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THE NEURAL REPRESENTATION OF ORAL TEXTURE INCLUDING FAT TEXTURE

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ABSTRACT

The brain areas that represent taste also provide a representation of oral texture. Fat texture is represented by neurons independently of viscosity: some neurons respond to fat independently of viscosity, and other neurons encode viscosity. The neurons that respond to fat also respond to silicone and paraffin oil, indicating that the sensing is texture- not chemo-specific. This fat sensing is not related to free fatty acids such as linoleic acid; a few other neurons with responses to free fatty acids typically do not respond to fat in the mouth. Fat texture-sensitive neurons are found in the primary taste cortex, the secondary taste cortex in the orbitofrontal cortex where the pleasantness of food is represented, and in the amygdala. Different neurons respond to different combinations of texture, taste, oral temperature, and in the orbitofrontal cortex to olfactory and visual properties of food. Complementary human functional neuroimaging studies are described.

PRACTICAL APPLICATIONS

This research has implications for understanding how fat in the mouth is sensed. It therefore has implications for the design of foods that may mimic the mouthfeel of fat, but not its energy content.

INTRODUCTION

The aims of this paper are to describe how oral texture, including fat, is represented in the brain. This is an important issue, for it is not yet clear how oral fat is sensed, and evidence from neuroscience is providing indications about this by showing what must have been transduced by receptors in the mouth, in order to produce the neuronal responses found in the brain. Moreover, fat in the diet may be pleasant, yet its intake must be controlled, and understanding the rules by which the pleasantness of fat is regulated is important. In addition, the brain's representation of oral fat is frequently in terms of particular combinations with other sensory aspects of food, including taste, texture and olfactory inputs, and these combinations are important for understanding the full impact of the fat in food in the mouth on the pleasantness of food.

Because the representation of oral texture in the mouth is closely linked to taste processing in the brain, we start with an overview of taste pathways and processing in the brain, before we consider how oral texture is represented in the same brain areas, and is represented frequently but not always in combination with taste. To make the results relevant to understanding the control of human food intake, complementary evidence is provided by neurophysiological studies in non-human primates in which the taste and related pathways are similar to those in humans (Norgren 1984; Rolls and Scott 2003; Rolls 2005; Rolls and Grabenhorst 2008; Small and Scott 2009), and by functional neuroimaging studies in humans. A broad perspective on brain processing involved in hedonic aspects of the control of food intake and in affective responses more generally is provided by Rolls (2005). By oral texture, I mean texture, somatosensory, signals produced by stimuli in the mouth. By oral fat texture I mean the oral texture stimulus produced by fat in the mouth. The perceptual qualities of these stimuli have been investigated by Kadohisa *et al.* (2005a).

TASTE PROCESSING IN THE PRIMATE BRAIN

Pathways

A diagram of the taste and related olfactory, somatosensory and visual pathways in primates is shown in Fig. 1. The multimodal convergence that enables single neurons to respond to different combinations of taste, olfactory, texture, temperature and visual inputs to represent different flavors produced often by new combinations of sensory input is afforded by the convergence of processing pathways evident in brain areas such as the orbitofrontal cortex (Rolls 2007; Rolls and Grabenhorst 2008).

The Primary Taste Cortex

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

The Secondary Taste Cortex

A secondary cortical taste area in primates was discovered by Rolls *et al.* (1990) in the caudolateral orbitofrontal cortex,

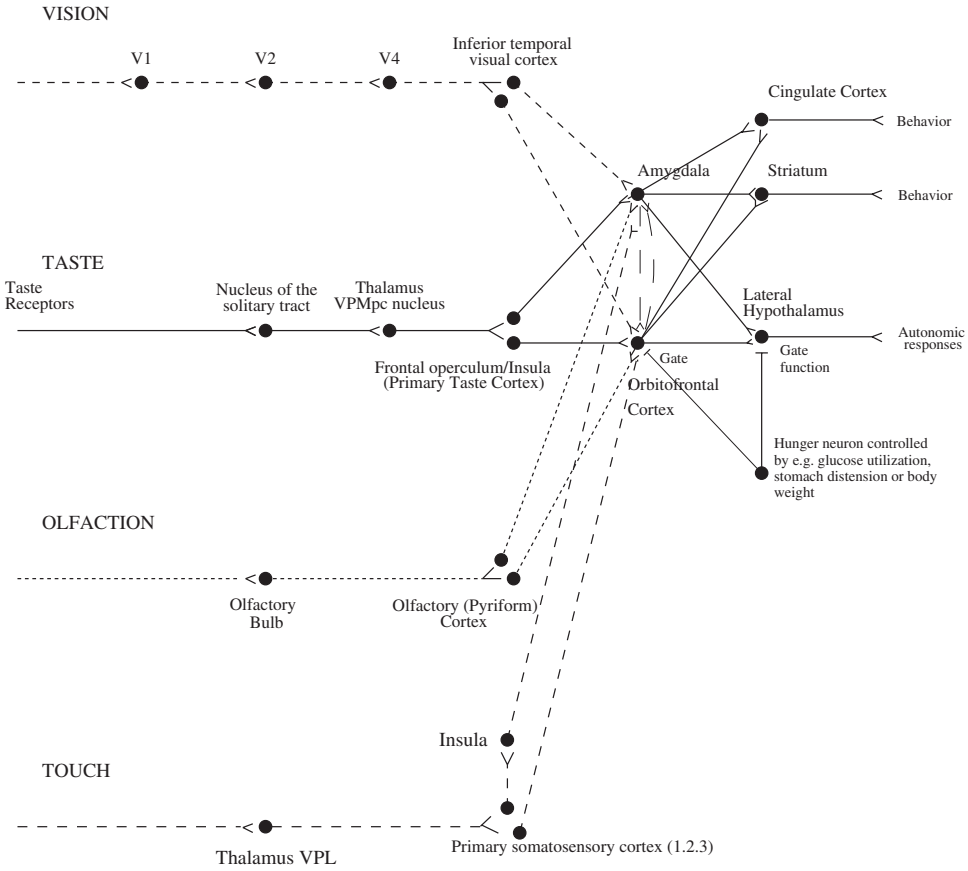

FIG. 1. SCHEMATIC DIAGRAM OF THE TASTE AND OLFACTORY PATHWAYS IN PRIMATES, INCLUDING HUMANS, SHOWING HOW THEY CONVERGE WITH EACH OTHER AND WITH VISUAL PATHWAYS

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, ventral posteromedial thalamic nucleus; V1, V2, V4, visual cortical areas.

extending several millimeters in front of the primary taste cortex, and defined to be secondary taste cortex by its inputs shown anatomically from the primary taste cortex (Baylis *et al.* 1995). The area that corresponds to this in humans is the caudal orbitofrontal cortex, as shown by its cytoarchitectonics (Carmichael and Price 1994; Öngür *et al.* 2003; Price 2006), and by the nature of its activations in neuroimaging investigations, as shown below with further discussion of the topology by Rolls (2005, 2008a). 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 cortices, there are many neurons that respond best to each of the four classical prototypical tastes: sweet, salt, bitter and sour (Rolls 1997; Rolls and Scott 2003), but there are also many neurons that respond best to umami tastants such as glutamate (which is present in many natural foods such as tomatoes, mushrooms and milk; Baylis and Rolls 1991) and inosine monophosphate (which is present in meat and some fish such as tuna; Rolls *et al.* 1996a). This evidence, taken together with the identification of possible glutamate taste receptors (Zhao *et al.* 2003; Maruyama *et al.* 2006), leads to the view that there are five prototypical types of taste information channels, with umami contributing, often in combination with corresponding olfactory inputs (Rolls *et al.* 1998; McCabe and Rolls 2007), to the flavor of protein. In addition, other neurons respond to water, and others to somatosensory texture-related stimuli including astringency, as exemplified by tannic acid (Critchley and Rolls 1996c), and capsaicin (Rolls *et al.* 2003c; Kadohisa *et al.* 2004).

The Pleasantness of the Taste of Food

The modulation of the reward value of a sensory stimulus such as the taste of food by motivational state, for example, hunger, is one important way in which motivational behavior is controlled (Rolls 1999, 2005). 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 the early stages of the primate gustatory system. The responsiveness of taste neurons in the nucleus of the solitary tract (Yaxley *et al.* 1985) and in the primary taste cortex (frontal opercular, Rolls *et al.* 1988; insular, Yaxley *et al.* 1988) is not attenuated by feeding to satiety. In contrast, in the secondary taste cortex, 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 behavior turned from avid acceptance to active rejection (Rolls *et al.* 1989). This modulation of responsiveness of the gustatory responses of the orbitofrontal cortex neurons by satiety could not have been 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 (Rolls *et al.* 1989; Critchley and Rolls 1996a).

