

# Functions of the orbitofrontal and pregenual cingulate cortex in taste, olfaction, appetite and emotion

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Received: 10 July 2007

Accepted: 10 October, 2007

Complementary neurophysiological recordings in macaques and functional neuroimaging in humans 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. The representation of taste and other food-related stimuli in the orbitofrontal cortex of macaques is found from its lateral border throughout area 13 to within 7 mm of the midline, and in humans the representation of food-related and other pleasant stimuli is found particularly in the medial orbitofrontal cortex. 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 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 which drives food intake. A neuronal representation of taste is also found in the pregenual cingulate cortex, which receives inputs from the orbitofrontal cortex, and in humans many pleasant stimuli activate the pregenual cingulate cortex, pointing towards this as an important area in motivation and emotion.

**Keywords:** taste, olfaction, neuronal activity, fMRI, appetite, emotion, orbitofrontal cortex, cingulate cortex

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The aims of this 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 to the brain mechanisms underlying the control of appetite and food intake. 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 humans. A broad perspective on brain processing involved in emotion and in hedonic aspects of the control of food intake is provided by Rolls (1).

## 1. Taste processing in the primate brain

### Pathways

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

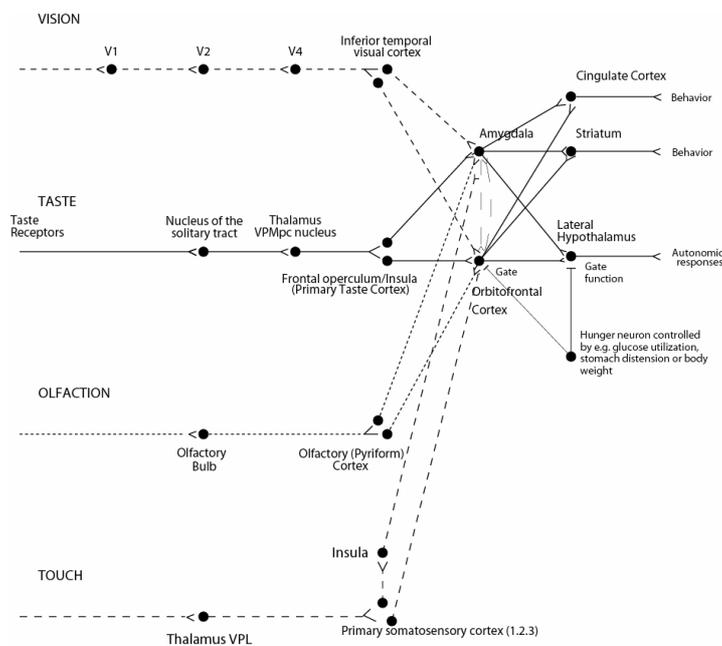


Fig. 1. Schematic diagram of the taste and olfactory pathways in primates including humans showing how they converge with each other and with visual pathways. Hunger modulates the responsiveness of the representations in the orbitofrontal cortex of the taste, smell, texture and sight of food (indicated by the gate function), and the orbitofrontal cortex is where the palatability and pleasantness of food is represented. VPMpc: ventralposteromedial thalamic nucleus; V1, V2, V4: visual cortical areas

*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 (2–4), and umami as exemplified by monosodium glutamate (5, 6), but also other neurons that encode oral somatosensory stimuli including viscosity, fat texture, temperature, and capsaicin (7). 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 (7). Neurons in the primary taste cortex do not represent the reward value of taste, that is the appetite for a food, in that their firing is not decreased to zero by feeding the taste to satiety (8, 9).

*The secondary taste cortex*

A secondary cortical taste area in primates was discovered by Rolls, Yaxley and Sienkiewicz (10) in the caudolateral orbitofrontal cortex, extending several mm 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 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 (4, 11), 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) (5) and inosine monophosphate (which is present in meat and some fish such as tuna) (6). This evidence, taken together with the identification of a glutamate taste receptor (12), leads to the view that there are five prototypical types of taste information channels, with umami contributing, often in combination with corresponding olfactory inputs (13, 14), to the flavour of protein. In addition, other neurons respond to water, and others to somatosensory stimuli including astringency as exemplified by tannic acid (15), and capsaicin (16, 17).

*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, for example hunger, is one important way in which motivational behaviour is controlled (1, 18). The subjective correlate of this modulation is that food tastes pleasant when hungry, and tastes hedonically neutral when it has been eaten to satiety. We have found that the modulation of taste-evoked signals by motivation is not a property found in early stages of the primate gustatory system. The responsiveness of taste neurons in the nucleus of the solitary tract (19) and in the primary taste cortex

(frontal opercular 8, insular 9) is not attenuated by feeding to satiety. In contrast, in the secondary taste cortex, in the caudolateral part of the orbitofrontal cortex, it has been shown that the responses of the neurons to the taste of glucose decreased to zero while the monkey ate it to satiety, during the course of which the behaviour turned from avid acceptance to active rejection (20). This modulation of responsiveness of the gustatory responses of the orbitofrontal cortex neurons by satiety could not have been due to peripheral adaptation in the gustatory system or to altered efficacy of gustatory stimulation after satiety was reached, because modulation of neuronal responsiveness by satiety was 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 was also found that the decreases in the responsiveness of the neurons were relatively specific to the food with which the monkey had been fed to satiety. An example for a neuron that had taste, olfactory, and visual responses to food is shown in Figure 2. Feeding to satiety with blackcurrant juice produced a larger decrease in the neuron's response to the blackcurrant juice than to most of the other stimuli in all three sensory modalities (20, 21).

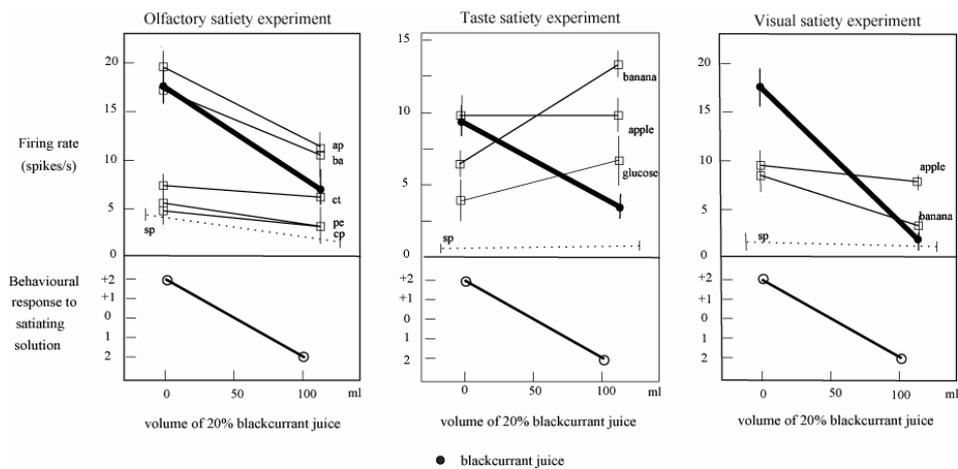


Fig. 2. Orbitofrontal cortex neuron with visual, olfactory and taste responses, showing the responses before and after feeding to satiety with blackcurrant juice. The solid circles show the responses to blackcurrant juice. The olfactory stimuli included apple (ap), banana (ba), citral (ci), phenylethanol (pe), and caprylic acid (cp). The spontaneous firing rate of the neuron is shown (sp). The taste panel is for the flavour of food in the mouth. Below the neuronal response data for each experiment, the behavioural measure of the acceptance or rejection of the solution on a scale from +2 to -2 is shown. The values shown are the mean firing rate and its s.e. After Critchley and Rolls (21)

This evidence shows that the reduced acceptance of food which occurs when food is eaten to satiety, and the reduction in the pleasantness of its taste (22–28), 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, humans reported that the taste of the food on which they had been satiated tasted almost as intense as when they were hungry, though much less pleasant (49). 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 (30) 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 (See further 4, 18, 31, 32–35). 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 Figure 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 (1).

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 we are not hungry.

#### *A representation of taste throughout area 13 in primates*

Functional neuroimaging studies have shown that the most medial part of the human orbitofrontal cortex is activated by taste, oral texture, and olfactory stimuli (14, 36–46), and that the activations correlate with ratings of pleasantness (1, 47). This most medial part of the orbitofrontal cortex has been little explored in macaques, and a study has recently been performed to investigate how extensive the representation of taste is in the macaque orbitofrontal cortex (48), to help provide a foundation for understanding the functions of the medial orbitofrontal cortex in humans.

In macaques it is known that the secondary taste cortex in the caudolateral part of the orbitofrontal cortex projects to a more anterior part of the orbitofrontal cortex that extends medially (as shown by more anterior orbitofrontal cortex injections of horseradish peroxidase which filled neurons in the more caudal orbitofrontal cortex, but not the primary taste cortex) (49) and indeed taste neurons have been shown to extend medially through area 13 m in a region that is approximately 7–12 mm from the midline (6, 15, 50, 51) see Figure 3 with cytoarchitectonic areas indicated after (52, 53–55). Whether neurons that are responsive to taste stimuli are present even more medially than area 13 m in the orbitofrontal cortex (i.e. medial to 7 mm lateral from the midline) (e.g. area 14), and possibly within areas of medial wall cortex (e.g. areas 10, and 25 or subgenual cingulate cortex, see Fig. 3) has not been previously investigated.

Taste neurons have been established previously as being present in the main part of area 13 (6, 15, 50, 51), as well as extending out laterally to area 12 (10, 16, 17, 20, 56, 57).

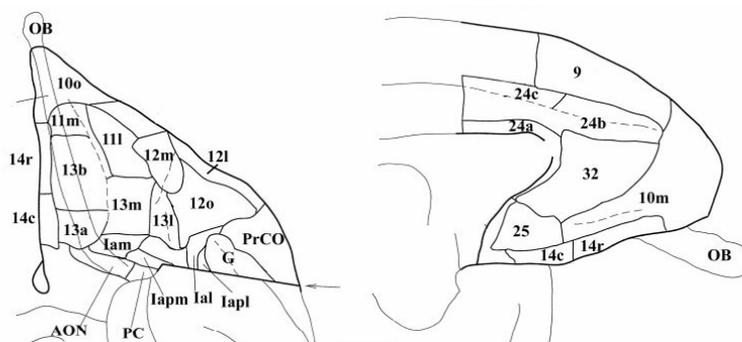


Fig. 3. Architectonic subdivisions of the macaque orbital (at left) and medial (at right) prefrontal cortex. Scale bar = 5 mm. AON – anterior olfactory nucleus; G – primary gustatory cortex; lai, lal, lam, lapm – subdivisions of the agranular insular cortex; OB – olfactory bulb; PC – pyriform cortex; PrCO – precentral opercular area. After Carmichael and Price (52)

The data were obtained in two rhesus macaques in recordings that included the medial orbitofrontal cortex and adjoining areas that extended as far anterior as approximately 10 mm with respect to the sphenoid reference (with the recording sites shown in Fig. 5) (48) using the same methods as in previous studies (7, 16, 17). We screened 1753 neurons and found taste neurons in the mid and medial orbitofrontal cortex region extending to within approximately 7 mm of the midline in area 13 m, but very few in the more medial areas (10, 14 and 25, as shown in Figure 4).

