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The Representation of Information About Taste and Odor in the Orbitofrontal Cortex

Edmund T. Rolls · Hugo D. Critchley · Justus V. Verhagen · Mikiko Kadohisa

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Abstract 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, and these neurons encode food reward in that they only respond to food when hungry and in that activations here correlate with subjective pleasantness and with individual differences in and cognitive modulation of the hedonic value of food. Information theory analysis shows a robust representation of taste in the orbitofrontal cortex, with an average mutual information of 0.45 bits for each neuron about which of six tastants (glucose, NaCl, HCl, quinine-HCl, monosodium glutamate, and water) was present, averaged across 135 gustatory neurons. The information increased with the number of neurons in the ensemble, but less than linearly, reflecting some redundancy. There was less information per neuron about which of six odors was present from orbitofrontal olfactory neurons, but the code was robust in that the information increased linearly with the number of neurons, reflecting independent information encoded by different neurons. Although some neurons were sharply tuned to individual tastants, the average encoding was quite distributed.

Keywords Orbitofrontal Cortex · Taste · Gustatory Cortex · Information Theory · Sparseness · Smell · Information · Neuronal Responses · fMRI

E. T. Rolls · H. D. Critchley · J. V. Verhagen · M. Kadohisa
Department of Experimental Psychology, University of Oxford,
South Parks Road,
Oxford OX1 3UD, UK

H. D. Critchley
e-mail: H.Critchley@bsms.ac.uk

J. V. Verhagen
e-mail: jverhagen@jbpierce.org

E. T. Rolls (✉)
Oxford Centre for Computational Neuroscience,
Oxford, UK
e-mail: Edmund.Rolls@oxcns.org
URL: www.oxcns.org

J. V. Verhagen
The John B. Pierce Laboratory,
290 Congress Avenue,
New Haven, CT 06519, USA

Present Address:
H. D. Critchley
Department of Psychiatry, Brighton and Sussex Medical School,
University of Sussex,
Brighton BN1 9PX, UK

Introduction

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, how cognitive factors modulate these affective representations, and how these affective representations play an important role in the control of appetite and food intake based on a series of studies we have performed. 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. We describe

new information theoretic analyses of the nature of the taste and olfactory representations provided by orbitofrontal cortex neurons.

Taste Processing in the Primate Brain

Pathways

A diagram of the taste and related olfactory, somatosensory, and visual pathways in macaques 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 a theme of recent research that will be described.

The Primary Taste Cortex

The primary taste cortex in the primate anterior insula and adjoining frontal operculum contains not only taste neurons tuned to sweet, salt, bitter, sour (Scott et al. 1986; Yaxley et al. 1990; Rolls and Scott 2003), and umami as exemplified by monosodium glutamate (Baylis and Rolls 1991; Rolls et al. 1996c), 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, extending several millimeters in front of the primary taste cortex. This was shown to be a secondary taste cortical area in a neuroanatomical study using horseradish peroxidase in which it was shown that the area of the caudolateral orbitofrontal cortex functionally identified as containing taste responsive neurons receives projections from the primary taste cortex in the insula and frontal operculum, and projects on to other regions of the orbitofrontal cortex (Baylis et al. 1995), throughout which taste neurons are

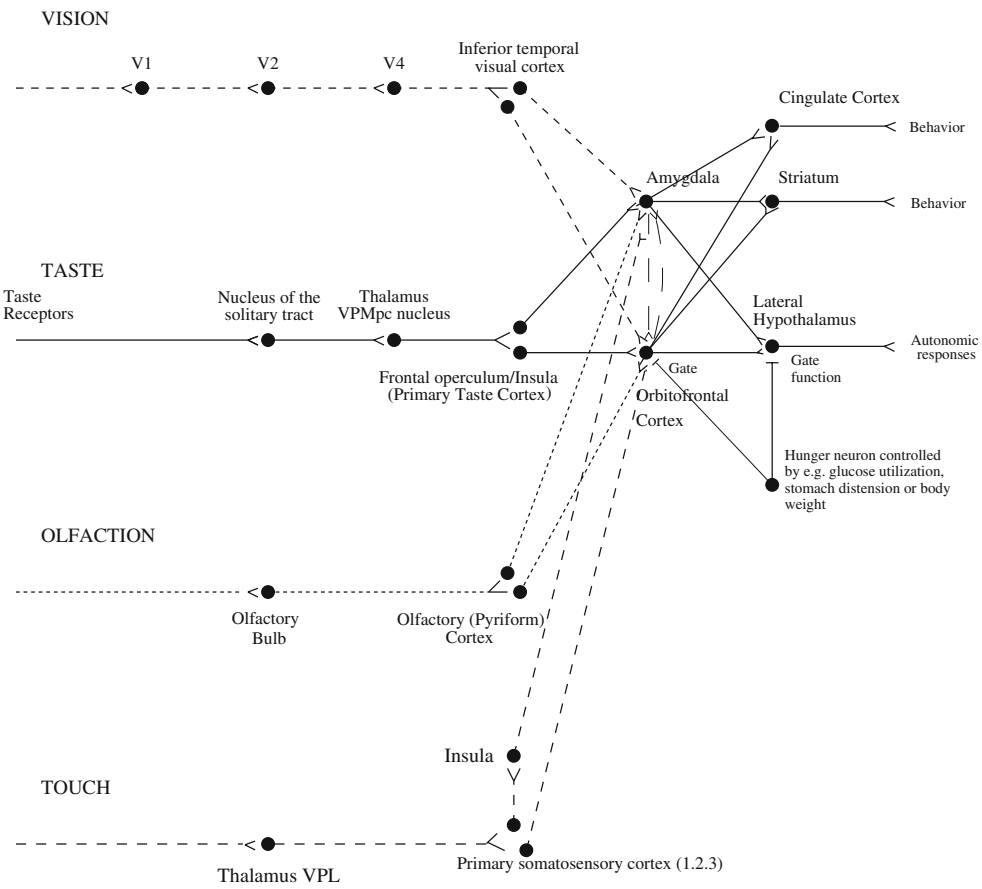

Fig. 1 Schematic diagram of the taste and olfactory pathways in primates including humans showing how they converge with each other and with visual pathways. Hunger modulates the responsiveness of the representations in the orbitofrontal cortex of the taste, smell, texture, and sight of food (indicated 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