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

It is an important principle that the identity of a taste and its intensity are represented separately from its pleasantness

(Grabenhorst and Rolls 2008, 2011; Rolls and Grabenhorst 2008; Grabenhorst *et al*. 2008a). Thus, it is possible to represent what a taste is and to learn about it, even when we are not hungry.

THE REPRESENTATION OF FLAVOR: 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 flavor (see Fig. 1). We found (Rolls and Baylis 1994) 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 odor. 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 flavor representations are built, where flavor is taken to mean a representation which is evoked best by a combination of gustatory and olfactory input. This orbitofrontal region does appear to be an important region for convergence, for there is only a low proportion of bimodal taste and olfactory neurons in the primary taste cortex (Rolls and Baylis 1994; Verhagen *et al*. 2004).

The bimodal neurons appear to be built by learning. Critchley and Rolls (1996b) showed that 35% of orbitofrontal cortex olfactory neurons categorized odors based on their taste association in an olfactory-to-taste discrimination task. Rolls *et al*. (1996a) found that 68% of orbitofrontal cortex odor-responsive neurons modified their responses, in some way following changes in the taste reward associations of the odorants during olfactory-taste discrimination learning and its reversal. (In an olfactory discrimination experiment, if a lick response to one odor, the S+, is made, a drop of glucose taste reward is obtained; if a lick response is made to another odor incorrectly, the S-, a drop of aversive saline is obtained. At some time in the experiment, the contingency between the odor and the taste is reversed, and when the "meaning" of the two odors alters, so does the behavior. 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 odor depends on the taste with which it is associated, and does not depend primarily on the physicochemical structure of the odor). 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 odor is associated (Rolls 2001, 2002a,b).

THE REPRESENTATION OF THE PLEASANTNESS OF ODOR 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 odor is represented in the orbitofrontal cortex. In satiety experiments, Critchley and Rolls (1996a) showed that the responses of some olfactory neurons to a food odor are decreased during feeding to satiety with a food (e.g., fruit juice or cream) containing that odor. In particular, seven of nine olfactory neurons that were responsive to the odors of foods, such as blackcurrant juice, were found to decrease their responses to the odor of the satiating food. The decrease was typically at least partly specific to the odor 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. 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.

THE RESPONSES OF ORBITOFRONTAL CORTEX NEURONS TO THE TEXTURE AND TEMPERATURE OF FOOD

The orbitofrontal cortex (OFC) 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, 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

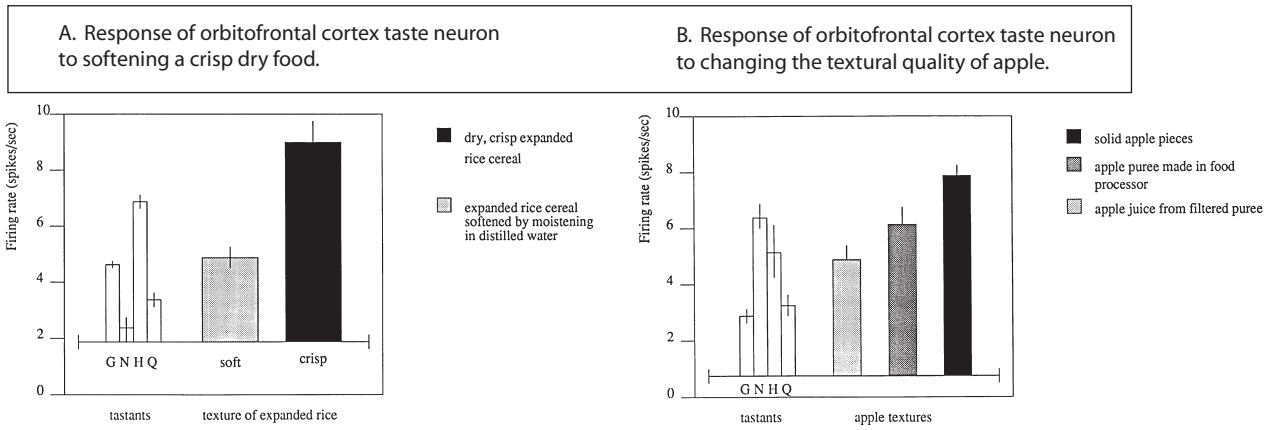

FIG. 2. EXAMPLES OF THE EFFECTS ON ORBITOFRONTAL CORTEX TASTE RESPONSIVE NEURONS OF ALTERING THE TEXTURAL PROPERTIES OF FOODS (A) A neuron that responded more to the texture of a crisp dry expanded rice cereal than when it was made soft with water. (B) A neuron that responded more to a crisp slice of fresh apple than to a puree made from the apple, which in turn produced a larger response than the apple juice from the filtered puree. The response measured is the firing rate of the single neuron in spikes/s with the mean and SEM over 4–10 trials shown. The responses of the neurons to 1 M glucose (G), 0.1 M NaCl (N), 0.01 M hydrochloric acid (H) and 0.001 M quinine are also shown. The responses are shown as changes from the baseline spontaneous firing rate of the neurons (previously unpublished experiments of H.D. Critchley and E.T. Rolls, 1995).

manipulated by the addition of methyl cellulose or gelatine, or by puréeing a semi-solid food (Rolls 1998, 1999). Examples of the effects on orbitofrontal cortex taste responsive neurons of altering the textural properties of foods are illustrated in Fig. 2. A neuron that responded more to the texture of a crisp, dry, expanded rice cereal than when it was made soft with water is illustrated in Fig. 2A. A neuron that responded more to a crisp slice of fresh apple than to a puree made from the apple, which in turn produced a larger response than the apple juice from the filtered puree, is illustrated in Fig. 2B.

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 [cP]), and that others independently encode the particulate quality of food in the mouth, produced quantitatively, for example, by adding 20–100 μm microspheres to 1,000 cP methyl cellulose ("Gritty") (Rolls *et al.* 2003c). The two neurons shown as examples in Fig. 3 illustrate some of these properties. Neuron bk244 had a graded increase of firing rate to viscosity in the range of 10–1,000 cP, had no taste responses, did respond to oils and did not respond to capsaicin. The responses of these viscosity-sensitive neurons parallel that of humans' subjective ratings of the thickness of the same methyl cellulose viscosity series: the human subjective ratings of thickness were linearly related to the log of the measured viscosity of the stimuli (Kadohisa *et al.* 2005a). Neuron bo34 also had a graded increase of firing rate to viscosity in the range of 10–10,000 cP, did respond to some tastes (glucose, sweet; HCl, sour; and quinine, bitter) but not to others (NaCl and MSG), did not respond to oils and did respond to capsaicin. These neurons illustrate that taste, viscosity, fatty oils and capsaicin can be coded for independently by a population of neurons of which these are examples. The independence arises from the fact that different neurons respond to different combinations of these stimuli. The oils used in this study included mineral oil, silicone oil, vegetable oil, coconut oil and safflower oil (see Table 1) (Rolls *et al.* 2003c).

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 (Kadohisa *et al.* 2004).

Neurons in the insular primary taste cortex (Verhagen *et al.* 2004), and in the amygdala (Kadohisa *et al.* 2005b), also respond to these oral texture signals, including viscosity and fat texture, and to temperature. One difference is that neurons in the insular primary taste cortex have these taste and oral texture responses, but are little affected by olfactory stimuli or by the sight of food (Verhagen *et al.* 2004; Kadohisa *et al.* 2005a). These olfactory and visual inputs are added to the representation in the orbitofrontal cortex (Rolls and Baylis 1994; Critchley and Rolls 1996a,b; Rolls *et al.* 1996b,c). Other differences between these areas are that in the primary taste cortex, taste and viscosity are more likely to activate different neurons, with more convergence onto single neurons particularly in the OFC and amygdala. This reflects the hierarchical organization shown in Fig. 1. The different responses of different OFC neurons to different combinations of these oral sensory stimuli potentially provide a basis for different behavioral responses. Consistently, the mean correlations between