Of the neurons recorded in the more medial parts of area (13, 25) (2.9%) responded to taste and/or oral texture. Figure 6 shows the responses of a neuron (bo375) in the medial orbitofrontal cortex to the set of stimuli used. This neuron had taste responses (to glucose but not NaCl, HCl or QuinineHCl). It also had responses related to oral viscosity, with increasing firing rates in the range 10–10,000 cP, and its responses to fats were approximately related to their viscosity. The neuron also had different responses to different oral temperatures. This neuron was thus classified as having taste and texture responsiveness.

As shown in Figures 4 and 5, regions of cortex sampled more medially than approximately 5 mm lateral to the midline contained few neurons with taste or oral texture responses – these regions included areas 14 and 10 and the subgenual cingulate cortex, area 25. In particular, in the medial part of area 13, 25/871 neurons responded to taste, whereas more medially in areas 14/10/25 only 2/507 neurons responded to taste. A Chi-square test showed that these proportions were different. In particular, taking the taste and oral texture cells and the number of unresponsive cells showed a significant difference, with  $\chi^2=8.67$ ,  $df=1$ ,  $p<0.01$ . This statistical test provides clear

evidence that whereas taste cells are found in area 13, the proportion of taste-responsive cells in the more medial areas 14/10/25 is much less. Although cells were recorded in area 25 and some in area 32 at this anterior-posterior level, only 1 responded to taste (Figs 4 and 5).

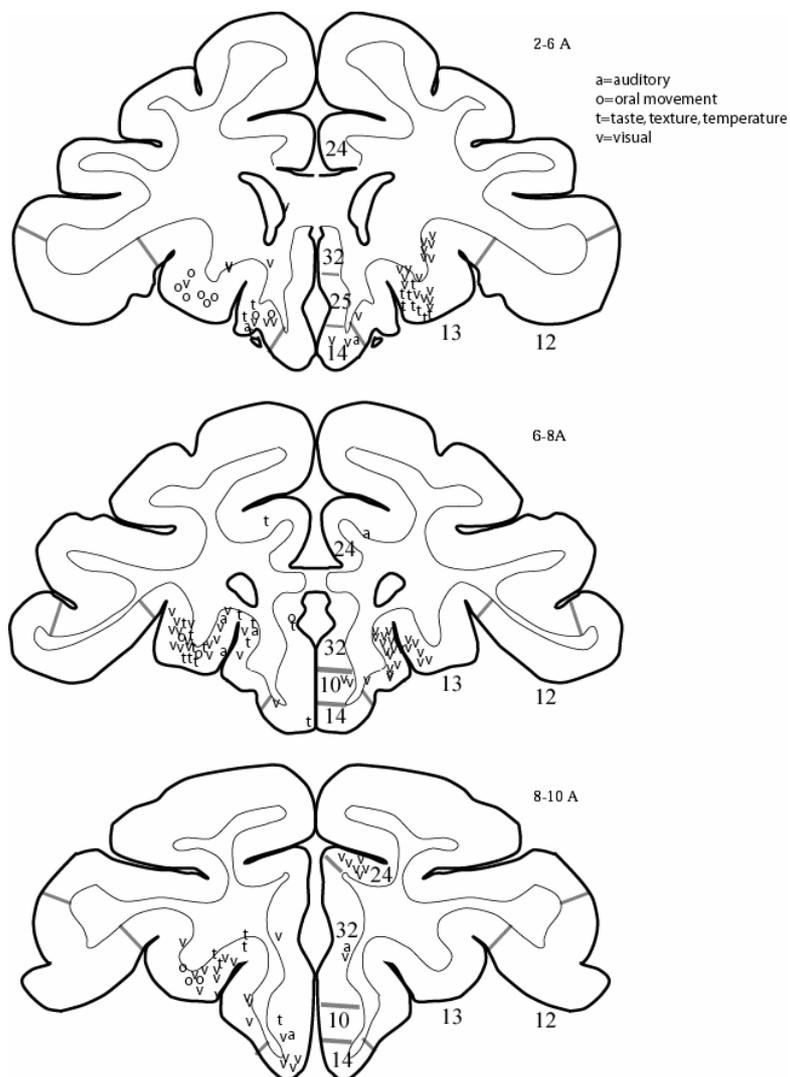


Fig. 4. The reconstructed positions of the neurons with different types of response, with the cytoarchitectonic boundaries determined after Carmichael and Price (52). The neurons within different planes at distances in mm anterior (A) to the sphenoid reference point are shown on the coronal sections. After Rolls et al. (48)

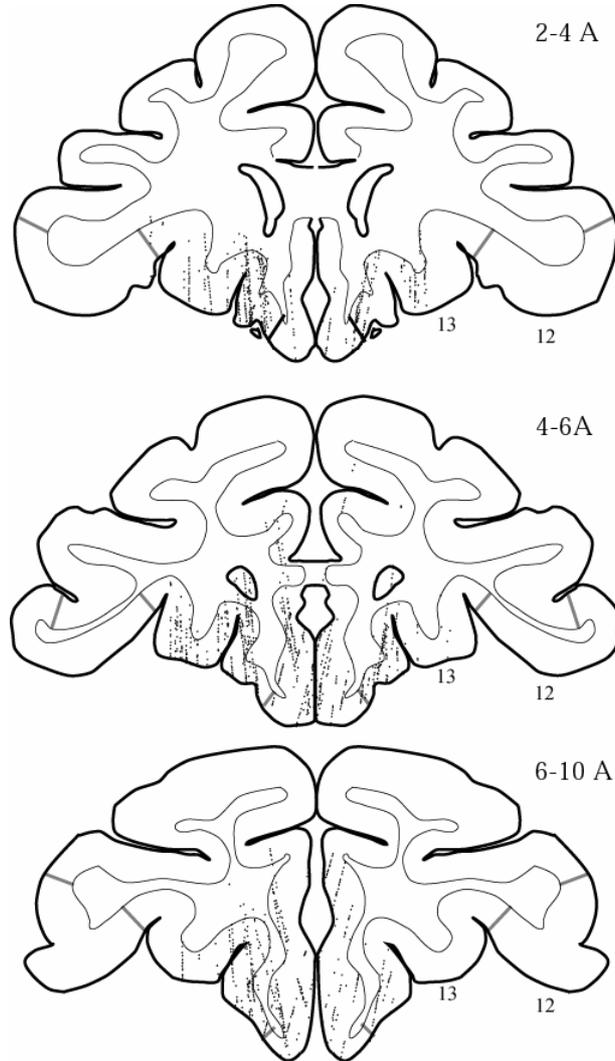


Fig. 5. The locations of the 1753 neurons recorded in the medial orbitofrontal cortex and adjacent medial wall areas in the macaques in which the neurons shown in Figure 4 were found are indicated to show the regions sampled. After Rolls et al. (48)

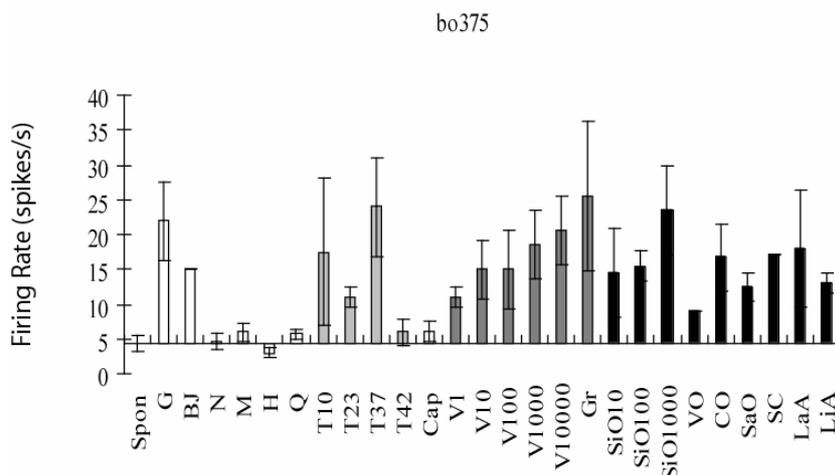


Fig. 6. Responses of a medial orbitofrontal cortex neuron (bo375) with differential responses to tastes and oral viscosity stimuli. The mean ( $\pm$ SEM) firing rate responses to each stimulus calculated in a 1 s period over several trials are shown. The spontaneous (Spon) firing rate is shown by the horizontal line. The taste stimuli were 1 M glucose (G), 0.1 M NaCl (N), 0.1 M MSG (M), 0.01 M HCl (H) and 0.001 M QuinineHCl (Q); the temperature stimuli were T10, T23, T37 and T42 where the number indicates the temperature in  $^{\circ}$ C; the viscosity stimuli were V1, V10, V100, V1000 and V10000 where the numeral indicates the viscosity in cP at 23  $^{\circ}$ C; fat texture stimuli were SiO10, SiO100, SiO1000 (silicone oil with the viscosity indicated), vegetable oil (VO), coconut oil (CO) and safflower oil (SaO). BJ is fruit juice; Cap is 10  $\mu$ M capsaicin; LaA is 0.1 mM lauric acid; LiA is 0.1 mM linoleic acid; Gr is the gritty stimulus. The light grey shading shows the set of temperature stimuli; medium grey the viscosity stimuli; and dark grey the fat/fatty acid stimuli.

After Rolls et al. (48)

The finding that there are taste neurons in the orbitofrontal cortex in regions more lateral than 7 mm from the midline, including area 13 (Fig. 3), is consistent with previous findings in macaques that taste neurons have been shown to extend throughout area 13 in a region that is approximately 7–12 mm from the midline (6, 15, 50), the exact area in which Pritchard et al. (51) also found a population of taste neurons see Figure 3 with cytoarchitectonic areas indicated after (52, 53–55). We showed in our previous studies that these taste neurons extend from approximately 4 mm anterior to the clinoid process of the sphenoid bone to 12 mm anterior. (Pritchard et al. (51) focussed their investigation on a region 5–9 mm anterior to the sphenoid.) Although Pritchard et al. (51) commented that in their study there was a good proportion of taste neurons in this area, we, in comparing the proportions of taste neurons in different parts of the orbitofrontal cortex extending out laterally through area 12, find similar proportions of taste neurons throughout this mediolateral extent (from 7 mm to 20 mm lateral) (6, 10, 15–17, 20, 50, 57, 58). Moreover, even in area 13 m, in the region

7–12 mm lateral where Pritchard et al. (51) found taste neurons, we know that many other properties are represented, including oral texture as exemplified by astringency and fat texture (15, 59); and olfactory properties (21, 31, 60) which can become associated by learning with taste stimuli (61). Thus area 13 m contains taste, oral texture, and olfactory representations, some of these cells are multimodal in these modalities (15, 50, 61), and the majority of these neurons have their responses to taste and/or olfactory stimuli modulated by hunger (21).