found (Rolls and Baylis 1994; Critchley and Rolls 1996a; Rolls et al. 1996c; Pritchard et al. 2005; Rolls 2008b). Neurons in this region respond not only to each of the four classical prototypical tastes sweet, salt, bitter, and sour (Rolls 1997; Rolls and Scott 2003), but also there are many neurons that respond best to umami tastants such as glutamate (which is present in many natural foods such as tomatoes, mushrooms, and milk; Baylis and Rolls 1991) and inosine monophosphate (which is present in meat and some fish such as tuna; Rolls et al. 1996c). This evidence, taken together with the identification of glutamate taste receptors (Zhao et al. 2003; Maruyama et al. 2006), leads to the view that there are five prototypical types of taste information channel, with umami contributing, often in combination with corresponding olfactory inputs (Rolls et al. 1998; McCabe and Rolls 2007; Rolls 2009a), to the flavor of protein. In addition, other neurons respond to water, and others to somatosensory stimuli including astringency as exemplified by tannic acid (Critchley and Rolls 1996a), and capsaicin (Rolls et al. 2003a; Kadohisa et al. 2004). Taste responses are found in a large mediolateral extent of the orbitofrontal cortex (Rolls and Baylis 1994; Critchley and Rolls 1996a; Rolls et al. 1996c; Pritchard et al. 2005; Rolls 2008b; Rolls and Grabenhorst 2008), as is well illustrated in Fig. 8 which shows the recording sites of the neurons in the studies of Critchley and Rolls (1996a) and Rolls et al. (1996c, 1999).

The Pleasantness of the Taste of Food, Sensory-Specific Satiety, and the Effects of Variety on Food Intake

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 2005, 2007a). The subjective correlate of this modulation is that food tastes pleasant when hungry and tastes hedonically neutral when it has been eaten to satiety. Following the discovery of sensory-specific satiety revealed by the selective reduction in the responses of lateral hypothalamic neurons to a food eaten to satiety (Rolls 1981; Rolls et al. 1986), it has been shown that this is implemented in a region that projects to the hypothalamus, the orbitofrontal (secondary taste) cortex, for the taste, odor, and sight of food (Rolls et al. 1989; Critchley and Rolls 1996b).

This evidence shows that the reduced acceptance of food that occurs when food is eaten to satiety, the reduction in the pleasantness of its taste and flavor, and the effects of variety to increase food intake (Cabanac 1971; Rolls and Rolls 1977, 1982, 1997; Rolls et al. 1981a, b, 1982, 1983a, b, 1984; Rolls and Hetherington 1989; Hetherington 2007) are produced in the orbitofrontal cortex, but not at earlier stages of processing including the primary taste cortex where the responses reflect factors such as the intensity of the taste, which is little affected by satiety (Rolls et al. 1983c; Rolls and Grabenhorst 2008). 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 the thalamus and insula (Cechetto and Saper 1987; Craig 2002; Critchley 2005), and possibly hypothalamic nuclei) and there modulate the representation of food, resulting in an output that reflects the reward (or appetitive) value of each food (Rolls 2005).

The Representation of Flavor: Convergence of Olfactory, Taste, and Visual Inputs in the Orbitofrontal Cortex

Taste and olfactory pathways are brought together in the orbitofrontal cortex where flavor is formed by learned associations at the neuronal level between these inputs (see Fig. 1; Rolls and Baylis 1994; Critchley and Rolls 1996c; Rolls et al. 1996a; Verhagen et al. 2004). Visual inputs also become associated by learning in the orbitofrontal cortex with the taste of food to represent the sight of food and contribute to flavor (Thorpe et al. 1983; Rolls 1996). The visual and olfactory as well as the taste inputs represent the reward value of the food, as shown by sensory-specific satiety effects (Critchley and Rolls 1996b). Most neurons in the taste insula did not respond to odor. Of 24 neurons in the insular taste cortex tested fully during experiments described by Verhagen et al. (2004) with a range of odors, two had marginally significantly different responses between odors (close to $p<0.05$ with no correction for the number of tests applied), and the evoked changes in firing rate were on average even for these two neurons a small proportion (27%) of the changes elicited by taste in the same neurons. Consistent with this, activations in the human insular cortex can sometimes be found to odor (Verhagen and Engelen 2006; Grabenhorst et al. 2007; Grabenhorst and Rolls 2009; Rolls et al. 2009a), and these may reflect backprojections (Grabenhorst et al. 2007; Rolls 2008a), which are implicated in memory recall (Treves and Rolls 1994; Rolls 2008a), for when an odor or flavor retrieves a representation of a sweet taste, the insula is activated (Veldhuizen and Small, personal communication). The agranular insula, anterior to the primary taste cortex, is activated by both taste and odor (de Araujo et al. 2003c; see also Small et al. (2004)). The mid-insula is activated by oral texture (de Araujo and Rolls 2004). More posterior regions of the insula contain a representation of one's own body (McCabe et al. 2008).