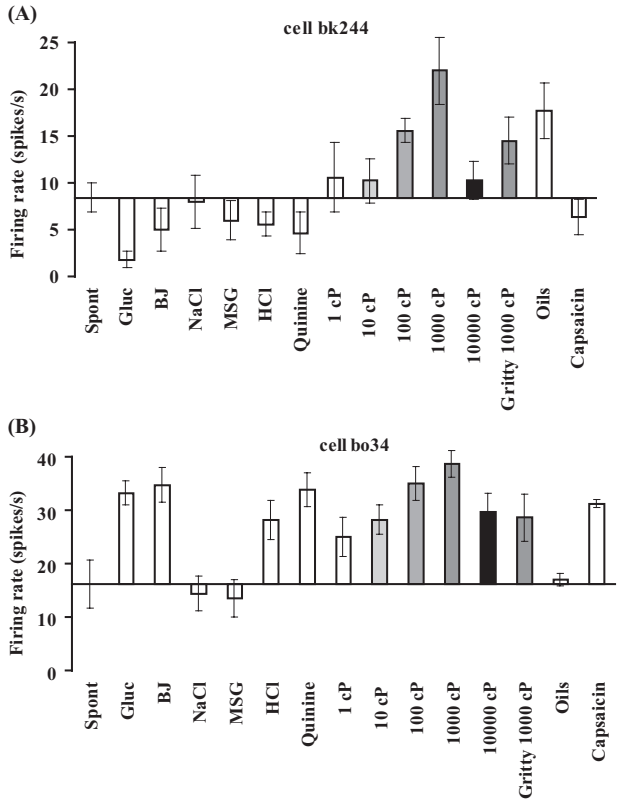

FIG. 3. ORAL SOMATOSENSORY AND TASTE INPUTS TO ORBITOFRONTAL CORTEX NEURONS
(A) Firing rates (mean ± SEM) of viscosity-sensitive neuron BK244 which did not have taste responses, in that it did not respond differentially to the different taste stimuli. The firing rates are shown to the viscosity series (carboxy-methyl-cellulose 1–10,000 centipoise, to the gritty stimulus (1,000 cP carboxymethylcellulose with Fillite microspheres), to the taste stimuli 1 M glucose (Gluc), 0.1 M NaCl, 0.1 M MSG, 0.01 M HCl and 0.001 M QuinineHCl, and to fruit juice (BJ). SPONT = spontaneous firing rate. (B) Firing rates (mean ± SEM) of viscosity-sensitive neuron bo34 which had no response to the oils (mineral oil, vegetable oil, safflower oil and coconut oil, which have viscosities that are all close to 50 cP). The neuron did not respond to the gritty stimulus in a way that was unexpected given the viscosity of the stimulus, was taste tuned, and did respond to capsaicin (after Rolls *et al*. 2003c).

the representations of the different stimuli provided by the population of OFC neurons were lower (0.71) than for the insula (0.81) and amygdala (0.89). Further, the encoding was sparser in the OFC (0.67) than in the insula (0.74) and amygdala (0.79) (Kadohisa *et al*. 2005a). Multidimensional scaling indicates that the insular primary taste cortex and amygdala emphasize the representation of oral viscosity, and that the orbitofrontal cortex emphasizes the representation of pleasant tastes such as glucose and fruit juice (see Fig. 2 of Kadohisa *et al*. 2005a). (The distances between stimuli in a multi dimensional scaling space reflects how closely correlated the responses of a set of neurons are to each pair of stimuli.)

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 *et al*. (1999) discovered a population of neurons that responds to the texture of fat in the mouth. Figure 4 shows an example of one of these neurons. The neuron increased its firing rate to cream (double and single cream, with the fat proportions shown), and responded to texture rather than the chemical structure of the fat, in that it also responded to 0.5 mL of silicone oil $(Si(CH_3)_2O)_n$ or paraffin oil (hydrocarbon). The neuron did not have a taste input. The firing rate responses are shown against the baseline spontaneous firing rate of the neuron.

Figure 5 shows an example of a fat-responsive neuron in the orbitofrontal cortex from the study of Verhagen *et al*. (2003b), where the evoked neuronal activity to the indicated stimuli is plotted as a function of viscosity. The cell showed strong and similar responses to all the oils tested, but did not respond to any of the carboxy-methyl-cellulose (CMC) viscosity series below 10,000 cP, and to none of the CMC viscosity series with viscosities in the range of the oils (the stimuli used and their abbreviations are in Table 1). The neuronal responses were significantly different between the oils and the spontaneous firing rate and V10–V100 (both $P < 0.001$). Further, in contrast to the robust excitatory responses to safflower oil (45 spikes/s) and coconut oil (50 spikes/s), which are rich in linoleic and lauric acid bound into triglycerides, the responses to linoleic and lauric acid were slightly below the spontaneous rate, providing evidence that the neurons did not respond to fats based on gustatory sensitivity to the fatty acids. Figure 6 shows another example of a fat-sensitive neuron in the orbitofrontal cortex.

A different type of neuron is now described, to make it clear how selective the type of neuron shown in Figs 5 and 6 is for fat texture. In this comparison type of neuron, the responses to oils were apparently determined by the viscosity of the oils, and the neurons were effectively viscosity-sensitive rather than fat-sensitive. For example, the neuron illustrated in Fig. 7 showed an increasing neuronal response as the viscosity of the CMC series increased from V10 to V1000, and the responses to mineral, vegetable and silicone oil, plotted at their viscosities, follow this viscosity sensitivity curve closely.

We also observed neurons that did respond to the CMC viscosity series, but not to the oils (Verhagen *et al*. 2003b). This type of neuronal response, which also illustrates how neurons can be tuned to a range of viscosities, is exemplified by the neuron shown in Fig. 8. The neuronal responses show an upward trend with increasing viscosity (V1–V1000), and a reduction at V10000. However, none of the oils evoked

TABLE 1. STIMULI

Stimulus	Abbreviation	Concentration	MW	App. viscosity (cP)	Chemical group
Glucose	G	1 M	180	1	monosaccharide aldohexose
Blackcurrant juice	BJ	20%		1	mixture
Monosodium glutamate	M	0.1 M	187	1	amino acid salt
NaCl	N	0.1 M	58	1	inorganic salt
HCl	H	0.01 M	36	1	inorganic acid
Quinine HCl	Q	0.001 M	387	1	alkaloid
Water	V1 or 1 cP	5 mM NaCl		1	
CMC†	V10 or 10 cP	0.2 g + 1l V1	70,000	10	polysaccharide
CMC†	V100 or 100 cP	4.0 g + 1l V1	70,000	100	polysaccharide
CMC†	V1,000 or 1,000 cP	11.0 g + 1l V1	70,000	1,000	polysaccharide
CMC†	V10,000 or 10,000 cP	24.0 g + 1l V1	70,000	10,000	polysaccharide
Mineral oil	MO	100%		25	hydrocarbon mixture
Silicone oil	SiO or SilO	100%		100 or 280	silicon-oxygen polymer
Vegetable oil	VOo or VOf	100%		55	fat
Coconut oil	CO	100%		40	fat
Safflower oil	SaO or SafO	100%		50	fat
Single cream	SC	100%		12	emulsion
Lauric acid C12:0	LaA	100 μM		1	FFA
Linoleic acid C18:2	LiA	100 μM		1	FFA

† Carboxy-methyl-cellulose.
FFA, free fatty acids.

significant activity. Thus, the responses of this neuron show another way in which orbitofrontal cortex neurons can discriminate between fat texture and viscosity, by in this case, responding to information conveyed through a viscosity information channel but not through a fat-sensitive information channel. Part of the interest of this type of neuron is that although the oils had viscosities that were in the range of 25–100 cP (see Table 1), the neuron did not respond to this level of viscosity when it was expressed through the presence of an oil. This provides evidence that oils must therefore have other textural properties (reflected for example in their slickness) that prevent this type of neuron from responding. This neuron had firing rates to linoleic and lauric acid (four, three spikes/s, respectively) that were predictable by their viscosity, as shown in Fig. 8.

In this study, 5.4% of the orbitofrontal cortex neurons responded to fat, viscosity and/or taste (Verhagen *et al.* 2003b). Of the 14 neurons with responses to fat in the mouth where the response to fat was independent of viscosity (i.e., could not be predicted from viscosity) (1.6% of all screened neurons), nine responded to both taste and to fat, four to taste and to viscosity, and one did not respond to taste or to

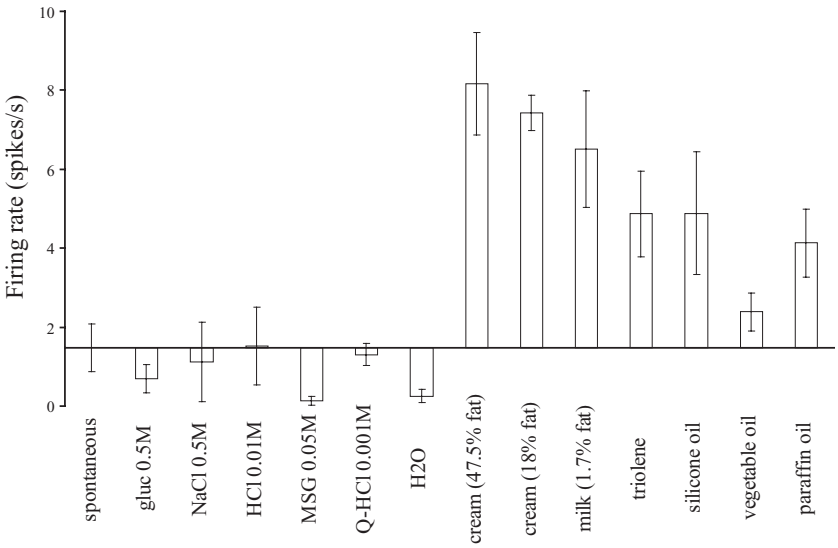

FIG. 4. A NEURON IN THE PRIMATE ORBITOFRONTAL CORTEX RESPONDING TO THE TEXTURE OF FAT IN THE MOUTH
The neuron increased its firing rate to cream (double and single cream, with the fat proportions shown), and responded to texture rather than the chemical structure of the fat in that it also responded to 0.5 mL of silicone oil $(Si(CH_3)_2O)_n$ or paraffin oil (hydrocarbon). the neuron did not have a taste input. Gluc, glucose; NaCl, salt; HCl, sour; Q-HCl, quinine, bitter. The spontaneous firing rate of the cell is also shown (after Rolls *et al*. 1999).