An implication of the orbitofrontal cortex recordings described here is that the human medial orbitofrontal cortex region activated by many types of reward may have shifted medially somewhat with respect to its location in macaques. It is quite clear from a retrograde neuronal tracing study with horseradish peroxidase administered to a region containing taste neurons in the macaque lateral orbitofrontal cortex that the lateral part of the orbitofrontal cortex receives direct inputs from the primary taste cortex in the insula (see Baylis et al. (49)). The location of the macaque primary taste cortex was described by Pritchard et al. (62). More medial orbitofrontal cortex areas may also receive inputs directly from the insular and frontal opercular primary taste cortical areas, for taste neurons are also common in area 13 more medially, as shown here and elsewhere (see references given above). An anatomical study of the forward projections of the primary taste cortex would be useful in clarifying this, though we note that the secondary taste cortex in more lateral regions (12o) does project medially (63). The more middle/medial part of the orbitofrontal cortex (area 13 m) also has neurons that decrease their taste responses in relation to sensory-specific satiety, and some that do not (21, 64). Thus the macaque posterior orbitofrontal cortex contains taste, and also olfactory and visual, neurons throughout its mediolateral extent, except that the proportion of taste neurons in the most medial 7 mm is much lower, as shown in this investigation. In contrast, the taste and olfactory reward areas in humans appear to reach to the midline, and probably do not extend as far lateral as in non-human primates (1, 47, 56, 65). We suggest that as the frontal lobes have developed from macaques to humans, the dorsolateral prefrontal cortex involved in working memory, attention and executive function (66–68) has greatly expanded to displace ventral areas of the frontal cortex medially in humans. As a result, the main orbitofrontal areas of macaques may have been displaced more medially in humans in whom they extend to the midline.

#### *A neuronal representation of taste in the pregenual cingulate cortex*

The orbitofrontal cortex, including the extensive areas where taste neurons noted above are found, projects to the pregenual cingulate cortex area 32 (63). In human imaging studies it has been shown that reward-related stimuli, such as the taste of sucrose and the texture of oral fat, activate the pregenual cingulate cortex (1, 43, 69). However, little is known at the neuronal level of whether the responses of single neurons in the pregenual cingulate cortex are tuned to taste stimuli and respond differentially to different taste stimuli. We have therefore recorded from single neurons in the macaque pregenual cingulate cortex, in order to obtain evidence on these issues (48). It is of

fundamental importance to analyse whether such taste neurons are present in these regions, since they could provide specific information about the nature and potential reward value of food in the mouth, especially as the anterior cingulate cortex has been implicated in complex reward probability learning (70), in action selection (71), and in emotion and emotional disorders (69, 72, 73).

The data for the pregenual cingulate cortex and adjacent areas were obtained in two rhesus macaques in recordings that extended from approximately 10 mm anterior with respect to the sphenoid reference to approximately 13 mm anterior, with the recording sites of all the neurons shown in Figure 8b.

The responses of a pregenual cingulate cortex neuron with taste responses are shown in Figure 7a. The neuron had significantly different responses to the different stimuli as shown by a one-way ANOVA ( $F[9,46]=17.7$ ,  $p<10^{-10}$ ). The neuron increased its firing rate primarily to glucose, fruit juice and cream, with some response to the oily texture of silicone oil, to monosodium glutamate, and to quinine.

To investigate whether neurons of this type are modulated in their responsiveness to taste by the hunger versus satiety state, the macaque was fed to satiety while recordings were being made from this neuron. As shown in Figure 7b, the firing rate to the taste of fruit juice in the prefeeding to satiety state of the same neuron was approximately 11.6 spikes/s. After feeding to satiety with 155 ml of the fruit juice, the response to the fruit juice has decreased to 2.7 spikes/s, which was approximately the spontaneous level of activity, as shown in Figure 7b. (The firing rate to water was not affected by the satiety with fruit juice, as shown in Figure 7b ( $t=1.4$ ,  $df=6$ , ns.) The decrease of response to the fruit juice produced by satiety was significant ( $t=9.0$ ,  $df=11$ ,  $p<10^{-6}$ ). Further, there was no significant difference between the firing rate to the fruit juice after satiety and the spontaneous activity ( $t=1.6$ ,  $df=18$ , ns). The neuron was however still capable of responding to other foods not fed to satiety, in that the mean response to other foods that had not been fed to satiety (banana, apple and orange) was 5.4 spikes/s (which was significantly higher than the response to fruit juice,  $t=2.5$ ,  $df=13$ ,  $p<0.02$ ). Thus the neuronal response was related to sensory-specific satiety, and indeed the behavioral acceptability of the fruit juice when hungry on a scale from +2 to -2, see (21) was +1.5 (corresponding to clear acceptance indicated by opening the mouth and avidly licking to obtain the solution) and when satiated was -0.2 (corresponding to mild rejection). Noteworthy is that after feeding to satiety with fruit juice, the macaque was still willing to eat the other foods.

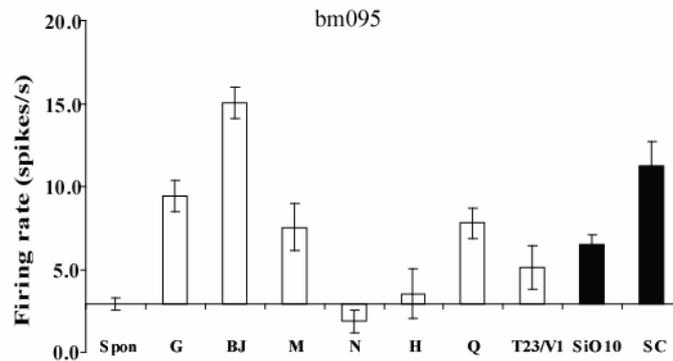


Fig. 7a. Responses of a pregenual cingulate cortex neuron (bm095) with differential responses to tastes and oral fat texture stimuli. The mean ( $\pm$ SEM) firing rate responses to each stimulus calculated in a 5 s period over several trials are shown. The spontaneous (Spon) firing rate of 3 spikes/s is shown by the horizontal line, with the responses indicated relative to this line. The taste stimuli were 1 M glucose (G), blackcurrant fruit juice (BJ), 0.1 M NaCl (N), 0.1 M MSG (M), 0.01 M HCl (H) and 0.001 M QuinineHCl (Q); water (T23/V1); single cream (SC); and silicone oil with a viscosity of 10 cP (SiO10)

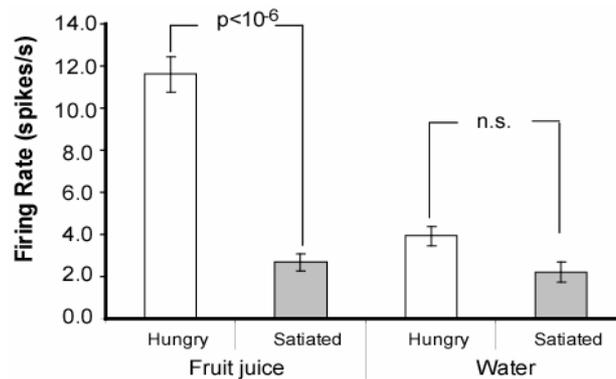


Fig. 7b. Effect of feeding to satiety with fruit juice (BJ) on the responses of a pregenual cingulate cortex neuron to fruit juice. The response to the fruit juice, and also to water in the mouth, is shown in spikes/s ( $\pm$ SEM) before and after feeding to satiety with the fruit juice. After Rolls et al. (48)

Out of 749 neurons screened in the region indicated in Figure 8b, 12 neurons (1.6%) responded to taste, with statistically significant increases in firing rate to one (or for some neurons more than one) of the taste stimuli. Eleven of these neurons were in the pregenual cingulate cortex (area 32), as illustrated in Figure 8a. The remainder of the neurons, 737, were unresponsive to the taste stimuli used. The responses of these 12 neurons to taste were in most cases highly statistically significant (e.g. one neuron  $p=3 \times 10^{-11}$ , one  $p=2 \times 10^{-6}$ , two  $p=0.001$ , six  $p<0.01$ ), and a Fisher exact probability test

(74–76) for whether the set of probability values from the whole set of 749 neurons recorded could have arisen by chance was significant at  $p < 0.03$ . These analyses thus confirmed that there is a population of neurons in the cingulate cortex area 32 with statistically significant responses to taste stimuli. Although a small proportion of the neurons were classified as responding to taste, this proportion is not out of line with the proportion of taste neurons recorded with identical techniques in the same laboratory in the primary taste cortex in the macaque anterior insula and adjoining frontal opercular cortex 48.

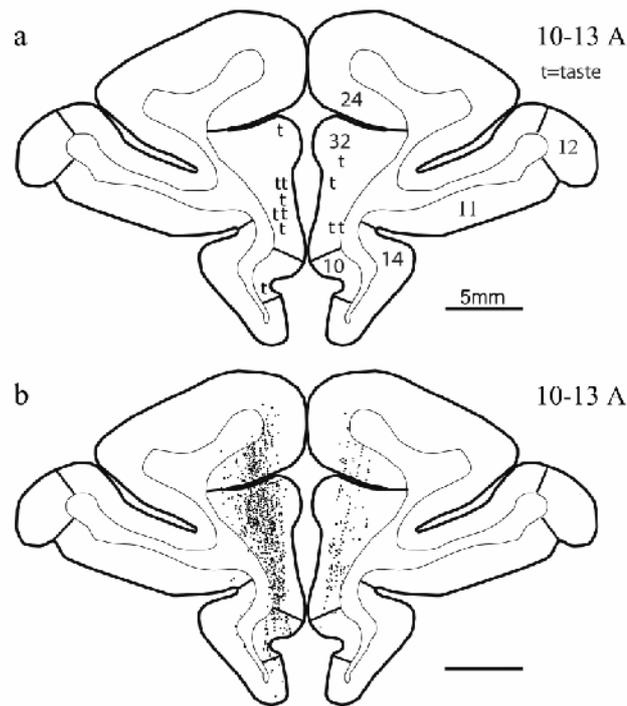


Fig. 8a. The reconstructed positions of the anterior cingulate neurons with taste (t) responses, together with the cytoarchitectonic boundaries determined by Carmichael and Price (52). Most (11/12) of the taste neurons were in the pregenual cingulate cortex (area 32), as shown. The neurons are shown on a coronal section at 12 mm anterior (A) to the sphenoid reference point. The recording sites were reconstructed using X-radiographs made on every track and subsequent histology using the methods described by Rolls et al. (16). b. The locations of all the 749 neurons recorded in the anterior cingulate region in this study are indicated to show the regions sampled. After Rolls et al. (48)

Of the 12 responsive neurons in the medial wall cortex, 11 had best responses to sweet stimuli (glucose and/or fruit juice) (as illustrated in Figure 7), and one had best responses to quinine and NaCl. The spontaneous firing rates of neurons in the pregenual cingulate cortex were typically in the range 0–5 spikes/s, which increased significantly to 20–30 spikes/s when the neurons were responding selectively to specific taste stimuli.