The Texture of Food, Including Fat Texture

Some orbitofrontal cortex neurons have oral texture-related responses that encode parametrically the viscosity of food in the mouth (shown using a methyl cellulose series in the range 1–10,000 cP), others independently encode the particulate quality (gritty texture) of food in the mouth, produced quantitatively for example by adding 20- to 100-μm microspheres to methyl cellulose (Rolls et al. 2003a), and others encode the oral texture of fat (Rolls et al. 1999; Verhagen et al. 2003), as illustrated in Fig. 2. The fat-responsive neurons respond to naturally fatty foods such as dairy cream, vegetable oil, triolein, and chocolate and also to non-fat oils including silicone oil and mineral oil and do not respond to the fatty acid linoleic acid (Rolls et al. 1999; Verhagen et al. 2003). The basis of oral fat sensation is thus largely by oral texture. Moreover, the pleasantness or reward value of fat in the mouth is mediated by this system in that feeding to satiety reduces the responses of these fat-responsive neurons to zero (Rolls et al. 1999). A few cortical neurons do respond to fatty acids in the mouth (Verhagen et al. 2003), consistent with a peripheral fatty acid sensing mechanism (Gilbertson 1998), but these cortical neurons do not respond to the fats just described in the mouth (Verhagen et al. 2003, 2004). It may be that free fatty acids in foods act as a warning signal and are unpleasant (Mattes 2009), and consistent with this, food manufacturers aim to keep free fatty acids to a minimum.

In addition, recent findings (Kadohisa et al. 2004, 2005) have revealed that some neurons in the orbitofrontal cortex reflect the temperature of substances in the mouth and that this temperature information is represented independently of other sensory inputs by some neurons and in combination with taste or texture by other neurons.

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 (Francis et al. 1999; O'Doherty et al. 2001; de Araujo et al. 2003a). Activation in more widespread brain areas has been reported by others (Small et al. 2003). 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 to rewarding stimuli. Zald et al. (1998) had shown earlier that the amygdala, as well as the orbitofrontal cortex, responds to aversive (saline) taste stimuli.

Umami taste stimuli, of which an exemplar is monosodium glutamate (MSG) and which capture what is described as the taste of protein, activate the insular (primary), orbitofrontal (secondary), and anterior cingulate (tertiary; Rolls 2008b) taste cortical areas (de Araujo et al. 2003b). When the nucleotide 0.005 M inosine 5′-monophosphate (IMP) was added to MSG (0.05 M), the blood oxygenation-level dependent (BOLD) signal in an anterior part of the orbitofrontal cortex showed supralinear additiv-

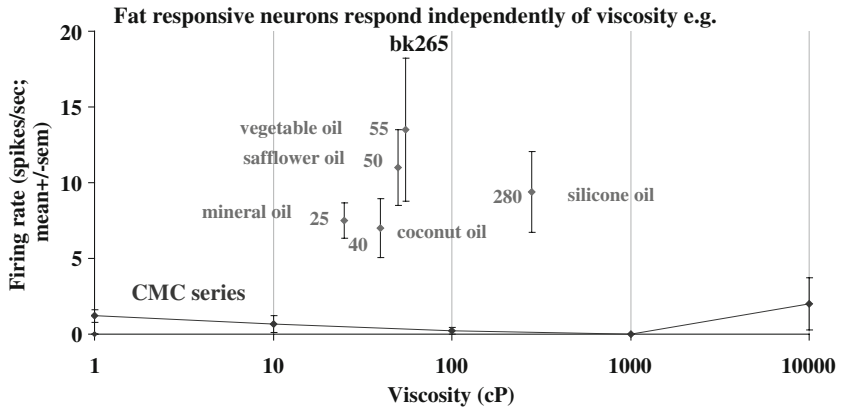

Fig. 2 A neuron in the primate orbitofrontal cortex responding to the texture of fat in the mouth independently of viscosity. The cell (bk265) increased its firing rate to a range of fats and oils (the viscosity of which is shown in centipoise). The information that reaches this type of neuron is independent of a viscosity sensing channel in that the neuron did not respond to the methyl cellulose (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. After Verhagen et al. (2003)

ity, and this may reflect the subjective enhancement of umami taste that has been described when IMP is added to MSG (Rolls 2009a). 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 and may help to make the food pleasant.

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 a strong and consistent activation of the orbitofrontal cortex by olfactory stimuli (Zatorre et al. 1992; Francis et al. 1999), and this region appears to represent the pleasantness of odor, as shown by a sensory-specific satiety experiment with banana vs vanilla odor (O'Doherty et al. 2000). Furthermore, pleasant odors tend to activate the medial and unpleasant odors the more lateral, orbitofrontal cortex (Rolls et al. 2003b), adding to the evidence that it is a principle that there is a hedonic map in the orbitofrontal cortex and also in the anterior cingulate cortex, which receives inputs from the orbitofrontal cortex (Rolls and Grabenhorst 2008).

Olfactory–Taste Convergence to Represent Flavor and the Influence of Satiety

Convergence for taste (e.g., sucrose) and odor (e.g., strawberry), and in some cases supralinearity reflecting interactions, were found in the orbitofrontal cortex and the adjoining agranular insula and anterior cingulate cortex (de Araujo et al. 2003c; Small et al. 2004; Small and Prescott 2005; Verhagen and Engelen 2006; Verhagen 2007). These activations in the orbitofrontal and anterior cingulate cortex were correlated with the pleasantness ratings given by the participants (de Araujo et al. 2003c). 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 and that this reflected activations in the pregenual cingulate cortex and medial orbitofrontal cortex. The principle is that certain sensory combinations can produce very pleasant food stimuli, which may of course be important in driving food intake.