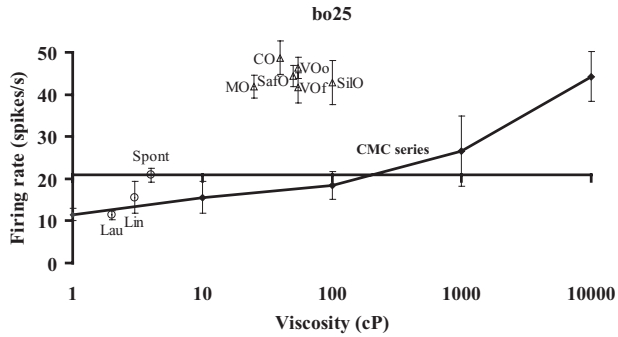

FIG. 5. EVOKED ACTIVITY GRAPHED AGAINST APPARENT STIMULUS VISCOSITY FOR FAT-RESPONSIVE NEURON BO25
The line indicates the responses to the carboxy-methyl-cellulose (CMC) viscosity series. The mean and the standard error of the mean responses calculated in a 1 s period over four to six trials are shown here and elsewhere, unless otherwise indicated. The oils evoked significantly higher activity than either the spontaneous activity or CMC at corresponding apparent viscosities. The oils were vegetable oil (VOo, VOf), safflower oil (SO), coconut oil (CO), silicone oil (SilO) and mineral oil (MO). Linoleic acid (Lin) and lauric acid (Lau) were also tested. Details of the stimuli are in Table 1. The information that reaches this type of neuron is independent of a viscosity sensing channel, in that the neuron did not respond to the methyl cellulose (CMC) viscosity series (after Verhagen *et al*. 2003b).

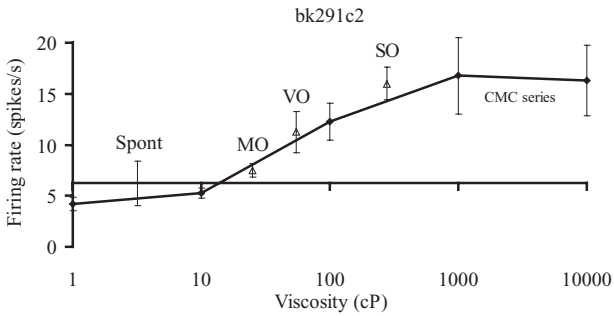

FIG. 7. EVOKED ACTIVITY GRAPHED AGAINST APPARENT STIMULUS VISCOSITY FOR VISCOSITY-SENSITIVE NEURON BK291C2
The line indicates the responses to the carboxy-methyl-cellulose (CMC) series. The oil-evoked activity follows that evoked by the CMC-viscosity stimuli at corresponding apparent viscosities. For abbreviations see Table 1 (after Verhagen *et al*. 2003b). (BK291c2 respVSvisco.eps)

viscosity. Thirteen of the 18 neurons responsive to viscosity also responded to taste, four of those responded to fat – where the response to the fat could be predicted from the viscosity – and five responded to only viscosity. In addition, the number of neurons that were tuned to the CMC viscosity series and which did not respond to fat in the way that would be predicted by the CMC viscosity tuning (see example in Fig. 8) was 4 of the 50 neurons analyzed.

The results of these studies on orbitofrontal cortex neurons (Rolls *et al*. 1999; Verhagen *et al*. 2003b) show that fat-sensitive neurons respond not only to fats such as vegetable oil and other fatty oils in the mouth, and to substances rich in fat such as cream and chocolate, but also to chemically different substances which have a similar slick or oily texture such as mineral oil (pure hydrocarbon) and silicone oil $(Si(CH_3)_2O)_n$. This evidence thus indicates that the mechanisms that sense fat, and to which these neurons respond, are sensing a physical rather than a chemical property of the stimuli. The results also provide evidence that the

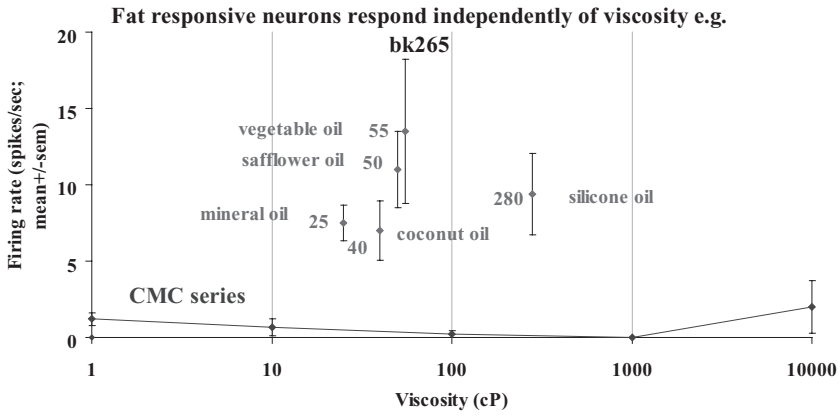

FIG. 6. A NEURON IN THE PRIMATE ORBITOFRONTAL CORTEX RESPONDING TO THE TEXTURE OF FAT IN THE MOUTH INDEPENDENTLY OF VISCOSITY
The cell (bk265) increased its firing rate to a range of fats and oils (the viscosity of which is shown in centipoise). The information that reaches this type of neuron is independent of a viscosity sensing channel, in that the neuron did not respond to the methyl cellulose (carboxy-methyl-cellulose [CMC]) viscosity series. The neuron responded to the texture rather than the chemical structure of the fat in that it also responded to silicone oil $(Si(CH_3)_2O)_n$ and paraffin (mineral) oil (hydrocarbon). Some of these neurons have taste inputs. For abbreviations see Table 1 (after Verhagen *et al*. 2003b).

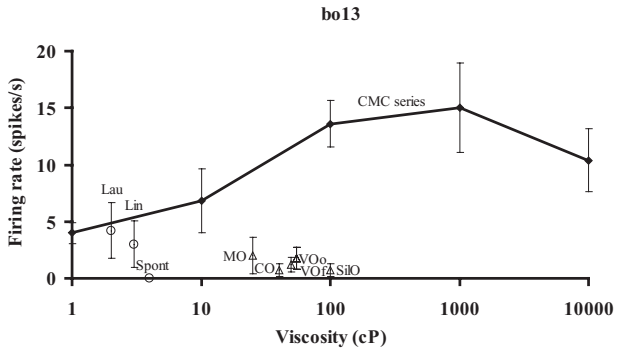

FIG. 8. EVOKED ACTIVITY GRAPHED AGAINST APPARENT STIMULUS VISCOSITY FOR NEURON BO13. THE LINE INDICATES THE RESPONSES TO THE CMC SERIES. THIS NEURON DID RESPOND TO VISCOSITY (OF THE CARBOXY-METHYL-CELLULOSE [CMC] SERIES) BUT NO ACTIVITY WAS EVOKED BY THE OILS
For abbreviations see Table 1 (after Verhagen *et al*. 2003b).

responses of fat-sensitive neurons are not based on a texture information channel that is tuned to viscosity. In particular, although some neurons in the orbitofrontal cortex are tuned to viscosity (see examples in Figs 7 and 8) (Rolls *et al*. 2003c), many (10/14) of the fat-sensitive neurons did not respond to the viscosity series of stimuli (see examples in Figs 5 and 6), or had responses to the fats and some of the CMC viscosity series, where the response to fat could not be accounted for by viscosity (4/14); four neurons were responsive to viscosity but did not respond to fat (see example in Fig. 8). The latter type of neuron (Fig. 8) is rather interesting, for the implication is that although there is a viscosity-sensing channel that responds to stimuli, including fats based on their viscosity (Fig. 7), there is also a mechanism for representing viscosity when it is not produced by a fatty oily stimulus, as in Fig. 8.