The recording sites of the taste-responsive neurons in the anterior cingulate cortex and adjacent cortical areas are shown in Figure 8a. As shown, most of these neurons were in area 32, with one taste neuron in area 10. These data provide direct novel neurophysiological evidence showing the existence of neurons with taste responses in macaque pregenual cingulate cortex.

This is the first time that taste-responsive neurons with profiles of the type illustrated in Fig. 7a and which are similar to the types of taste responsive neuron found in other cortical areas (10, 59) have been described in the pregenual cingulate area 32. This study now provides a foundation for examining in more detail the exact nature of the representation of taste by these neurons in the primate pregenual cingulate cortex. The majority of these taste neurons had their best responses to sweet taste (as exemplified by glucose). This is of interest, for activations in human pregenual cingulate cortex in fMRI investigations are produced by the taste of sucrose and the oral texture of fat (43), and by pleasant touch (77), and also are correlated with the pleasantness of odour (39). In human fMRI studies the pregenual cingulate cortex is also activated by the flavour or sight of chocolate, with significantly larger correlations with the subjective pleasantness of the chocolate in chocolate cravers than in chocolate non-cravers (46). The neurophysiological data from the present study are of importance in relation to the interpretation of these human fMRI studies, because they show that taste neurons with properties similar to those found in other taste areas, and which do not require the macaque to be performing any task apart from tasting the solutions administered intra-orally, are found in this region. Thus the pregenual cingulate cortex appears to contain a representation of a primary reinforcer, and moreover for many cells this representation is of a highly palatable taste. Consistent with this evidence that the pregenual cingulate cortex includes a representation of tastes that are rewarding, we found in the satiety experiment shown in Figure 7b that a neuron located in the pregenual cingulate cortex decreased its responses to zero when the monkey was fed to satiety and the taste became no longer rewarding. Other rewarding stimuli activate the pregenual cingulate cortex in humans, including sweet taste, olfactory, and oral texture stimuli (40, 43), though the mapping of pleasant stimuli to pregenual cingulate cortex and unpleasant stimuli more dorsally in the anterior cingulate cortex is not always found (1, 78).

The presence of a neuronal representation of a primary (unlearned) reinforcer, taste, in the pregenual cingulate cortex is of importance for understanding the functions more generally of the anterior cingulate cortex in complex reward-related learning (70), in action selection (71), for the evidence described here shows that primary rewards are represented in at least one part of the anterior cingulate cortex – the pregenual cingulate cortex area 32. Neurons responding to fruit juice used as a reinforcer in saccade countermanding have been found in the dorsal part of the anterior cingulate sulcus area

24c (79), and the pregenual cingulate cortex provides a source of inputs to area 24 (63). Indeed, establishing that the pregenual cingulate cortex contains a representation of a primary reinforcer is of importance more generally in relation to understanding the functions of the pregenual cingulate in emotion, in that some disorders of emotion in humans produced by anterior cingulate damage include deficits in responding to what are probably other primary reinforcers, face and voice expression (1, 72). Moreover, some of the changes in emotional behaviour produced by anterior cingulate damage, which include not noticing when other people are angry and doing things (impulsively) without thinking, and changed subjective affect, may be related to impairments in responding appropriately to social and other reinforcers (69, 72, 80). In this context, the finding described here at the neurophysiological level, that some pregenual cingulate neurons are tuned to taste and related oral reinforcing stimuli helps to establish a foundation for understanding better the functions of the pregenual cingulate cortex in health and disease, by establishing at the neuronal level that a primary taste reinforcer is represented in the pregenual cingulate cortex.

## **2. 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, for example with olfactory inputs to form a representation of flavour (Fig. 1). We found (50) that in the orbitofrontal cortex taste areas, of 112 single neurons which responded to any of these modalities, many were unimodal (taste 34%, olfactory 13%, visual 21%), but were found in close proximity to each other. Some single neurons showed 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 had corresponding sensitivities in the two modalities, in that they responded best to sweet tastes (e.g. 1 M glucose), and responded more in a visual discrimination task to the visual stimulus which signified sweet fruit juice than to that which signified saline; or responded to sweet taste, and in an olfactory discrimination task to fruit odour. The different types of neurons (unimodal in different modalities, and multimodal) were 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 which is evoked best by a combination of gustatory and olfactory input. Moreover, these representations are built by olfactory-to-taste associative learning (61), so that the representations of odours is transformed from one specified by olfactory receptor genes to one influenced by associations with taste (1, 81). 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 (7, 50).

### **3. The rules underlying the formation of olfactory representations in the primate cortex**

Critchley and Rolls (31) showed that 35% of orbitofrontal cortex olfactory neurons categorised odours based on their taste association in an olfactory-to-taste discrimination task. Rolls et al. (6) found that 68% of orbitofrontal cortex odour-responsive neurons modified 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, the S+, is made a drop of glucose taste reward is obtained; if incorrectly a lick response is made to another odour, the S-, a 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 upon, the taste with which the odour is associated (82–84).

It was of interest however that this modification was less complete, and much slower, than the modifications found for orbitofrontal visual neurons during visual – taste reversal (60). 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 did not encode information in relation to the taste with which the odour was associated (31), showing that there is also a taste-independent representation of odour in this region.

### **4. 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 and Rolls (21) showed 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 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 (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. This is 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 E. T. Rolls in 1974 and illustrated for example in (85), experiments were performed to determine whether satiety was specific to foods eaten in humans. It was found that the pleasantness of the taste of food eaten to satiety decreased more than for foods that had not been eaten (23). One consequence of this is that if one food is eaten to satiety, appetite reduction for other foods is often incomplete, and this will lead to enhanced eating when a variety of foods is offered (23, 24, 86). Because 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” (23–27, 87). 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) (22, 88, 89), whereas sensory-specific satiety is a change in the pleasantness of sensory inputs which is accounted for at least partly by the external sensory stimulation received (such as the taste of a particular food), in that as shown above 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 and Rolls (90) measured humans’ responses to the smell of a food which was eaten to satiety. It was found that the pleasantness of the odour of a food, but much less significantly its intensity, was decreased when the subjects ate it to satiety. It was also found that the pleasantness of the smell of other foods (i.e. foods not eaten in the meal) showed much less decrease. This finding has clear implications for the control of food intake; for ways to keep foods presented in a meal appetitive; and for effects on odour pleasantness ratings that could occur following meals. In their investigation of the mechanisms of this odour-specific sensory-specific satiety, Rolls and Rolls (90) also allowed humans 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. It is not yet known which is the earliest stage of

olfactory processing at which this modulation occurs. It is unlikely to be in the receptors, because the change in pleasantness found was much more significant than the change in the intensity (90).

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, today in humans, when a wide variety of foods is readily available, this may be a factor that can lead to overeating and obesity (65, 91). In a test of this in the rat, it has been found that variety itself can lead to obesity (92, 93).

### **5. 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 (50), reverse rapidly in visual discrimination reversal (see above and Rolls et al. (61), and only respond to the sight of food if hunger is present (21). This part of the orbitofrontal cortex thus seems to implement a mechanism which can flexibly alter the responses to visual stimuli depending on the reinforcement (e.g. the taste) associated with the visual stimulus see (32, 94). This enables prediction of the taste associated with ingestion of what is seen, and thus enables the visual selection of foods (1, 18, 34). 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. We have shown for example in recent recordings that single neurons influenced by taste in this region can in some cases have their responses modulated by the texture of the food. This was shown in experiments in which the texture of food was manipulated by the addition of methyl cellulose or gelatine, or by puréeing a semi-solid food (18, 95). It has been shown that some of these neurons with texture-related responses encode parametrically the viscosity of food in the mouth (using a methyl cellulose series in the range 1–10,000 centiPoise), and that others independently encode the particulate quality of food in the mouth, produced quantitatively for example by adding 20–100  $\mu\text{m}$  microspheres to methyl cellulose (16).

In addition, we have shown 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 (17).

### **6. 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. In the orbitofrontal cortex, Rolls, Critchley et al (59) have found a

population of neurons that responds when fat is in the mouth. 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, in that 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 to silicone oil ( $\text{Si}(\text{CH}_3)_2\text{O}_n$ ). Moreover, the texture channel through which these fat-sensitive neurons are activated is separate from viscosity sensitive channels, in that the responses of these neurons cannot be predicted by the viscosity of the oral stimuli (57). Some of the fat-related neurons do though have convergent inputs from the chemical senses, in that in addition to taste inputs, some of these neurons respond to the odour associated with a fat, such as the odour of cream (59). 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 is not decreased by feeding to satiety with cream (59). 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 macaque primary taste cortex in the rostral insula and adjoining frontal operculum (7).

These oral sensory properties of food, and also the sight and smell of food, are also represented in the primate amygdala (4, 58, 96, 97). Interestingly, the responses of these amygdala neurons do not correlate well with the preferences of the macaques for the oral stimuli (58), and feeding to satiety does not produce the large reduction in the responses of amygdala neurons to food (4, 97) that is typical of orbitofrontal cortex neurons.

### **7. Learning about the sight of food: orbitofrontal cortex vs amygdala**

Differences between the primate orbitofrontal cortex and amygdala are also found 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 (61, 94), 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 (97, 98). 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 (1, 4, 97). Part of the underlying basis for at least the rapid reward reversal learning shown by primate orbitofrontal cortex 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 (68, 99). This 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 (1, 99). In addition, habituation with a time course of several minutes of the afferent synapses to the orbitofrontal cortex provides a probable neurophysiological basis for sensory-specific satiety (1).

## 8. Imaging studies in humans

### *Taste*

In humans 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 (37, 100, 101). It has been shown that within individual subjects separate areas of the orbitofrontal cortex are activated by sweet (pleasant) and by salt (unpleasant) tastes (100).

Francis et al. (37) also found activation of the human amygdala by the taste of glucose. Extending this study, O'Doherty et al. (100) showed that the human amygdala was as much activated by the affectively pleasant taste of glucose as by the affectively negative taste of NaCl, and thus provided evidence that the human amygdala is not especially involved in processing aversive as compared to rewarding stimuli. Zald et al. (78) had shown earlier that the amygdala, as well as the orbitofrontal cortex, respond to aversive (saline) taste stimuli. The study above (100), however, shows that there is nothing special about aversive taste stimuli in relation to the brain areas activated, for pleasant stimuli also activate the amygdala and orbitofrontal cortex.