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. The foods eaten to satiety were either chocolate milk or tomato juice. A decrease in activation by the food eaten to satiety relative to the other food was found in the orbitofrontal cortex (Kringelbach et al. 2003), but not in the primary taste cortex. This study provided evidence that the subjective pleasantness of the flavor of food and sensory-specific satiety are represented in the orbitofrontal cortex. Further evidence that the reward value of food is represented in the orbitofrontal cortex is that activations to taste in the orbitofrontal cortex (OFC) but not in the insula are enhanced by paying attention to pleasantness (Grabenhorst and Rolls 2008). Furthermore, activations related to the affective value of umami taste and flavor (as shown by correlations with pleasantness ratings) in the orbitofrontal cortex were modulated by cognitive word-level descriptors (such as "rich delicious taste") that enhanced the pleasantness of the taste and flavor. Affect-related cognitive modulations were not found in the insular taste cortex where the intensity but not the pleasantness of the taste was represented (and it would have been interesting to check for a dissociation in a study in which expectancy reduced the aversiveness of a bitter taste (Nitschke et al. 2006), as we have done between correlations of activations in different brain regions with intensity vs affective value.

In our studies, we have been careful to identify the taste insula as the region that responds in a contrast of a pure taste stimulus—a tasteless control (O'Doherty et al. 2001; de Araujo et al. 2003b; Grabenhorst and Rolls 2008; Grabenhorst et al. 2008), and this region is at the anterior end of the human insula (with Y coordinates; Collins et al. 1994) in the approximate range of 14 to 3 mm (de Araujo et al. 2003c; Grabenhorst et al. 2008). This is a region where we have found that activations correlate with the intensity but not pleasantness ratings of taste and are enhanced to a taste when paying attention to its intensity but not to its pleasantness (Grabenhorst and Rolls 2008; Grabenhorst et al. 2008). In a more mid or posterior part of the insula (Y=−14), activations to oral texture are found (de Araujo and Rolls 2004), there is a reduction in activations to chocolate when it is eaten to satiety (Kringelbach et al. 2003), and water (which refreshes the dry sensation in the mouth) produces a larger activation when thirsty than when satiated (de Araujo et al. 2003a). There may therefore be a representation of the pleasantness of oral texture in the mid (somatosensory) insula. In front of the insular taste cortex is agranular insula (close to Y=15), and this is a multimodal region at the posterior boundary of the orbitofrontal cortex in which taste and olfactory convergence occur (de Araujo et al. 2003c), and this could be a region continuous with the

orbitofrontal cortex in which the pleasantness of flavor is represented. When performing satiety experiments and finding little change of activation in the insular taste cortex, we use normal physiological hunger with just a few hours (e.g., 3–4) of deprivation, we allow participants to feed themselves to normal satiety rather than give a predetermined load that may not fully satiate or may oversatiate, and we measure responses to the particular food eaten to satiety with responses to a food that has not been eaten to satiety in a sensory-specific satiety design (Kringelbach et al. 2003; Grabenhorst et al. 2009). Possible differences between studies with respect to whether the taste insula of humans is affected by internal state to represent the reward value of taste (Smeets et al. 2006; Uher et al. 2006; Haase et al. 2009) may reflect different ways in which the experiments were performed or not separating the taste insula from other parts of the insula. An effect in both the orbitofrontal cortex and the insula of reinforcer devaluation by satiety in a visual to olfactory association task has been reported (Gottfried et al. 2003). Also, effects of the appetite-increasing hormone ghrelin on activations to the sight of food were found in the orbitofrontal cortex, insula, and many other areas including the pulvinar (Malik et al. 2008). We note that other parts of the insula may map visceral/interoceptive activity (Craig 2002, 2009) and play a role in autonomic activity (Critchley 2005), which may be related to state-dependent effects of for example satiety (Gautier et al. 2001).

Oral Viscosity and Fat Texture

The viscosity of food in the mouth is represented in the human primary taste cortex (in the anterior insula) and also in a mid-insular area that is not taste cortex but which represents oral somatosensory stimuli (de Araujo and Rolls 2004). Oral viscosity is also represented in the human orbitofrontal and perigenual cingulate cortices, and it is notable that the perigenual cingulate cortex, an area in which many pleasant stimuli are represented, is strongly activated by the texture of fat in the mouth and also by oral sucrose (de Araujo and Rolls 2004; Grabenhorst et al. 2009).

The Sight of Food

O'Doherty et al. (2002) showed that visual stimuli associated with the taste of glucose activated the orbitofrontal cortex and some connected areas, consistent with the primate neurophysiology. Simmons et al. (2005) found that showing pictures of foods, compared to pictures of locations, can also activate the orbitofrontal cortex. Similarly, the orbitofrontal cortex and connected areas were also found to be activated after presentation of food stimuli to food-deprived subjects (Wang et al. 2004). Backprojections from these multimodal areas in the orbitofrontal cortex that receive visual inputs from the inferior temporal visual cortex (Rolls and Baylis 1994; Rolls 2000, 2008a) may produce some activations to the sight of food in earlier cortical areas.

Cognitive Effects on Representations of Food

To what extent does cognition influence the hedonics of food-related stimuli and how far 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 flavor, presented orthonasally using an olfactometer) was paired with a descriptor word on a screen, which on different trials was "cheddar cheese" or "body odor." Participants rated the affective value of the test odor as significantly more pleasant when labeled "cheddar cheese" than when labeled "body odor," and these effects reflected activations in the medial OFC/rostral anterior cingulate cortex that had correlations with the pleasantness ratings (de Araujo et al. 2005; see Fig. 3). 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 down into sensory processing, so that hedonic representations of odors are affected (de Araujo et al. 2005). Similar cognitive effects and mechanisms have now been found for the taste and flavor of food (Grabenhorst et al. 2008).