Important conclusions then about the representation of oral texture in the brain (and illustrated by the types of neuron shown in Figs 5–8) are:

(1) There is an information channel that represents fat independently of viscosity.

(2) There is an information channel that represents viscosity and also responds to fat based on the viscosity of the fat. This channel thus responds to viscosity, independently of whether the eliciting stimulus is a nonfat or a fat.

(3) There is an information channel that encodes viscosity, provided that it is not associated with an oily substance such as a fat. The third type of channel could reflect a separate sensing mechanism in the mouth, or it could reflect competitive and expansion recoding processes (Rolls and Deco 2002; Rolls 2008b) produced in the cortex by inputs reflecting, for example, fat sensitivity without viscosity in a first channel, and viscosity with fat sensitivity in another channel.

Gustatory mechanisms have been revealed in rat oral taste cells that may mediate a possible fat taste: the slow modulation of K-channels by polyunsaturated free fatty acids such as linoleic acid (Gilbertson *et al*. 1997; Gilbertson 1998). However, salivary lipase, which could release fatty acid from fat in rats to activate such a mechanism, is hardly present in humans (Gilbertson *et al*. 1997; Gilbertson 1998), thus, this mechanism may not be important in humans. Further evidence that this chemical-sensing mechanism may not be important in primates, including humans, is that the time course of the activation of the K-channel mechanism is very slow (Gilbertson *et al*. 1997; Gilbertson 1998) and does not match the rapidly developing subjective sensation of fat in the mouth. However, to test this possibility, responses by the population of orbitofrontal cortex neurons to the free fatty acids (FFA), linoleic acid (LiA) and lauric acid (LaA) were measured; for most neurons, responses were not found, that is, for most neurons the activity evoked by these stimuli was indistinguishable to that evoked by water (Verhagen *et al*. 2003b). In particular, of 37 neurons tested with lauric and linoleic acid, 34 had no significant responses compared with water. Of the three neurons that had statistically significant responses in this comparison, all three consisted of a smaller response than was obtained to water, and in two cases, the statistical significance was marginal, i.e., $P \approx 0.05$. To assess whether the firing rates obtained to lauric and linoleic acid could predict the responses of the neurons to coconut oil (high in lauric conjugated to glycerol) and to safflower (high in linoleic conjugated to glycerol), linear regression analysis was performed across the sample of 14 fat-sensitive neurons in the orbitofrontal cortex (Verhagen *et al*. 2003b). There was no significant correlation between the responses to the fatty acids and these two fat stimuli (for lauric acid, $r = 0.45$, $P = 0.20$; for linoleic, $r = 0.61$, $P = 0.06$). Thus, the responses to fats by this population of neurons cannot be accounted for by sensitivity to lauric acid and linoleic acid. By contrast, the responses to fats could be predicted by their response to the texture of silicone oil (for silicone oil, versus coconut oil $r = 0.99$, $P < 0.001$; while for silicone oil versus safflower oil $r = 0.99$, $P < 0.001$). Together, these points of evidence (Verhagen *et al*. 2003b) suggest that fat in the mouth can be sensed in primates, independently of any oral gustatory mechanism for free fatty acids (a mechanism suggested by Gilbertson [1998] in rodents). These data suggest that different sensing mechanisms and percepts are evoked by FFA as compared with fatty oils. Perceptual responses to FFA, if large enough not to also taste sour (Forss 1972), depend at least partly on the trigeminal-nociceptive pathway and may be associated with the percept of oral irritation. To the extent that fatty acid taste may occur in humans, it may tend to make food unpleasant, with a rancid flavor; also consistent with this, food manufacturers minimize the content of free fatty acids in foods (Mattes 2009). The oils, whether triglyceride-based or not, are sensed by a somatosensory-textural pathway and may be associated with the mouth feel of fatty/slickness.

It is the fat texture component that may impart pleasant sensory attributes to fat, as shown by the evidence that orbitofrontal cortex fat texture neurons in macaques respond less to fat texture after feeding to satiety with a high-fat food (Rolls *et al.* 1999), with the pleasantness of oral fat represented in humans in the orbitofrontal and pregenual cingulate cortex (Grabenhorst *et al.* 2010b).

Some of the fat-related neurons do, however, receive convergent inputs from the chemical senses, in that in addition to taste inputs, some of these neurons respond to the odor associated with a fat such as the odor of cream (Rolls *et al.* 1999). Feeding to satiety with fat (e.g., cream) decreases the responses of these orbitofrontal cortex neurons to zero on the food eaten to satiety (including its odor [Critchley and Rolls 1996a]), but if the neuron receives a taste input from, for example, glucose taste, that is not decreased by feeding to satiety with cream (Rolls *et al.* 1999). Thus, there is a representation of the macronutrient fat in this brain area, and the activation produced by fat is reduced by eating fat to satiety. It is thus the reward, affective or hedonic value of fat that is represented in the orbitofrontal cortex.

The common perceptual quality among the oils is the slick/fatty mouth feel. The function of the fat texture-sensitive neurons (Rolls *et al.* 1999; Verhagen *et al.* 2003b) may be to allow recognition of fatty substances in the mouth, based on texture information received through the somatosensory system. Consistent with this, Mela (1988) reported that humans rate the fat content of dairy products based on their textural properties. I note that the types of neuron described here, responding to fat independently of viscosity, to viscosity whether it is produced by nonfat or by fat, and to viscosity when it is not being produced by a fatty/oily texture, provide an excellent representation of many textural properties of food, including creaminess, for which ratings provided by humans depend on a variety of textural properties (Bourne 2002). Further breadth to the representation is provided by the taste and olfactory inputs to some fat-sensitive neurons (Critchley and Rolls 1996a; Rolls *et al.* 1999; Verhagen *et al.* 2003b). This is consistent with the hypothesis that a food's flavor (and appearance) is represented in the orbitofrontal cortex by integration of somatosensory, gustatory, temperature, olfactory, visual and cognitive information in such multimodal neurons (Rolls and Baylis 1994; Critchley and Rolls 1996a,b; Rolls *et al.* 1996b, 2008a; Kadohisa *et al.* 2004; Guest *et al.* 2007; Rolls 2007, 2008a, 2010b; Grabenhorst and Rolls 2008; Grabenhorst *et al.* 2008a; Rolls and Grabenhorst 2008).

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 (Verhagen *et al.* 2004). This could reflect convergence of taste and texture inputs in the insular cortex, or the convergence could be present already at earlier stages of taste processing. It is known that some neurons in the taste thalamus (nucleus ventral posteromedial thalamic nucleus) have thermal responsiveness in monkeys (Pritchard *et al.* 1989) and rats (Verhagen *et al.* 2003a). In the periphery, it is known that chorda tympani fibers in the monkey (Sato *et al.* 1975) and hamster (Ogawa *et al.* 1968) show significant correlations between the responses to HCl and those to cooling (20C), and between the responses to sucrose and warming (to 40C). Some lingual nerve fibers in monkeys were activated by cooling to 15C but not by taste (Danilova and Hellekant 2002). There may be no studies in the periphery of the effects of food-relevant oral stimuli such as viscosity and fat texture. It is also possible that oral somatosensory information reaches the anterior insular/frontal opercular primary taste cortex via cortico-cortical connections, perhaps from area 3b which contains oral somatosensory representations of, for example, touch to the tongue, teeth and palate (Manger *et al.* 1996; Jain *et al.* 2001), and which might send afferents to the anterior insular/frontal opercular primary taste cortex (Mufson and Mesulam 1982; Friedman *et al.* 1986).

Given that an important input to the orbitofrontal cortex is from the primary taste cortex (Baylis *et al.* 1995), the responses of orbitofrontal cortex neurons to fat texture, and also oral viscosity, temperature and taste, are likely to be produced at least in a large part via the primary taste cortex.

These oral sensory properties of food, including viscosity and fat texture, and also the sight and smell of food, are also represented in the primate amygdala (Rolls 2000a; Rolls and Scott 2003; Kadohisa *et al.* 2005a,b), which also receives inputs from the primary taste cortex (Fig. 1). Interestingly, the responses of these amygdala neurons do not correlate well with the preferences of the macaques for the oral stimuli (Kadohisa *et al.* 2005a), and feeding to satiety does not produce the large reduction in the responses of amygdala neurons to food (Rolls 2000a; Rolls and Scott 2003) that is typical of orbitofrontal cortex neurons.

ACTIVATION OF THE HUMAN BRAIN BY ORAL SIGNALS, INCLUDING FAT TEXTURE

Taste

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

Francis *et al.* (1999) also found activation of the human amygdala by the taste of glucose. Extending this study, O'Doherty *et al.* (2001) 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 with rewarding stimuli. Zald *et al.* (1998) had shown earlier that the amygdala, as well as the orbitofrontal cortex, respond to aversive (saline) taste stimuli. The study above (O'Doherty *et al.* 2001), 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 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 (de Araujo *et al.* 2003a). 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.