Another study has shown that umami taste stimuli, of which an exemplar is monosodium glutamate (MSG) and which capture 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 (42). A part of the rostral anterior cingulate cortex (ACC) was also activated. When the nucleotide 0.005 M inosine 5'-monophosphate (IMP) was added to MSG (0.05 M), the BOLD (blood oxygenation-level dependent) signal in an anterior part of the orbitofrontal cortex showed supralinear additivity, and this may reflect the subjective enhancement of umami taste that has been described when IMP is added to MSG. 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 humans, in addition to activation of the pyriform (olfactory) cortex (102–104), there is strong and consistent activation of the orbitofrontal cortex by olfactory stimuli (36, 37). In an investigation of where the pleasantness of olfactory stimuli might be represented in humans, O'Doherty et al. (38) showed that the activation of an area of the orbitofrontal cortex to banana odour was decreased (relative to a control vanilla

odour) after bananas were eaten to satiety. Thus activity in a part of the human orbitofrontal cortex olfactory area is related to sensory-specific satiety, and this is one brain region where the pleasantness of odour is represented.

An important issue is whether there are separate regions of the brain discriminable with fMRI that represent pleasant and unpleasant odours. To investigate this, we measured the brain activations produced by three pleasant and three unpleasant odours. The pleasant odours chosen were linalyl acetate (floral, sweet), geranyl acetate (floral) and alpha-ionone (woody, slightly food-related). (Chiral substances were used as racemates.) The unpleasant odours chosen were hexanoic acid, octanol and isovaleric acid. We found that they activated dissociable parts of the human brain (39). Pleasant but not unpleasant odours were found to activate a medial region of the rostral orbitofrontal cortex (Fig. 9). Further, there was a correlation between the subjective pleasantness ratings of the six odours given during the investigation with activation of a medial region of the rostral orbitofrontal cortex. 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 (39). 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, we performed an event-related fMRI study with sucrose and MSG taste, and strawberry and methional (chicken) odours, delivered unimodally or in different combinations (41). The brain regions that were activated by both taste and smell included 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 was 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 (Fig. 10). Similarly, Small et al. (105) also found supradadditive interactions between congruent taste and smell stimuli in areas including the caudal orbitofrontal cortex, and anterior cingulate cortex see also (106). These results provide evidence on the neural substrate for the convergence of taste and olfactory stimuli to produce flavour in humans, and where the pleasantness of flavour is represented in the human brain.

McCabe and Rolls (14) have shown that the convergence of taste and olfactory information appears to be important for the delicious flavour of umami. They showed that when glutamate is given in combination with a consonant, savory, odor (vegetable), the resulting flavor can be much more pleasant than the glutamate taste or vegetable odour alone. Moreover, they found using functional brain imaging with fMRI that the glutamate and savoury odor combination produced 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 correlated with the pleasantness, consonance of the taste and olfactory components, and the fullness of the flavor, of the stimuli. Similar non-linear effects were not found for sodium chloride and vegetable odor. McCabe and Rolls thus proposed that glutamate acts by the non-linear effects it can produce when combined with a consonant odor. They further proposed the concept that umami can be thought of as a rich and delicious flavor that is produced by a combination of glutamate taste and a consonant savoury odor. Glutamate is thus a flavor enhancer because of the way that it can combine non-linearly with consonant odors.

To assess how satiety influences the brain activations to a whole food which produces taste, olfactory, and texture stimulation, we measured brain activation by whole foods before and after the food is eaten to satiety (42). 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 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 (107) but not in the primary taste cortex (Fig. 11). This study provided evidence that the pleasantness of the flavour of food, and sensory-specific satiety, are represented in the orbitofrontal cortex.

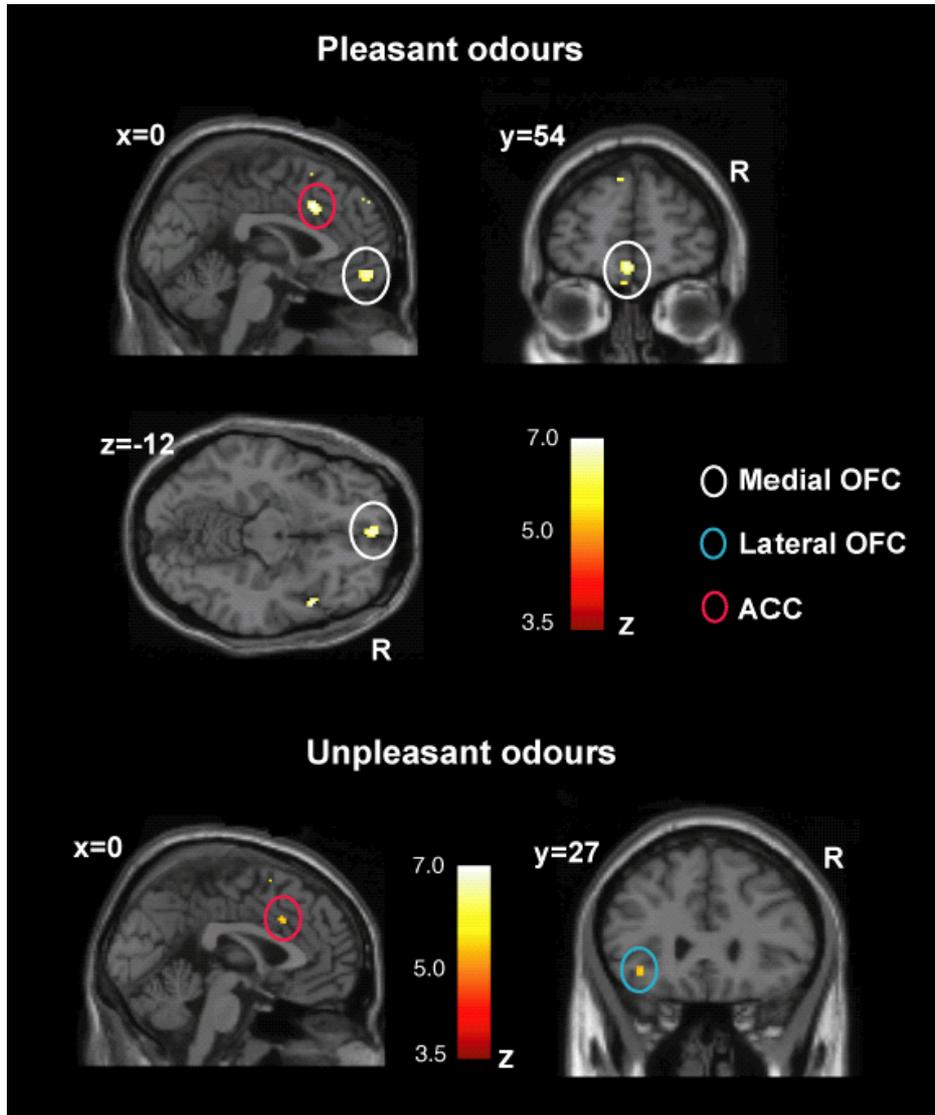


Fig. 9. The representation of pleasant and unpleasant odours in the human brain. Above: Group conjunction results for the 3 pleasant odours. Saggital, horizontal and coronal views are shown at the levels indicated, all including the same activation in the medial orbitofrontal cortex, OFC (X, Y, Z=0,54,-12;  $z=5.23$ ). Also shown is activation for the 3 pleasant odours in the anterior cingulate cortex, ACC (X, Y, Z=2, 20, 32;  $z=5.44$ ). These activations were significant at  $p<0.05$  fully corrected for multiple comparisons. Below: Group conjunction results for the 3 unpleasant odours. The saggital view (left) shows an activated region of the anterior cingulate cortex (X, Y, Z=0,18, 36;  $z=4.42$ ,  $p<0.05$ , S.V.C.). The coronal view (right) shows an activated region of the lateral orbitofrontal cortex (-36,27,-8;  $z=4.23$ ,  $p<0.05$ , S.V.C.). All the activations were thresholded at  $p<0.00001$  to show the extent of the activations. After Rolls et al. (39)

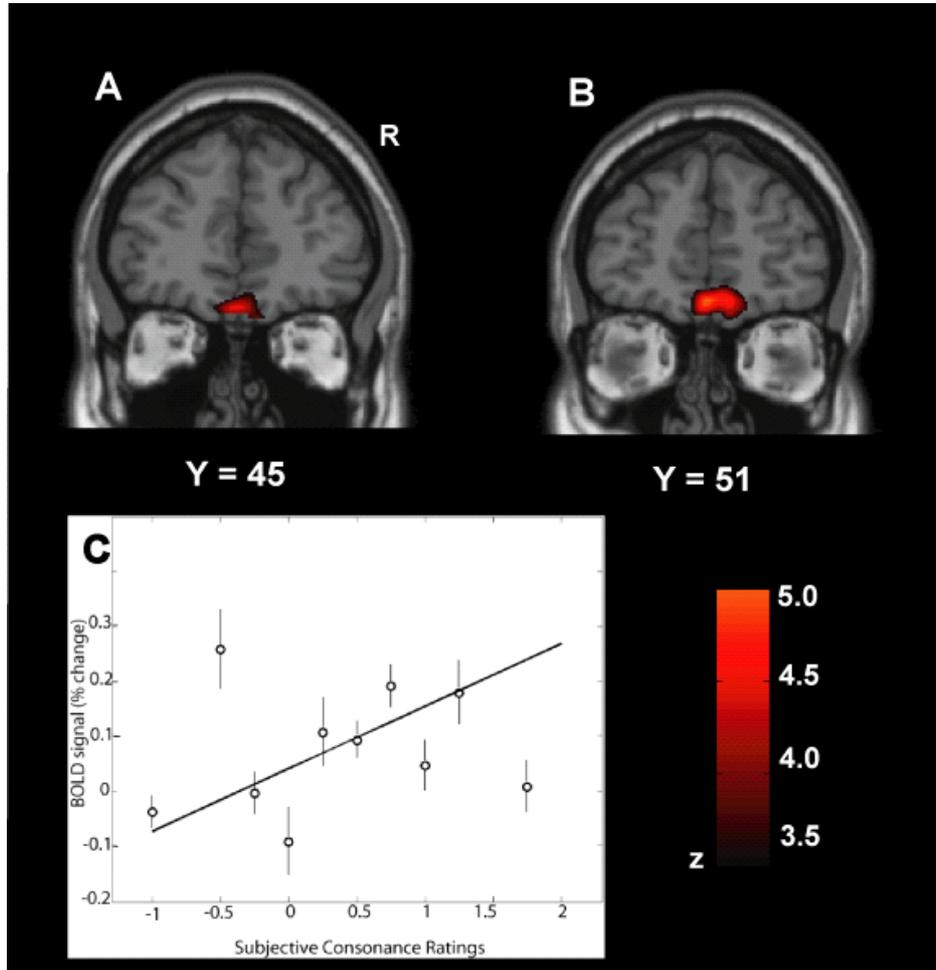


Fig. 10. Flavour formation in the human brain, shown by cross-modal olfactory-taste convergence. Brain areas where activations were correlated with the subjective ratings for stimulus (taste-odour) consonance and pleasantness. (A) A second-level, random effects analysis based on individual contrasts (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  $p < 0.0001$  for illustration. (C) The relation between the BOLD signal from the cluster of voxels in the medial orbitofrontal cortex shown in (A) and the subjective consonance ratings. The analyses shown included all the stimuli included in this investigation. The means and standard errors of the mean across subjects are shown, together with the regression line, for which  $r = 0.52$ . After de Araujo et al. (41)