In addition, it has been found that with taste, flavor, and olfactory food-related stimuli, attention to pleasantness modulates representations in the orbitofrontal cortex, whereas attention to intensity modulates activations in areas such as the primary taste cortex (Grabenhorst and Rolls 2008; Rolls et al. 2008; cf. Veldhuizen et al. 2007).

When one reward is delivered, it can influence the pleasantness of the next reward. Using fMRI, we investigated how the subjective pleasantness of an odor is influenced by whether the odor is presented in the context of a relatively more pleasant or less pleasant odor (Grabenhorst and Rolls 2009). We delivered two of a set of four odors separated by a delay of 6 s, with the instruction to rate the pleasantness of the second odor, and searched for brain regions where the activations were correlated with the absolute pleasantness rating of the second odor and for brain regions where the activations were correlated with the difference in pleasantness of the second from the first odor, that is, with relative pleasantness. Activations in the anterolateral orbitofrontal cortex tracked the relative subjective pleasantness, whereas activations in the anterior insula tracked the relative subjective unpleasantness. In contrast, in the medial and mid-orbitofrontal cortex, activations

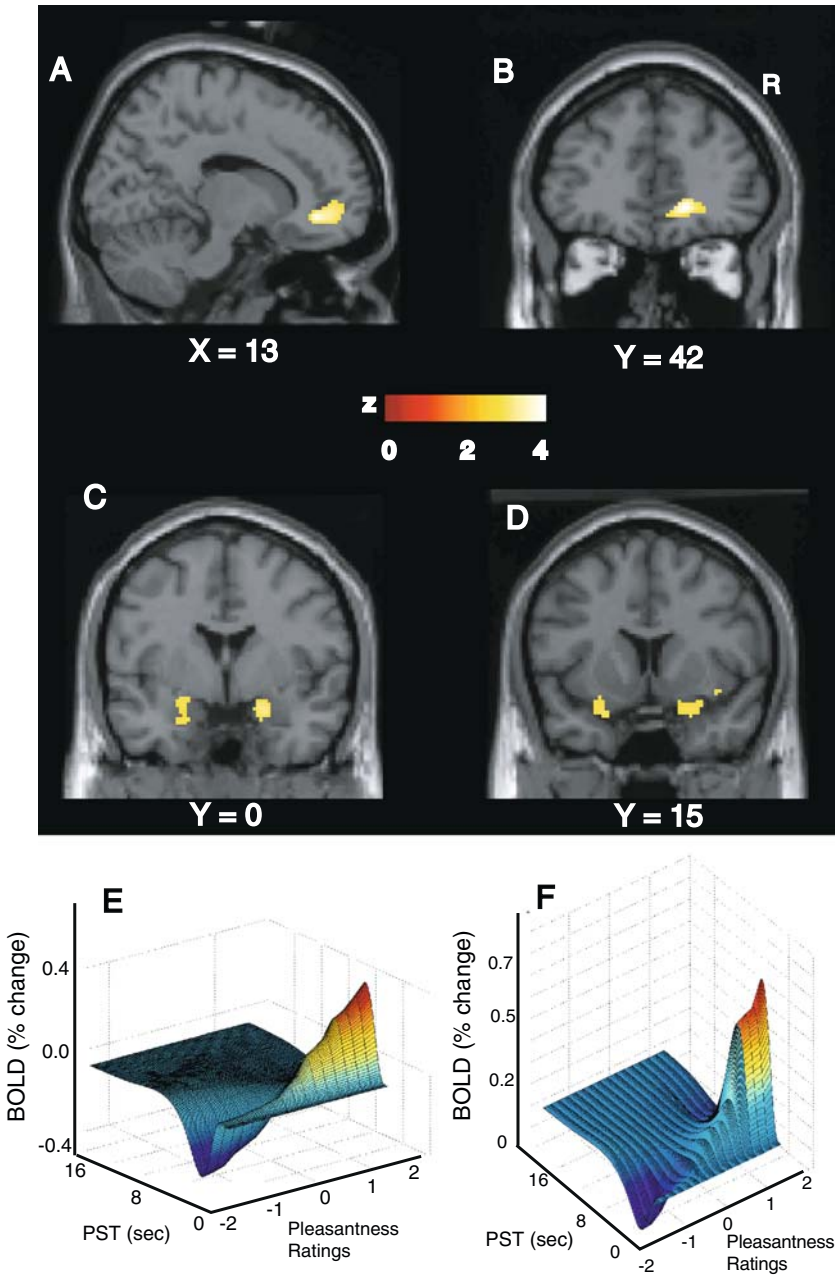

Fig. 3 Cognitive influences on olfactory representations in the human brain. Group (random) effects analysis showing the brain regions where the BOLD signal was correlated with pleasantness ratings given to the test odor. The pleasantness ratings were being modulated by the word labels. **a** Activations 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 de Araujo et al. (2005)

tracked the absolute pleasantness of the stimuli. Thus, both relative and absolute subjective value signals which provide important inputs to decision-making processes about which stimulus to choose are separately and simultaneously represented in the human brain (Grabenhorst and Rolls 2009). Relative reward value is important for the choice between a set of available rewards, and absolute reward value for stable and consistent economic choice.

These findings have important implications for sensory testing and for ways in which the palatability and acceptability of foods can be influenced.