Odor

In humans, in addition to activation of the pyriform (olfactory) cortex (Zald and Pardo 1997; Sobel *et al.* 2000; Poellinger *et al.* 2001), there is strong and consistent activation of the orbitofrontal cortex by olfactory stimuli (Zatorre *et al.* 1992; Francis *et al.* 1999). In an investigation of where the pleasantness of olfactory stimuli might be represented in humans, O'Doherty *et al.* (2000) showed that the activation of an area of the orbitofrontal cortex to banana odor was decreased (relative to a control vanilla odor) after bananas were eaten to satiety. Thus, activity in a part of the human orbitofrontal cortex olfactory area (Rolls *et al.* 2003a, 2008a, 2010b,c,d; de Araujo *et al.* 2005; Grabenhorst *et al.* 2007, 2011; Rolls and Grabenhorst 2008) is related to sensory-specific satiety, and this is one brain region where the pleasantness of odor is represented (Rolls *et al.* 2003a).

An important issue is whether there are separate regions of the brain discriminable with fMRI that represent pleasant versus unpleasant odors. To investigate this, we measured the brain activations produced by three pleasant and three unpleasant odors. The pleasant odors chosen were linalyl acetate (floral, sweet), geranyl acetate (floral) and alpha-ionone (woody, slightly food related). The unpleasant odors chosen were hexanoic acid, octanol and isovaleric acid. We found that they activated dissociable parts of the human brain (Rolls *et al.* 2003a). Pleasant but not unpleasant odors were found to activate a medial region of the rostral orbitofrontal cortex. Further, there was a correlation between the subjective pleasantness ratings of the six odors 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 odors was found in regions of the left and more lateral orbitofrontal cortex. Activation was also found in the ACC, with a middle part of the anterior cingulate activated by both pleasant and unpleasant odors, and a more anterior part of the ACC showing a correlation with the subjective pleasantness ratings of the odors (Rolls *et al.* 2003a). 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 (Grabenhorst and Rolls 2011). Such a map could facilitate comparison and scaling of the reward value produced by different stimuli onto a similar value scale by competitive inhibition implemented by local inhibitory inter-neurons, and this may be important for inputs to a decision mechanism (Rolls 2005; Grabenhorst *et al.* 2010a;Rolls and Deco 2010; Grabenhorst and Rolls 2011).

Olfactory-Taste Convergence to Represent Flavor, and the Influence of Satiety

To investigate where in the human brain interactions between taste and odor stimuli may be realized to implement flavor, we performed an event-related fMRI study with sucrose and MSG taste, and strawberry and methional (chicken) odors, delivered unimodally or in different combinations (de Araujo *et al.* 2003c). 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 the ACC. It was shown that a small part of the anterior (putatively agranular) insula responds to unimodal taste and to unimodal olfactory stimuli; also, 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. Similarly, Small *et al.* (2004) also found supra-additive interactions between congruent taste and smell stimuli in areas including the caudal orbitofrontal cortex and ACC (see also Small and

Prescott 2005). These results provide evidence on the neural substrate for the convergence of taste and olfactory stimuli to produce flavor in humans, and where the pleasantness of flavor is represented in the human brain.

McCabe and Rolls (2007) have shown that the convergence of taste and olfactory information appears to be important for the delicious flavor 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 odor alone. Moreover, they found that, using functional brain imaging with fMRI, the glutamate and savory 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 nonlinear effects were not found for sodium chloride and vegetable odor. Rolls and McCabe thus proposed that glutamate acts by the nonlinear 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 savory odor. Glutamate is thus a flavor enhancer because of the way that it can combine nonlinearly with consonant odors.

Oral Viscosity and Fat Texture

To investigate the representation of oral including fat texture in the human brain, de Araujo and Rolls (2004) used event-related fMRI while stimuli of three viscosities (1 cP and carboxymethyl cellulose 50 and 1,000 cP), a fatty oil or 1 M sucrose used to localize taste areas, were delivered intra-orally in volumes of 0.75 mL. The fat stimulus was vegetable oil (rapeseed oil consisting of 6.1 g of saturate fat, 54.4 g of monounsaturated fat and 26.9 g of poly-unsaturated fat per 100 mL, Sainsbury's Supermarkets, U.K.) with a measured viscosity of 50 cP. This oil was chosen as it was the most odorless and tasteless of those that could be obtained. A tasteless solution (containing the main ionic components of saliva, 25 mM KCl + 2.5 mM $NaHCO_3$ in distilled water (de Araujo *et al.* 2003b) was used as a control. which was subtracted from the activations to the test stimuli.

First, we found activation of the anterior insular (putative primary) taste cortex of humans by oral viscosity stimuli (Fig. 9 middle), in a region that was shown to be taste-related by its activations to oral sucrose. Indeed, the BOLD activation here was proportional to the log of the viscosity of the oral stimuli. Fat also activated this region (Fig. 9 middle), though not in a way that was identified with the fMRI method as being qualitatively different from the activation produced by a viscosity stimulus made to the same viscosity value with CMC. We hypothesized, therefore, that the activation of this

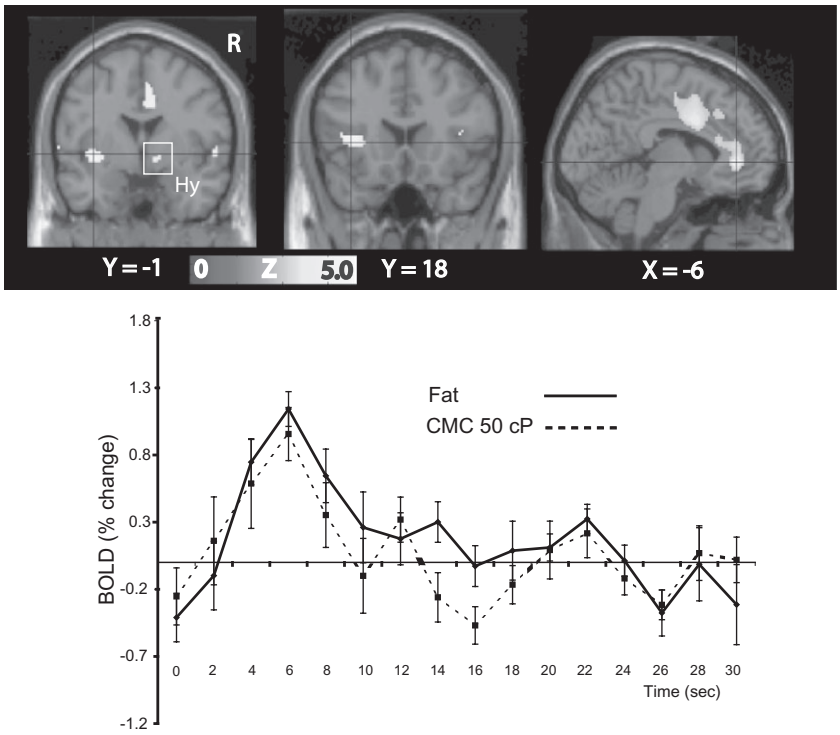

FIG. 9. FUNCTIONAL MAGNETIC RESONANCE IMAGING STUDY OF THE RESPONSES TO THE ORAL DELIVERY OF FAT AS ASSESSED BY THE COMPARISON [FAT – CONTROL]. ACTIVATIONS WERE OBSERVED IN THE MID-INSULA AND HYPOTHALAMUS (HY) (TOP ROW LEFT), ANTERIOR INSULA (TOP ROW MIDDLE) AND ANTERIOR CINGULATE CORTEX (TOP ROW RIGHT)
The average time–course data (across trials and subjects) from the mid-insular cortex (from the voxels marked by the cross hairs in the top row left) are shown in the bottom row for the conditions fat and carboxy-methyl-cellulose (CMC) 50 cP (after de Araujo and Rolls 2004).