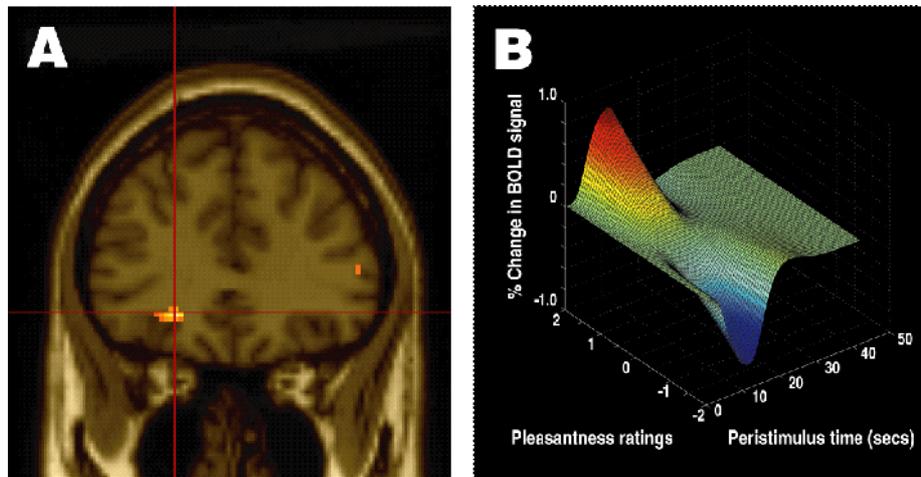


Fig. 11. Areas of the human orbitofrontal cortex with activations correlating with pleasantness ratings for food in the mouth. (A) Coronal section through the region of the orbitofrontal cortex from the random effects group analysis showing the peak in the left orbitofrontal cortex (Talairach co-ordinates  $x, y, z = -22, 34, -8$ ,  $Z\text{-score} = 4.06$ ), in which the BOLD signal in the voxels shown in yellow was significantly correlated with the subjects' subjective pleasantness ratings of the foods throughout 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 against the subjective pleasantness ratings (on a scale from  $-2$  to  $+2$ ) and peristimulus time in seconds.

After Kringelbach et al. (107)

#### *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 (43). In these regions, the fMRI BOLD activations are proportional to the log of the viscosity of carboxymethyl cellulose in the mouth. Oral viscosity is also represented in the human orbitofrontal and pregenual cingulate cortices, and it is notable that the pregenual cingulate cortex, an area in which many pleasant stimuli are represented (1, 81), is strongly activated by the texture of fat in the mouth and also by oral sucrose (43).

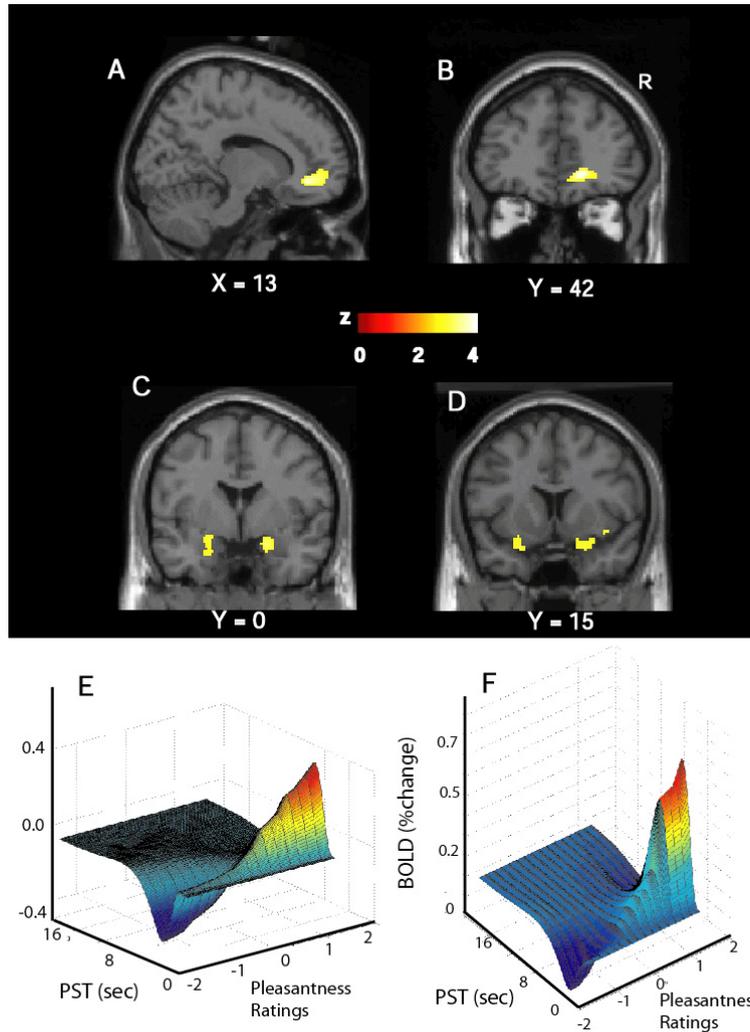


Fig. 12. Cognitive influences on olfactory representations in the human brain. Group (random) effects analysis showing the brain regions where the BOLD signal was correlated with pleasantness ratings given to the test odor. The pleasantness ratings were being modulated by the word labels. (A) Activations in the rostral anterior cingulate cortex, in the region adjoining the medial OFC, shown in a sagittal slice. (B) The same activation shown coronally. (C) Bilateral activations in the amygdala. (D) These activations extended anteriorly to the primary olfactory cortex. The image was thresholded at  $p < 0.0001$  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. After DeAraujo et al. (40)

*The sight of food*

O'Doherty et al. (108) showed that visual stimuli associated with the taste of glucose activated the orbitofrontal cortex and some connected areas, consistent with the primate neurophysiology. Simmons, Martin & Barsalou (109) found that showing pictures of foods, compared to pictures of locations, can also activate the orbitofrontal cortex and some connected areas, though taste stimuli were not used in this study, so that one can not be sure to what extent the activations to the sight and taste of food overlapped. Consistent with these findings, Pelchat et al. (110) found that after consuming a monotonous diet, subjects that were instructed to imagine foods that they craved showed more activation in some brain areas, including part of the insula, than subjects who had consumed a normal diet. Similarly, the orbitofrontal cortex and connected areas were also found to be activated after presentation of food stimuli to food-deprived subjects (111).

**9. Cognitive effects on representations of food**

Brie 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 this influence the perception and hedonics of food-related stimuli, and if so, how far back down into the sensory system does the cognitive influence reach? To address this, we performed an fMRI investigation in which the delivery of a standard test odor (isovaleric acid combined with cheddar cheese flavour, presented orthonasally using an olfactometer) was paired with a descriptor word on a screen, which on different trials was "Cheddar cheese" or "Body odor". The subjects rated the pleasantness and the intensity of the odor on every trial. Alpha-ionone (pleasant, labelled "Flowers") and Octanol (unpleasant, labelled "Burned plastic") were used as reference pleasant and unpleasant stimuli for the psychophysics and neuroimaging. Subjects rated the affective value of the test odour as significantly more unpleasant when labelled "Body odour" than when labelled "Cheddar Cheese". We found that the medial orbitofrontal cortex (OFC)/rostral anterior cingulate cortex (ACC) was significantly more activated by the test stimulus labelled "Cheddar Cheese" than when labelled "Body odour", and that these activations were correlated with the pleasantness ratings (40) (Fig. 12). This cognitive modulation was also found in the medial amygdala olfactory area, and this 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 our 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 (40). Similar cognitive modulation effects have now been discovered for taste, flavour (112), and touch (113) processing.

## 10. Conclusions

The reward value of food, and its subjective complement, the rated affective pleasantness of food, is decoded in primates including humans 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 specialized cortical areas. The orbitofrontal cortex is moreover where multimodal representations of food are built, which include taste, texture, olfactory, and visual components. 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 human amygdala (4, 58, 96, 100, 114), the primate orbitofrontal cortex is more closely related to the changing affective value of food than the amygdala (4, 97, 98), in that the orbitofrontal cortex shows responses that decrease to zero as the reward decreases to zero with satiety, and in that 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 which makes the orbitofrontal cortex reward neurons fire, as they represent a goal for behaviour. 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 (1, 18), 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 Figure 1. Moreover, it is of interest that brain activations to food can now predict food intake, in that for example the orbitofrontal and pregenual cingulate cortex activations to the sight and flavour of chocolate are greater in chocolate cravers than in non-cravers, and are related to how much chocolate is eaten in a week (46).

Understanding the operation of the hedonic regulatory system for the sensory properties of food is important for understanding the normal regulation of food intake, and dysfunctions that can arise and contribute to obesity. Indeed, understanding the mechanisms that control appetite is becoming an increasingly important issue, given the increasing incidence of obesity (a three-fold increase in the UK since 1980 to a figure of

20% defined by a BMI>30) and the realization 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 minimize and treat obesity because many diseases are associated with a body weight that is much above normal. These diseases include hypertension, cardiovascular disease, hypercholesterolaemia, and gall bladder disease; and 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 (115–118). There are many factors that can cause or contribute to obesity in humans (116, 117, 119, 120), and our developing understanding of the sensory processing related to the appetitive value of food leads to many suggestions about their possible contribution to the development, prevention, and treatment of obesity (1, 56, 91, 121).

### Acknowledgments

This research was supported by the Medical Research Council.