Information Theoretic Analysis of the Representation of Taste and Odor in the Orbitofrontal Cortex

Taste

Two issues about the nature of the gustatory representation in the orbitofrontal cortex that have not been addressed previously are considered here. The first issue is how robust or reliable are the responses of primate orbitofrontal cortex gustatory neurons. To answer this, we apply an information theoretic approach and analyze how much information we

obtain on average on a single trial from the responses of one of these neurons. If they were noisy, then we would obtain little information from a single neuron on a single trial. If the neuron responded to only one stimulus in a large set of stimuli and had little response to all the other stimuli in the set, then again on average we would learn only little on a given trial from the responses of the neuron (assuming equiprobable stimuli). The second issue is how finely tuned the neurons are to the stimuli, that is whether a neuron responds to only one stimulus in a set or whether it responds to some but not other stimuli in the set. We analyzed this by using information theory to measure how much information was obtained from a cell for each stimulus in the set. If the neuron responded to one stimulus only in the set, then considerable information might be available from the neuron when that stimulus was presented (subject to noise), and little information would be available about each of the other stimuli in the set.

Methods

Neuronal Recordings

The information theoretic approach and its application to the analysis of neuronal data are described in detail elsewhere (Rolls and Treves 1998; Rolls and Deco 2002; Rolls 2008a). By way of introduction, information theory (Shannon 1948) provides the means for quantifying how much information neurons communicate to other neurons and thus provides a quantitative approach to fundamental questions about information processing in the brain. To investigate what in neuronal activity carries information, one must compare the amounts of information carried by different codes, that is, different descriptions of the same activity, to provide the answer. To investigate the speed of information transmission, one must define and measure information rates from neuronal responses. To investigate to what extent the information provided by different cells is redundant or instead independent, again one must measure amounts of information in order to provide quantitative evidence. To compare the information carried by the number of spikes, by the timing of the spikes within the response of a single neuron, and by the relative time of firing of different neurons reflecting for example stimulus-dependent neuronal synchronization, information theory again provides a quantitative and well-founded basis for the necessary comparisons. To compare the information carried by a single neuron or a group of neurons with that reflected in the behavior of the human or animal, one must again use information theory, as it provides a single measure which can be applied to the measurement of the performance of all these different cases. To compare the information encoded by neurons with that which can be read from brain activations obtained with functional neuroimaging, information theory again provides a common metric (Rolls et al. 2009b). In all these situations, there is no quantitative and well-founded alternative to information theory (Rolls 2008a).

The gustatory stimuli used were 1.0 M glucose (G), 0.1 M NaCl (N), 0.01 M HCl (H), 001 M QHCl (Q), and 0.1 M monosodium glutamate (M); and 0.001 M tannic acid was used as an astringent stimulus, and the recordings were from the macaque orbitofrontal cortex. The recordings are part of a series of investigations in which the functions of the orbitofrontal cortex are being analyzed to provide evidence on feeding, taste and olfaction, and their disorders (Rolls 2007a, b, 2009b) and on the causes of the emotional and motivational problems that can occur in patients with damage to this brain region (Rolls et al. 1994; Rolls 1999, 2005; Hornak et al. 2003; Berlin et al. 2004). It is important that such neurophysiological studies directed towards understanding the function of the orbitofrontal cortex in humans be performed on primates for even the anatomical connections of the taste and olfactory systems are very different in primates from those in rodents (Norgren 1984, 1988; Rolls 2008b), and in addition, the orbitofrontal cortex is considerably less developed in rodents compared to its great development in primates (Zald and Rauch 2006).

Single Cell Information Analysis

The single cell information analysis methods used have been described in detail (Rolls et al. 1996a, 1997b). A novel aspect of the data analysis methods is that we investigated how much information was available about each stimulus in the set. Because we have found that most of the cortical information about which stimulus was presented is made evident by measuring the firing rate of the neuron and not variations in its time course (Tovee et al. 1993; Rolls et al. 1996a; Rolls 2008a), the information theoretic analyses described here were based on the information available from the firing rate. The period in which this was measured was the post-stimulus period 100–600 ms with respect to the onset of the taste stimulus. Although there are some differences in the time courses of the neuronal responses to different tastes in the nucleus of the solitary tract (Scott et al. 1985; Hallock and Di Lorenzo 2006), we note that there are no strong indications that the time courses of the neuronal responses are very different for different tastants in the cortex, as shown by published examples (Scott et al. 1986; Yaxley et al. 1988, 1990; Rolls et al. 1990, 1996c, 1999, 2003a; Critchley and Rolls 1996a; Verhagen et al. 2003, 2004; Kadohisa et al. 2004) and in that our analyses provide similar results and similar tuning for 1-, 3-, or 5-s analyses, and in any case, the information theoretic analysis focused on the first 500 ms of cortical

neuronal responses where any possible differences are minor. Of course, as expected, oral texture stimuli may have different time courses, with very viscous stimuli producing longer responses as it takes longer to clear a thick stimulus from the mouth (Rolls et al. 2003a; Verhagen et al. 2004).