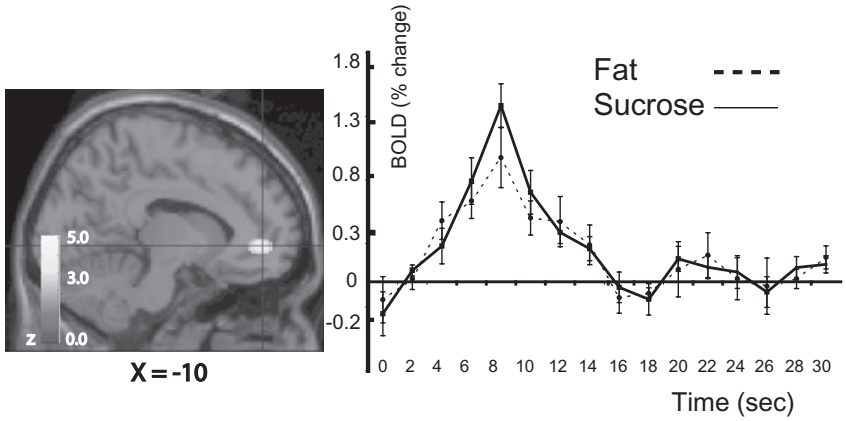

FIG. 10. TOP: ROSTRAL ANTERIOR CINGULATE CORTEX ACTIVATION BY [FAT – CONTROL] AND [SUCROSE – CONTROL], AS REVEALED BY CONJUNCTION ANALYSIS. BOTTOM: THE CORRESPONDING AVERAGE TIME–COURSE DATA (ACROSS TRIALS AND SUBJECTS) FROM THE VOXEL MARKED BY THE CROSS HAIRS ARE SHOWN (AFTER de Araujo and Rolls 2004).

region in humans corresponds to the details revealed by single neuron recording in macaques, namely that some neurons in the primary taste cortex are activated by taste unimodally, some by viscosity unimodally, some by both taste and viscosity, and some by fat texture (Verhagen *et al.* 2004). The fMRI findings on the human anterior insular cortex are consistent with the hypothesis that the same processing takes place in the human anterior insular cortex (de Araujo and Rolls 2004).

Second, we found activation of a mid-insular region behind the primary taste cortex that was activated by viscosity and by fat but not by taste (Fig. 9 left). This may be a purely somatosensory part of the insula that is a higher-order somatosensory cortical area, this part of which is devoted to intra-oral somatosensory inputs. The somatosensory representation of the oral cavity is located in this part of the insula extending anteriorly to the orbitofrontal cortex (Manger *et al.* 1996; Jain *et al.* 2001). This mid-insular cortex may represent a range of somatosensory properties of the oral activity, for in a study of the effects of intra-oral water, we found that activation in the same mid-insular region was produced by water when thirsty, but not after the thirst was quenched. We interpreted this as a somatosensory effect related to relief of a dry mouth by water, in that this region was again not activated by taste stimuli (de Araujo *et al.* 2003b).

Third, we found activations produced by fat in the mouth in the orbitofrontal cortex, where some neurons in macaques specifically encode oral fat independently of viscosity (Verhagen *et al.* 2003b; Rolls *et al.* 2003c), in a region to which this projects the pregenual cingulate cortex (Fig. 9 right, at the location shown by the crosshairs), and also more dorsally in the ACC (Fig. 9 right). The activation by fat in the human pregenual cingulate cortex was especially interesting, in that the activation here to fat was independent of viscosity (produced by CMC) (see Fig. 10). This pregenual cingulate region was also activated by sucrose taste, and is a strong candidate for a brain region activated by the hedonic properties of fat. This pregenual cingulate region has been shown to contain taste-responsive neurons (Rolls 2008a). Further evidence linking this pregenual cingulate region to pleasant affective properties (Bush *et al.* 2000) of sensory stimuli is that the same region is activated by water when it tastes pleasant during thirst (de Araujo *et al.* 2003b), by pleasant but not unpleasant odors (Rolls *et al.* 2003a), and by pleasant but not by painful touch (Rolls *et al.* 2003b). Further, this pregenual cingulate region is also implicated in the control of autonomic function (Critchley *et al.* 2004). Further, the ACC can be activated by hedonically relevant stimuli, including chemosensory and somatosensory stimuli (Zald *et al.* 1998; Small *et al.* 1999; Zatorre *et al.* 2000; Rolls 2005, 2009; McCabe and Rolls 2007; Rolls and McCabe 2007; Grabenhorst and Rolls 2008; Grabenhorst *et al.* 2008a; Mccabe *et al.* 2008; Rolls and Grabenhorst 2008; Rolls *et al.* 2008a,b).

The findings show that the representation of fat and oral texture, the details of which have been uncovered by single neuron analyses in the macaque insula, orbitofrontal cortex and connected areas, is likely to also apply in humans in the corresponding areas in which activations to similar stimuli have been found (de Araujo and Rolls 2004).

The Pleasantness of the Flavor of Food and of Oral Texture

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 (Kringelbach *et al.* 2003). The aim was to show, using a food that has olfactory, taste and texture components, the extent of the region that shows decreases in activation when the food becomes less pleasant, in order to identify the different brain areas where the pleasantness of the odor, taste and texture of food are represented. The foods eaten to satiety were either chocolate milk (which had a fat texture component) or tomato juice (which did not have a fat texture component). A decrease in activation by the food eaten to satiety relative to the other food was found in the orbitofrontal cortex (Kringelbach *et al.* 2003),

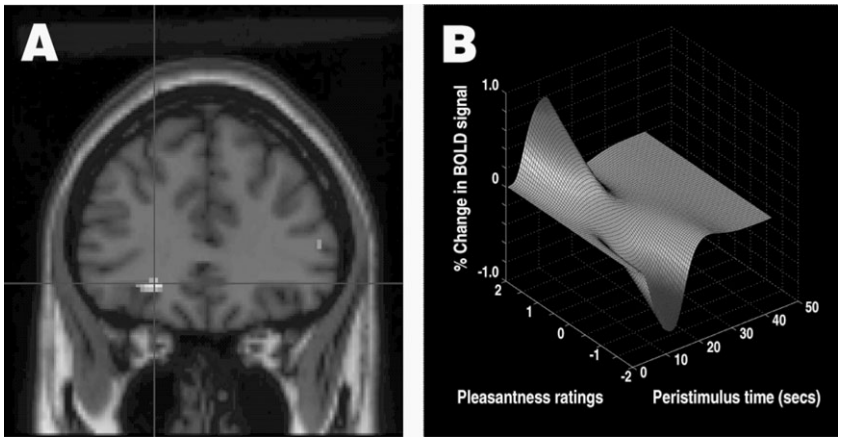

FIG. 11. AREAS OF THE HUMAN ORBITOFRONTAL CORTEX WITH ACTIVATIONS CORRELATING WITH PLEASANTNESS RATINGS FOR FOOD IN THE MOUTH

(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 coordinates x,y,z = –22,34,8, *z*-score = 4.06), in which the bold signal in the voxels shown in yellow was significantly correlated with the subjects' subjective pleasantness ratings of the foods throughout 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 hemodynamic 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*. 2003).

but not in the primary taste cortex (see Fig. 11). This study provided evidence that the pleasantness of the flavor of food and sensory-specific satiety are represented in the human orbitofrontal cortex.

We have recently shown that the pleasantness and reward value of fat texture is represented in the mid-orbitofrontal and ACC, where activations are correlated with the subjective pleasantness of oral fat texture (Rolls 2010a; Grabenhorst *et al*. 2010b). In this investigation, we correlated humans' subjective reports of the pleasantness of the texture and flavor of a high- and low-fat food with a vanilla or strawberry flavor, with neural activations measured with fMRI. Activity in the mid-orbitofrontal and ACC was correlated with the pleasantness of oral fat texture (see Fig. 12), and in nearby locations with the pleasantness of flavor. The pregenual cingulate cortex showed a supralinear response to the combination of high fat and pleasant, sweet flavor, implicating it in the convergence of fat texture and flavor to produce a representation of highly pleasant stimuli. This discovery of which brain regions track the subjective hedonic experience of fat texture (Grabenhorst *et al*. 2010b) will help to unravel possible differences in the neural responses in obese versus lean people to oral fat, a driver of food intake (Rolls 2010b).

Given that there are individual differences in the palatability of food, can these individual differences be related to the functioning of brain systems, such as the orbitofrontal and pregenual cingulate cortex involved in the affective (hedonic) representations of food?