### REFERENCES

1. Rolls ET (2005): *Emotion Explained*. Oxford: Oxford, University Press
2. Scott TR, Yaxley S, Sienkiewicz ZJ, Rolls ET: Gustatory responses in the frontal opercular cortex of the alert cynomolgus monkey. *J. of Neurophysiology* 56, 876–890 (1986)
3. Yaxley S, Rolls ET, Sienkiewicz ZJ: Gustatory responses of single neurons in the insula of the macaque monkey. *J. of Neurophysiology* 63, 689–700 (1990)
4. Rolls ET, Scott TR (2003): Central taste anatomy and neurophysiology. In: *Handbook of Olfaction and Gustation*. 2nd ed. (Ed.: Doty RL), New York, Dekker, pp. 679–705
5. Baylis LL, Rolls ET: Responses of neurons in the primate taste cortex to glutamate. *Physiology and Behavior* 49, 973–979 (1991)
6. Rolls ET, Critchley H, Wakeman EA, Mason R: Responses of neurons in the primate taste cortex to the glutamate ion and to inosine 5'-monophosphate. *Physiology and Behavior* 59, 991–1000 (1996)
7. Verhagen JV, Kadohisa M, Rolls ET: The primate insular/opercular taste cortex: neuronal representations of the viscosity, fat texture, grittiness, temperature and taste of foods. *J. of Neurophysiology* 92, 1685–1699 (2004)
8. Rolls ET, Scott TR, Sienkiewicz ZJ, Yaxley S: The responsiveness of neurones in the frontal opercular gustatory cortex of the macaque monkey is independent of hunger. *J. of Physiol.* 397, 1–12 (1988)
9. Yaxley S, Rolls ET, Sienkiewicz ZJ: The responsiveness of neurons in the insular gustatory cortex of the macaque monkey is independent of hunger. *Physiology and Behavior* 42, 223–229 (1988)
10. Rolls ET, Yaxley S, Sienkiewicz ZJ: Gustatory responses of single neurons in the caudolateral orbitofrontal cortex of the macaque monkey. *J. of Neurophysiology* 64, 1055–1066 (1990)
11. Rolls ET: Taste and olfactory processing in the brain and its relation to the control of eating. *Critical Reviews in Neurobiology* 11, 263–287 (1997)
12. Zhao GQ, Zhang Y, Hoon MA, et al.: The receptors for mammalian sweet and umami taste. *Cell* 115(3), 255–266 (2003)
13. Rolls ET, Critchley HD, Browning A, Hernadi I: The neurophysiology of taste and olfaction in primates, and umami flavor. *Annals of the New York Academy of Sciences* 855, 426–437 (1998)
14. McCabe C, Rolls ET: Umami: a delicious flavor formed by convergence of taste and olfactory pathways in the human brain. *Europ. J. of Neurosci.* 25, 1855–1864 (2007)

15. Critchley HD, Rolls ET: Responses of primate taste cortex neurons to the astringent tastant tannic acid. *Chemical Senses* 21, 135–145 (1996)
16. Rolls ET, Verhagen JV, Kadohisa M: Representations of the texture of food in the primate orbitofrontal cortex: neurons responding to viscosity, grittiness and capsaicin. *J. of Neurophysiology* 90, 3711–3724 (2003)
17. Kadohisa M, Rolls ET, Verhagen JV: Orbitofrontal cortex neuronal representation of temperature and capsaicin in the mouth. *Neuroscience* 127, 207–221 (2004)
18. Rolls ET (1999): *The Brain and Emotion*. Oxford, Oxford University Press
19. Yaxley S, Rolls ET, Sienkiewicz ZJ, Scott TR: Satiety does not affect gustatory activity in the nucleus of the solitary tract of the alert monkey. *Brain Research* 347, 85–93 (1985)
20. Rolls ET, Sienkiewicz ZJ, Yaxley S: Hunger modulates the responses to gustatory stimuli of single neurons in the caudolateral orbitofrontal cortex of the macaque monkey. *Europ. J. of Neurosci.* 1, 53–60 (1989)
21. Critchley HD, Rolls ET: Hunger and satiety modify the responses of olfactory and visual neurons in the primate orbitofrontal cortex. *J. of Neurophysiology* 75, 1673–1686 (1996)
22. Cabanac M: Physiological role of pleasure. *Science* 173, 1103–1107 (1971)
23. Rolls BJ, Rolls ET, Rowe EA, Sweeney K: Sensory specific satiety in man. *Physiology and Behavior* 27, 137–142 (1981)
24. Rolls BJ, Rowe EA, Rolls ET, et al.: Variety in a meal enhances food intake in man. *Physiology and Behavior* 26, 215–221 (1981)
25. Rolls BJ, Rowe EA, Rolls ET: How sensory properties of foods affect human feeding behavior. *Physiology and Behavior* 29, 409–417 (1982)
26. Rolls ET, Rolls BJ (1977): Activity of neurons in sensory, hypothalamic and motor areas during feeding in the monkey. In: *Food Intake and Chemical Senses*. Eds: Katsuki Y, Sato M, Takagi S, Oomura Y. Tokyo, University of Tokyo Press, pp. 525–549
27. Rolls ET, Rolls BJ (1982): Brain mechanisms involved in feeding. In: *Psychobiology of Human Food Selection*. Ed.: Barker LM. Westport, Connecticut, AVI Publishing Company, pp. 33–62
28. Rolls BJ, Rolls ET, Rowe EA: Body fat control and obesity. *Behavioral and Brain Sciences* 4, 744–745 (1983)
29. Rolls ET, Rolls BJ, Rowe EA: Sensory-specific and motivation-specific satiety for the sight and taste of food and water in man. *Physiology and Behavior* 30, 185–192 (1983)
30. Rolls ET, Murzi E, Yaxley S, Thorpe SJ, Simpson SJ: Sensory-specific satiety: food-specific reduction in responsiveness of ventral forebrain neurons after feeding in the monkey. *Brain Research* 368, 79–86 (1986)
31. Critchley HD, Rolls ET: Olfactory neuronal responses in the primate orbitofrontal cortex: analysis in an olfactory discrimination task. *J. of Neurophysiol.* 75, 1659–1672 (1996)
32. Rolls ET: The orbitofrontal cortex. *Philosophical Transactions of the Royal Society of London B* 351, 1433–1444 (1996)
33. Rolls ET: The orbitofrontal cortex and reward. *Cerebral Cortex* 10, 284–294 (2000)
34. Rolls ET (2000): Taste, olfactory, visual and somatosensory representations of the sensory properties of foods in the brain, and their relation to the control of food intake. In: *Neural and Metabolic Control of Macronutrient Intake*. Eds: Berthoud H-R, Seeley RJ. Boca-Raton, Florida, CRC Press, pp. 247–262
35. Scott TR, Yan J, Rolls ET: Brain mechanisms of satiety and taste in macaques. *Neurobiology* 3, 281–292 (1995)
36. Zatorre RJ, Jones-Gotman M, Evans AC, Meyer E: Functional localization of human olfactory cortex. *Nature* 360, 339–340 (1992)
37. Francis S, Rolls ET, Bowtell R, et al.: The representation of pleasant touch in the brain and its relationship with taste and olfactory areas. *Neuroreport* 10, 453–459 (1999)
38. O'Doherty J, Rolls ET, Francis S, et al.: Sensory-specific satiety related olfactory activation of the human orbitofrontal cortex. *Neuroreport* 11, 893–897 (2000)
39. Rolls ET, Kringelbach ML, de Araujo IET: Different representations of pleasant and unpleasant odors in the human brain. *Europ. J. of Neurosci.* 18, 695–703 (2003)

40. de Araujo IET, Rolls ET, Velazco MI, Margot C, Cayeux I: Cognitive modulation of olfactory processing. *Neuron* 46, 671–679 (2005)
41. de Araujo IET, Rolls ET, Kringelbach ML, McGlone F, Phillips N: Taste-olfactory convergence, and the representation of the pleasantness of flavour, in the human brain. *Europ. J. of Neurosci.* 18, 2374–2390 (2003)
42. de Araujo IET, Kringelbach ML, Rolls ET, Hobden P: The representation of umami taste in the human brain. *J. of Neurophysiol.* 90, 313–319 (2003)
43. de Araujo IET, Rolls ET: The representation in the human brain of food texture and oral fat. *J. of Neurosci.* 24, 3086–3093 (2004)
44. Li W, Luxenberg E, Parrish T, Gottfried JA: Learning to smell the roses: experience-dependent neural plasticity in human piriform and orbitofrontal cortices. *Neuron* 52(6), 1097–1108 (2006)
45. Gottfried JA, Small DM, Zald DH (2006): The chemical senses. In: *The Orbitofrontal Cortex*. Eds: Zald DH, Rauch SL. Oxford, Oxford University Press, pp. 125–171
46. Rolls ET, McCabe C: Enhanced affective brain representations of chocolate in cravers vs non-cravers. *Europ. J. of Neurosci.* 26, 1067–1076 (2007)
47. Kringelbach ML, Rolls ET: The functional neuroanatomy of the human orbitofrontal cortex: evidence from neuroimaging and neuropsychology. *Progress in Neurobiology* 72, 341–372 (2004)
48. Rolls ET, Verhagen JV, Gabbott PL, Kadohisa M: Taste and texture representations in the primate pregenual cingulate and medial orbitofrontal cortices. In preparation (2008)
49. Baylis LL, Rolls ET, Baylis GC: Afferent connections of the orbitofrontal cortex taste area of the primate. *Neuroscience* 64, 801–812 (1995)
50. Rolls ET, Baylis LL: Gustatory, olfactory, and visual convergence within the primate orbitofrontal cortex. *J. of Neurosci.* 14, 5437–5452 (1994)
51. Pritchard TC, Edwards EM, Smith CA, et al.: Gustatory neural responses in the medial orbitofrontal cortex of the old world monkey. *J. Neurosci.* 25, 6047–6056 (2005)
52. Carmichael ST, Price JL: Architectonic subdivision of the orbital and medial prefrontal cortex in the macaque monkey. *J. of Comparative Neurology* 346, 366–402 (1994)
53. Ongur D, Ferry AT, Price JL: Architectonic division of the human orbital and medial prefrontal cortex. *J. of Comparative Neurology* 460, 425–449 (2003)
54. Ongur D, Price JL: The organisation of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. *Cerebral Cortex* 10, 206–219 (2000)
55. Petrides M, Pandya DN: Comparative cytoarchitectonic analysis of the human and the macaque ventrolateral prefrontal cortex and corticocortical connection patterns in the monkey. *Europ. J. of Neurosci.* 16, 291–310 (2001)
56. Rolls ET: Brain mechanisms underlying flavour and appetite. *Philosophical Transactions of the Royal Society London B* 361, 1123–1136 (2006)
57. Verhagen JV, Rolls ET, Kadohisa M: Neurons in the primate orbitofrontal cortex respond to fat texture independently of viscosity. *J. of Neurophysiol.* 90, 1514–1525 (2003)
58. Kadohisa M, Rolls ET, Verhagen JV: Neuronal representations of stimuli in the mouth: the primate insular taste cortex, orbitofrontal cortex, and amygdala. *Chemical Senses* 30, 401–419 (2005)
59. Rolls ET, Critchley HD, Browning AS, Hernadi A, Lenard L: Responses to the sensory properties of fat of neurons in the primate orbitofrontal cortex. *J. of Neurosci.* 19, 1532–1540 (1999)
60. Rolls ET, Critchley HD, Treves A: The representation of olfactory information in the primate orbitofrontal cortex. *J. of Neurophysiol.* 75, 1982–1996 (1996)
61. Rolls ET, Critchley HD, Mason R, Wakeman EA: Orbitofrontal cortex neurons: role in olfactory and visual association learning. *J. of Neurophysiol.* 75, 1970–1981 (1996)
62. Pritchard TC, Hamilton RB, Morse JR, Norgren R: Projections of thalamic gustatory and lingual areas in the monkey, *Macaca fascicularis*. *J. of Comparative Neurology* 244, 213–228 (1986)
63. Carmichael ST, Price JL: Connectional networks within the orbital and medial prefrontal cortex of macaque monkeys. *J. of Comparative Neurology* 371, 179–207 (1996)
64. Scott TR, Edwards EM, Smith CA, et al.: Medial orbitofrontal cortex: its role in mediating satiety in the macaque. *Chem. Senses* 30(Suppl 1), i190 (2005)