The measure was the stimulus-specific information or surprise, *I(s,R)*, which is the amount of information the set of responses, *R*, has about a specific stimulus, *s*. The mutual information between the whole set of stimuli *S* and of responses *R* is the average across stimuli of this stimulus-specific information (note that *r* is an individual response from the set of responses *R*).

$$I(s,R) = \sum_{r \in R} P(r|s) \log_2 \frac{P(r|s)}{P(r)} \quad (1)$$

One hundred thirty-five neurons, representing 5.7% of the 2,374 orbitofrontal cortex and related neurons tested in three macaques, had gustatory responses (using a criterion of a significant difference, $p<0.001$ for most cells, between the responses to the different tastants in an ANOVA; Critchley and Rolls 1996a; Rolls et al. 1996c, 1999). As described in those papers, the well-isolated single neurons were recorded with glass-insulated tungsten microelectrodes (Merrill and Ainsworth 1972). The liquid taste stimuli were delivered manually in aliquots of 0.2 ml via a 1-ml syringe. The monkey's mouth was rinsed with distilled water during the intertrial interval, which lasted a minimum of 30 s or until activity returned to baseline levels. The manual presentation of taste stimuli was chosen to allow the repeated stimulation of a large receptive field despite changing mouth and tongue positions of the monkey (Scott et al. 1986; Rolls et al. 1990). The response properties of these 135 neurons, examples of their responses, and the criteria for identification have been described previously (Critchley and Rolls 1996a; Rolls et al. 1996c, 1999). The numbers of the 135 neurons with best responses to each of the tastants 1 M glucose G, 0.1 M NaCl N, 0.01 M HCl H, 0.001 M quinine-HCl Q, 0.1 M monosodium glutamate M, and distilled water W are shown in Fig. 5c. The responses of the neurons were measured in a 0.5-s period starting 100 ms after taste delivery. A further 110 neurons (4.8%) showed significant responses to the delivery of the tastants, but were either not tested fully or did not discriminate between the tastants (and thus were probably responding to somatosensory input associated with the delivery of the tastants into the mouth). Of the other neurons in the sample of 2,374 neurons, some responded to oral astringency as exemplified by tannic acid (Critchley and Rolls 1996a), some to oral fat texture (Rolls et al. 1999), some to olfactory stimuli (Critchley and Rolls 1996b, c; Rolls et al. 1996b, 1996a), some to food-related visual stimuli (Critchley and Rolls 1996b), and some visual neurons to face expression or face identity (Rolls et al. 2006).

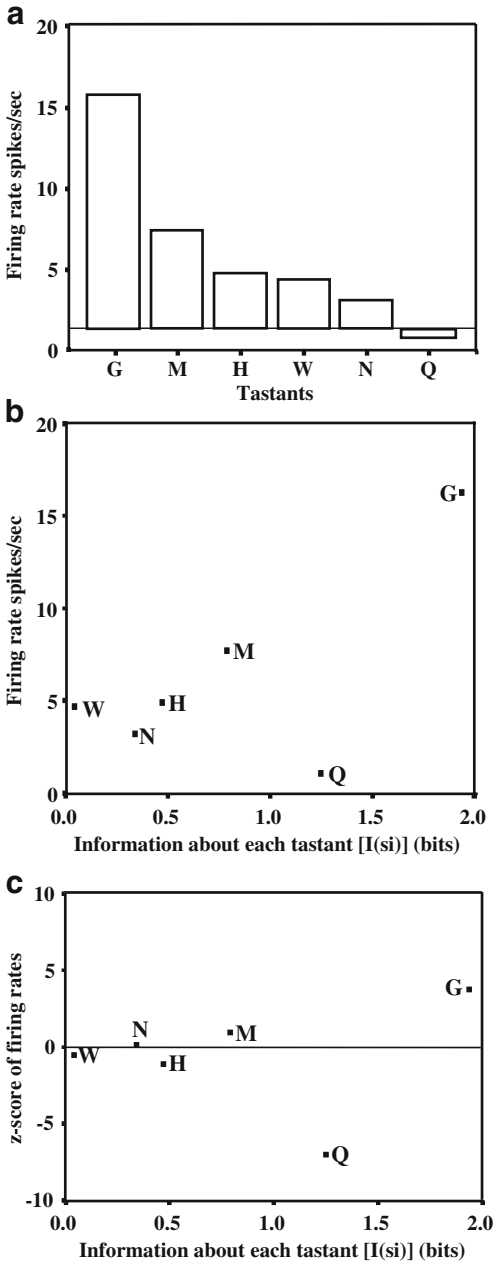

Fig. 4 **a** Response profile of a typical glucose-responsive neuron (aq103a) showing the mean evoked firing rate of the neuron to the tastants glucose, *G*, (1.0 M); NaCl, *N*, (0.1 M); HCl, *H*, (0.01 M); quinine-HCl, *Q*, (0.001 M), monosodium glutamate, *M*, (0.1 M), and distilled water, *W*. The evoked firing rates are plotted as changes from the spontaneous firing rate of the neuron. **b** Relationship between the firing rate of the neuron (ordinate) plotted as a function of the information ($I(s_i)$) in the responses of the neuron about each tastant *i*. **c** Relationship between the *z* score of the responses to each tastant (ordinate) plotted as a function of the information in the response to each tastant

Results

Single Cell Stimulus-Specific Information About Taste

Figure 4a illustrates the response profile of a typical taste neuron (aq103a). In Fig. 4b, the amount of information reflected in the response to each tastant is plotted against the mean evoked firing rates. The neuron responded to the taste of glucose with a mean evoked firing rate of 16.5 spikes per second. The remaining stimuli evoked firing rates of between 0.5 and 8 spikes per second, showing this cell to be a glucose-best neuron. Figure 4b shows $I(s_i)$, the information about each tastant when that tastant was presented, as a function of the firing rate of the neuron to the tastant being applied. The information from the responses to glucose ($I(s_i)$) approached 2.0 bits, but when quinine was delivered, more than 1 bit of information was available from the neuronal response, even though the neuron fired very little to the quinine. The explanation for this is clarified by Fig. 4c. In this figure, the information to each tastant is plotted against the number of standard deviations the neuronal response was away from the average response to all tastants (termed the *z* score in Fig. 4c). The *z* score was calculated from the difference between the mean firing rate to the tastant and the average evoked firing rate to all tastants divided by the standard deviation of the response to the tastant. The absolute magnitude of the *z* score thus reflects the probability that such a response will occur. It is shown in Fig. 4c (cell aq103a) that the considerable information provided when quinine was the stimulus was related to the fact that such a low neuronal response was improbable, and thus, much was learned when that response occurred. Similar types of graph were found for other neurons responding best to each of the other tastants.