Some individuals, chocolate cravers, report that they crave chocolate more than noncravers, and this is associated with increased liking of chocolate, increased wanting of chocolate and eating chocolate more frequently than noncravers (Rodriguez *et al*. 2007). In a test of whether these individual differences are reflected in the affective systems in the orbitofrontal cortex and pregenual cingulate cortex, Rolls and McCabe (2007) used fMRI to measure the response to the flavor of chocolate, to the sight of chocolate and to their combination, in chocolate cravers versus noncravers. It was shown that the sight of chocolate produced more activation in chocolate cravers than noncravers in the medial orbitofrontal cortex and ventral striatum. For cravers versus noncravers, a combination of a picture of chocolate with chocolate in the mouth produced a greater effect than the sum of the components (i.e., supralinearity) in the medial orbitofrontal cortex and pregenual cingulate cortex. Furthermore, the pleasantness ratings of the chocolate and chocolate-related stimuli had higher positive correlations with the fMRI BOLD signals in the pregenual cingulate cortex and medial orbitofrontal cortex in the cravers than in the noncravers. Thus, there were differences between cravers and noncravers in their responses to the sensory components of a craved food in the orbitofrontal cortex, pregenual cingulate cortex and ventral striatum, and in some of these regions, the differences are related to the subjective pleasantness of the craved foods. Differences in the insular taste cortex were not found. An implication is that individual differences in brain responses to very pleasant

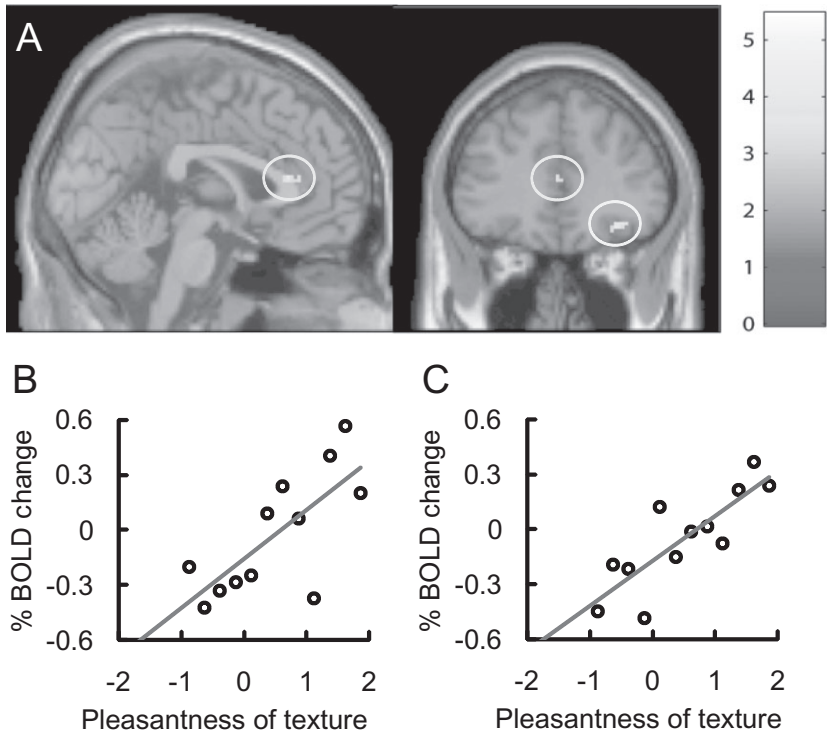

FIG. 12. BRAIN REGIONS IN WHICH THE ACTIVATIONS WERE CORRELATED WITH THE SUBJECTIVE PLEASANTNESS OF FAT TEXTURE. The relation between the % change in the BOLD signal and the rating of the pleasantness of the texture for the mid-orbitofrontal cortex ([32 34 –14] $z = 3.38$ $P = 0.013$) (A and C); and for the anterior cingulate cortex ([2 30 14] $z = 3.22$ $P = 0.016$) (A and B). After Grabenhorst *et al.* (2010b).

foods help to understand the mechanisms that drive the liking for specific foods by indicating that some (but not other brain systems such as the insular taste cortex) respond more to the rewarding aspects of some foods, and thus influence and indeed even predict the intake of those foods (which was much higher in chocolate cravers than noncravers) (Rolls and McCabe 2007). Although texture is of course not the only contributor to the effects of chocolate, it is one important aspect of the sensory properties of chocolate.

DISCUSSION

fMRI of the human orbitofrontal cortex is difficult because signal loss can occur in this region. However, we have developed procedures to overcome these difficulties, as described in the original papers and elsewhere (Wilson *et al.* 2002). Confidence in the conclusions reached on these oral texture and taste systems is that they are complemented by single neuron studies in macaques (Verhagen *et al.* 2003b, 2004; Rolls *et al.* 2003c, 2010a; Kadohisa *et al.* 2004, 2005a; Rolls and Grabenhorst 2008; Rolls 2008a). Moreover complementary results are now being obtained by a number of groups using fMRI in humans (Bender *et al.* 2009; Small 2010), with others cited above. I note that fMRI has limitations in analyzing neural encoding because it averages together the activity of thousands of neurons, whereas information about stimuli in the brain is encoded by the fact that different neurons respond to different stimuli, and that the information encoded by different neurons even in the same brain regions is almost independent (Rolls 2008b; Rolls *et al.* 2009; Rolls and Treves 2011).

The research described here indicates that oral fat sensing uses a specialized fat texture-sensing mechanism that is independent of viscosity. To what extent, therefore, could different fats in the mouth be differentiated? One mechanism is by their viscosity. Some neurons respond to fats in terms of their viscosity (see example in Fig. 7), and to the extent that different fats have different viscosities (a physical property which will depend on chemical composition, and on their temperature), this is one way that fats may be perceptually different. Another factor that could allow discrimination between different fats in the mouth is of course their odor, with butyrate content associated with some fatty foods (such as butter) being one example. Another factor might be taste-transduced fatty acids such as linoleic and lauric acids. However, none of the neurons we have recorded that responded to fat in the mouth responded to linoleic or lauric acid, so the few neurons that do respond to linoleic or lauric acid (and they do not respond to fat texture in the mouth) could provide a function in indicating whether a fat is going off, and is decomposing to release these fatty acids, which would then give the food containing such a free fatty acid a bad taste (Mattes 2009).

It is noted that the areas in which we have analyzed these fat texture-sensing neurons include the primary taste cortex in the anterior insula (Verhagen *et al.* 2004), the orbitofrontal secondary taste cortex (Rolls *et al.* 1999; Verhagen *et al.*

2003b) and the amygdala (Kadohisa *et al.* 2005b), where if there were neurons responding to oral fat because of fat taste, they might be expected to be present. Moreover, in these areas we did find a very small number of neurons that responded to fatty acids such as linoleic or lauric acid, but these neurons did not respond to fats in the mouth.

In future work, it will be important to follow up on our neuronal recording studies on fat texture (Rolls *et al.* 1999; Verhagen *et al.* 2003b; Kadohisa *et al.* 2005a) to identify the physical properties that lead to oral texture being transduced as fat. Discoveries here may have important applications, including in the prevention and treatment of obesity (Rolls 2010b), and in producing highly palatable yet nutritious food. It will also be of interest to know whether the top-down cognitive and attentional modulations of taste and olfactory (de Araujo *et al.* 2005; Grabenhorst and Rolls 2008, 2010; Grabenhorst *et al.* 2008a; Rolls *et al.* 2008a) and tactile and visual (Mccabe *et al.* 2008) processing also apply to oral, including fat texture; and if so, which brain systems are involved. It will also be interesting to know whether the reward value and pleasantness decision-making systems that follow the value representation systems in cortical processing (Rolls and Grabenhorst 2008; Grabenhorst *et al.* 2008b; Rolls *et al.* 2010b,c,d; Grabenhorst and Rolls 2011) apply also to choices and decisions about oral, including fat, texture.

CONCLUSIONS

Fat in the mouth is represented by its texture in the primary taste cortex in the insula, in the orbitofrontal cortex, in the amygdala and in the ACC. Fat texture is represented by neurons independently of viscosity: some neurons respond to fat independently of viscosity, and other neurons encode viscosity. The neurons that respond to fat also respond to silicone oil and paraffin oil, indicating that the sensing is not chemo-specific, but is instead based on texture. This fat sensing is not related to free fatty acids, in that these neurons typically do not respond to free fatty acids such as linoleic acid. Moreover, a few neurons with responses to free fatty acids typically do not respond to fat in the mouth. The fat texture representations by neurons may be combined with taste and/or oral temperature responses, and in the orbitofrontal cortex with olfactory responses. Different neurons respond to different combinations, providing a rich representation of the sensory properties of food. In the orbitofrontal cortex, feeding to satiety with one food decreases the responses of these neurons to that food, but not to other foods, showing that sensory-specific satiety and appetite modulation are represented in the orbitofrontal cortex. In humans, individual differences in activations in areas such as the orbitofrontal cortex and pregenual cingulate cortex to a complex food such as chocolate are related to the affective value of the foods, and how much is eaten. In summary, one way in which fat in the mouth is represented in the brain is by its texture, and an indication of what must be transduced has been provided by these neuroscience studies. Other oral texture representations found in the insular taste cortex, the orbitofrontal cortex, and the amygdala include representations of viscosity, astringency, grittiness, and a representation of oral temperature.

These investigations have implications for understanding how fat is sensed in the mouth; how the pleasantness of food is computed in the brain, and how this differs between individuals; how sensory-specific satiety is computed; how to develop new foods with sensory properties that produce good taste and mouth feel, yet are independent of energy content; and for developing new approaches to appetite control and obesity.

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