65. Rolls ET: Sensory processing in the brain related to the control of food intake. *Proceedings of the Nutrition Society* 66, 96–112 (2007)
66. Goldman-Rakic PS: The prefrontal landscape: implications of functional architecture for understanding human mentation and the central executive. *Philosophical Transactions of the Royal Society B* 351, 1445–1453 (1996)
67. Rolls ET, Deco G (2002): *Computational Neuroscience of Vision*. Oxford. Oxford University Press
68. Deco G, Rolls ET: Attention, short-term memory, and action selection: a unifying theory. *Progress in Neurobiology* 76, 236–256 (2005)
69. Rolls ET (2008): The anterior and midcingulate cortices and reward. In: *Cingulate Neurobiology & Disease*. Ed: Vogt BA. Oxford, Oxford University Press
70. Amiez C, Joseph JP, Procyk E: Reward encoding in the monkey anterior cingulate cortex. *Cerebral Cortex* 16, 1040–1055 (2006)
71. Rushworth MF, Walton ME, Kennerley SW, Bannerman DM: Action sets and decisions in the medial frontal cortex. *Trends in Cognitive Sciences* 8, 410–417 (2004)
72. Hornak J, Bramham J, Rolls ET, et al.: Changes in emotion after circumscribed surgical lesions of the orbitofrontal and cingulate cortices. *Brain* 126, 1691–1712 (2003)
73. Mayberg HS: Positron emission tomography imaging in depression: a neural systems perspective. *Neuroimaging Clin. N. Am.* 13(4), 805–815 (2003)
74. Fisher RA (1932): *Statistical Methods for Research Workers*. London, Oliver and Boyd
75. Littell RC, Folks JL: Asymptotic optimality of Fisher's method of combining independent tests. *J. Am. Stat. Assoc.* 66, 802–806 (1971)
76. Zaykin DV, Zhivotovsky LA, Westfall PH, Weir BS: Truncated product method for combining P-values. *Genet. Epidemiol.* 22, 170–185 (2002)
77. Rolls ET, O'Doherty J, Kringelbach ML, et al.: Representations of pleasant and painful touch in the human orbitofrontal and cingulate cortices. *Cerebral Cortex* 13, 308–317 (2003)
78. Zald DH, Lee JT, Fluegel KW, Pardo JV: Aversive gustatory stimulation activates limbic circuits in humans. *Brain* 121, 1143–1154 (1998)
79. Ito S, Stuphorn V, Brown JW, Schall JD: Performance monitoring by the anterior cingulate cortex during saccade countermanding. *Science* 302, 120–122 (2003)
80. Vogt BA Ed. (2008): *Cingulate Neurobiology & Disease*. Oxford. Oxford University Press
81. Rolls ET (2008): *Memory, Attention, and Decision-Making: A Unifying Computational Neuroscience Approach*. Oxford, Oxford University Press
82. Rolls ET: The rules of formation of the olfactory representations found in the orbitofrontal cortex olfactory areas in primates. *Chemical Senses* 26, 595–604 (2001)
83. Rolls ET (2002): The cortical representation of taste and smell. In: *Olfaction, Taste and Cognition*. Eds: Rouby G, Schaal B, Dubois D, Gervais R, Holley A. New York, Cambridge University Press, pp. 367–388
84. Rolls ET (2002): The functions of the orbitofrontal cortex. In: *Principles of Frontal Lobe Function*. Eds: Stuss DT, Knight RT. New York, Oxford University Press, Chap. 23, pp. 354–375
85. Rolls ET: Central nervous mechanisms related to feeding and appetite. *British Medical Bulletin* 37, 131–134 (1981)
86. Rolls BJ, Van Duijvenvoorde PM, Rolls ET: Pleasantness changes and food intake in a varied four-course meal. *Appetite* 5, 337–348 (1984)
87. Rolls BJ (1990): The role of sensory-specific satiety in food intake and food selection. In: *Taste, Experience, and Feeding*. Eds: Capaldi ED, Powley TL, Washington DC, American Psychological Association, pp. 197–209
88. Cabanac M, Fantino M: Origin of olfacto-gustatory alliesthesia: Intestinal sensitivity to carbohydrate concentration? *Physiology and Behavior* 10, 1039–1045 (1977)
89. Cabanac M, Duclaux R: Specificity of internal signals in producing satiety for taste stimuli. *Nature* 227, 966–967 (1970)
90. Rolls ET, Rolls JH: Olfactory sensory-specific satiety in humans. *Physiology and Behavior* 61, 461–473 (1997)

91. Rolls ET: Understanding the mechanisms of food intake and obesity. *Obesity Reviews* 8 (Suppl. 1), 67–72 (2007)
92. Rolls BJ, Van Duijvenoorde PM, Rowe EA: Variety in the diet enhances intake in a meal and contributes to the development of obesity in the rat. *Physiology and Behavior* 31, 21–27 (1983)
93. Rolls BJ, Hetherington M (1989): The role of variety in eating and body weight regulation. In: *Handbook of the Psychophysiology of Human Eating*. Ed: Shepherd R. Chichester, Wiley, pp. 57–84
94. Thorpe SJ, Rolls ET, Maddison S: Neuronal activity in the orbitofrontal cortex of the behaving monkey. *Experimental Brain Research* 49, 93–115 (1983)
95. Rolls ET: Taste and olfactory processing in the brain, and its relation to the control of eating. *Frontiers of Oral Biology* 9, 40–75 (1998)
96. Kadohisa M, Rolls ET, Verhagen JV: The primate amygdala: neuronal representations of the viscosity, fat texture, grittiness and taste of foods. *Neuroscience* 132, 33–48 (2005)
97. Rolls ET (2000): Neurophysiology and functions of the primate amygdala, and the neural basis of emotion. In: *The Amygdala: A Functional Analysis*. Ed.: Aggleton JP Second Edition. Oxford, Oxford University Press, pp. 447–478
98. Sanghera MK, Rolls ET, Roper-Hall A: Visual responses of neurons in the dorsolateral amygdala of the alert monkey. *Experimental Neurology* 63, 610–626 (1979)
99. Deco G, Rolls ET: Synaptic and spiking dynamics underlying reward reversal in orbitofrontal cortex. *Cerebral Cortex* 15, 15–30 (2005)
100. O'Doherty J, Rolls ET, Francis S, Bowtell R, McGlone F: The representation of pleasant and aversive taste in the human brain. *Journal of Neurophysiology* 85, 1315–1321 (2001)
101. de Araujo IET, Kringelbach ML, Rolls ET, McGlone F: Human cortical responses to water in the mouth, and the effects of thirst. *J. of Neurophysiol.* 90, 1865–1876 (2003)
102. Poellinger A, Thomas R, Lio P, et al.: Activation and habituation in olfaction – an fMRI study. *NeuroImage* 13, 547–560 (2001)
103. Sobel N, Prabhakaran V, Zhao Z, et al.: Time course of odorant-induced activation in the human primary olfactory cortex. *J. of Neurophysiol.* 83, 537–551 (2000)
104. Zald DH, Pardo JV: Emotion, olfaction, and the human amygdala: amygdala activation during aversive olfactory stimulation. *Proceedings of the National Academy of Sciences USA* 94, 4119–4124 (1997)
105. Small DM, Voss J, Mak YE, et al.: Experience-dependent neural integration of taste and smell in the human brain. *J. of Neurophysiol.* 92, 1892–1903 (2004)
106. Small DM, Prescott J: Odor/taste integration and the perception of flavor. *Experimental Brain Research* 166, 345–357 (2005)
107. Kringelbach ML, O'Doherty J, Rolls ET, Andrews C: Activation of the human orbitofrontal cortex to a liquid food stimulus is correlated with its subjective pleasantness. *Cerebral Cortex* 13, 1064–1071 (2003)
108. O'Doherty JP, Deichmann R, Critchley HD, Dolan RJ: Neural responses during anticipation of a primary taste reward. *Neuron* 33, 815–826 (2002)
109. Simmons WK, Martin A, Barsalou LW: Pictures of appetizing foods activate gustatory cortices for taste and reward. *Cerebral Cortex* 15, 1602–1608 (2005)
110. Pelchat ML, Johnson A, Chan R, Valdez J, Ragland JD: Images of desire: food-craving activation during fMRI. *NeuroImage* 23, 1486–1493 (2004)
111. Wang GJ, Volkow ND, Telang F, et al.: Exposure to appetitive food stimuli markedly activates the human brain. *NeuroImage* 21, 1790–1797 (2004)
112. Grabenhorst F, Rolls ET, Bilderbeck A: How cognition modulates affective responses to taste and flavor: top down influences on the orbitofrontal and pregenual cingulate cortices. *Cerebral Cortex* (in press 2007)
113. McCabe C, Rolls ET, Bilderbeck A, McGlone F: Cognitive influences on the representation of touch in the human brain. In preparation (2008)
114. Wilson FAW, Rolls ET: The primate amygdala and reinforcement: a dissociation between rule-based and associatively-mediated memory revealed in amygdala neuronal activity. *Neuroscience* 133, 1061–1072 (2005)
115. Garrow JS (1988): *Obesity and Related Diseases*. London, Churchill Livingstone

116. Barsh GS, Schwartz MW: Genetic approaches to studying energy balance: perception and integration. *Nature Reviews Genetics* 3, 589–600 (2002)
117. Cummings DE, Schwartz MW: Genetics and pathophysiology of human obesity. *Annual Reviews of Medicine* 54, 453–471 (2003)
118. Schwartz MW, Porte D: Diabetes, obesity, and the brain. *Science* 307, 375–379 (2005)
119. Brownell KD, Fairburn C (1995): *Eating Disorders and Obesity: a Comprehensive Handbook*. New York, Guildford Press
120. Horvath TL: The hardship of obesity: a soft-wired hypothalamus. *Nature Neuroscience* 8, 561–565 (2005)
121. Rolls ET: Taste, olfactory, and food texture processing in the brain, and the control of food intake. *Physiology and Behavior* 85, 45–56 (2005)