food selection, particularly in the obese (Schachter, 1971; Rodin, 1985). Portion size is another factor, with more food being eaten if a large portion is presented (Kral & Rolls, 2004), although whether it is a factor that can lead to obesity, rather than just altering meal size, is not yet clear. The driving effects of visual and other stimuli, including the effects of advertising, on the brain systems that are activated by food reward may be different in different individuals and may contribute to obesity.

Energy density of food

Although the gastric emptying rate is slower for high-energy-density foods, it does not fully compensate for the energy density of the food (Hunt & Stubbs, 1975; Hunt, 1980). Thus, eating energy-dense foods (e.g. high-fat foods) may not allow gastric distension to contribute sufficiently to satiety. Consequently, the energy density of foods may be an important factor that influences how much energy is consumed in a meal. Indeed, it is notable that obese individuals tend to eat foods of high energy density and visit restaurants serving high-energy-density (e.g. high-fat) foods. It is also a matter of clinical experience that gastric emptying is faster in the obese than in thin individuals, so that gastric distension may play a less-effective role in contributing to satiety in the obese.

Eating rate

A factor related to the effects associated with the energy density of food is eating rate, which is typically fast in the obese and may provide insufficient time for the operation of the full effect of satiety signals as food reaches the intestine.

Stress

Another potential factor in obesity is stress, which can induce eating and could contribute to a tendency to obesity. (In a rat model mild stress in the presence of food can lead to overeating and obesity. This overeating is reduced by anti-anxiety drugs.)

Food craving

Binge eating has some parallels to addiction. In one rodent model of binge eating access to sucrose for several hours

each day can lead to binge-like consumption of the sucrose over a period of days (Colantuoni *et al*. 2002; Avena & Hoebel, 2003*a*,*b*; Spangler *et al*. 2004), and the binge eating is associated with the release of dopamine. In this model binge eating is brought close to an addictive process, in that after the binge eating has become a habit sucrose withdrawal decreases dopamine release in the ventral striatum (a part of the brain involved in addiction to drugs such as amphetamine), altered binding of dopamine to its receptors in the ventral striatum is produced and signs of withdrawal from an addiction occur, including teeth chattering. In withdrawal the animals are also hypersensitive to the effects of amphetamine. Another rat model of binge eating is being used to investigate whether the reinforcing cues associated with the binge eating of fat can be reduced by the γ-aminobutyric acid-B receptor agonist baclofen (Corwin & Buda-Levin, 2004).

Energy output

If energy intake is greater than energy output, body weight increases. Energy output is thus an important factor in the equation. A lack of exercise or the presence of high room temperatures may tend to limit energy output and thus contribute to obesity. It should be noted, however, that obese individuals do not generally suffer from a very low metabolic rate. In fact, as a population, in line with their elevated body weight, obese individuals have higher metabolic rates than normal-weight individuals (Garrow, 1988); at least at their obese body weights, and it might be interesting to investigate this aspect further.

Cognitive factors

As shown earlier, cognitive factors, e.g. preconceptions about the nature of a particular food or odour, can reach down into the olfactory system in the orbitofrontal cortex, which controls the palatability of food, to influence the pleasantness rating of an olfactory stimulus (de Araujo *et al*. 2005). This process may have potential for controlling food intake and needs further investigation.

The psychology of compliance with information about risk factors for obesity

It is important to develop better ways to provide information that will be effective in the long term in decreasing food intake while maintaining a healthy diet, and in promoting an increase in energy expenditure by, for example, encouraging exercise.

Conclusions

The reward value of food and its subjective complement, the rated affective pleasantness of food, is decoded in primates, including man, only after several stages of analysis. First, the representation of the taste of the food (its identity and intensity) is made explicit in the primary taste cortex. Only later, in the orbitofrontal cortex, is the reward value made explicit in the representation, for it is here that satiety signals modulate the responses of the taste and flavour neurons. Thus, in the control of food intake the reward value or pleasantness is crucial to the design of how food intake is controlled, and the reward value is represented only in specialised cortical areas. The orbitofrontal cortex is, moreover, where multimodal representations of food, which include taste, texture, olfactory and visual components, are built. The actual satiety signals are complex and include sensory-specific satiety (computed in the orbitofrontal cortex), gastric distension, gut satiety signals, plasma glucose and hormones such as leptin.

Although representations of the taste and texture of food are found in the primate, including the human amygdala (O'Doherty *et al*. 2001; Rolls & Scott, 2003; Kadohisa *et al*. 2005*a*,*b*; Wilson & Rolls, 2005), the primate orbitofrontal cortex is more closely related to the changing affective value of food than the amygdala (Sanghera *et al*. 1979; Rolls, 2000*c*; Rolls & Scott, 2003), as the orbitofrontal cortex shows responses that decrease to zero as the reward decreases to zero with satiety and the orbitofrontal cortex tracks (and probably computes) the changing reward value of stimuli as they are altered by stimulus–reinforcer association learning and reversal. The outputs of the orbitofrontal cortex reach brain regions such as the striatum, cingulate cortex and dorsolateral prefrontal cortex, where behavioural responses to food may be elicited because these structures produce behaviour that makes the orbitofrontal cortex reward neurons (which represent a goal for behaviour) fire. At the same time, outputs from the orbitofrontal cortex and amygdala, in part via the hypothalamus, may provide for appropriate autonomic and endocrine responses to food to be produced, including the release of hormones such as insulin.

The brain areas where the pleasantness or affective value of smell and taste are represented are closely related to the brain areas involved in emotion. Emotions can usefully be defined as states elicited by rewards and punishers (Rolls, 1999, 2005*a*), and olfactory and taste stimuli can be seen as some of the classes of stimuli that can produce emotional states. An important basis for appetite and the regulation of food intake is that reward or affective responses to the sensory properties of food drive food intake and are modulated or gated by satiety signals, as indicated in Fig. 1. Understanding the operation of the hedonic regulatory system for the sensory properties of food is important, as shown earlier, for understanding the normal regulation of food intake and dysfunctions that can arise and contribute to obesity.

Acknowledgments

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