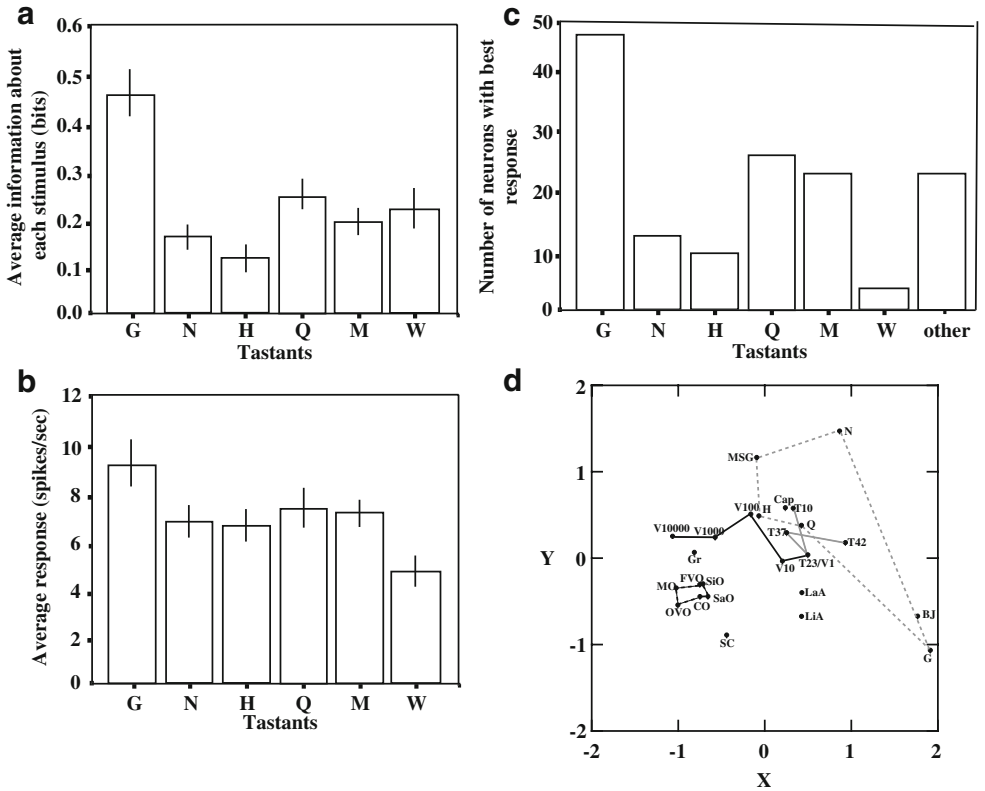

Fig. 5 **a** Information ($I(s_i)$) about the set of six tastants (glucose 1.0 M, NaCl, 0.1 M, HCl, 0.01 M, quinine-HCl 0.001 M, monosodium glutamate 0.1 M, and distilled water) averaged across the population of 135 gustatory neurons. **b** Average response evoked by each of the tastants averaged across the population of 135 neurons. **c** Number of neurons with optimal responses to each of the tastants in the population of 135 gustatory neurons (**a**–**c** new analyses of data of Critchley and Rolls 1996a; Rolls et al. 1996b, 1999). **d** Multidimensional space from 53 orbitofrontal cortex neurons' responses to taste, oral texture, and oral temperature stimuli from Kadohisa et al. (2005). 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 quinine-HCl (*Q*); the temperature stimuli were T10, T23, T37, and T42 where the number indicates the temperature in °C; the viscosity stimuli were V1, V10, V100, V1000, and V10000 where the numeral indicates the viscosity in centipoise; fat texture stimuli were SiO10, SiO100, SiO1000 (silicone oil with the viscosity indicated),vegetable oil (*VO*), coconut oil (*CO*), and safflower oil (*SaO*). *BJ* fruit juice, *Cap* 10 μM capsaicin, *LaA* 0.1 mM lauric acid, *LiA* 0.1 mM linoleic acid, *Gr* gritty stimulus. The *solid line* joins the members of the viscosity series. *Different line styles* join the members of the taste, temperature, and oil stimuli

Figure 5a shows the stimulus-specific information ($I(s_i)$) about each of the six tastants (glucose, NaCl, HCl, quinine-HCl, monosodium glutamate, and distilled water) averaged across the population of 135 taste-responsive cells. There was most information about the sweet taste of glucose. The data support and quantify what has been noted in previous studies (Rolls et al. 1990; Baylis and Rolls 1991; Rolls and Baylis 1994; Kadohisa et al. 2005) that the orbitofrontal cortical taste neurons tend to represent sweet tastes much more than other tastes. In Fig. 5b, the average responses (firing rate—spontaneous) evoked by the different tastants across the 135 cells is shown. This graph does not clearly illustrate the differential way in which these taste qualities are reflected by the neuronal responses across the population. In Fig. 5c, the number of neurons responding preferentially to each of the tastants is shown. In the latter graph, the proportion of cells responding preferentially to glucose is clearly much larger than the other tastants, yet this difference is not particularly evident from the average responses shown in Fig. 5b. However, Fig. 5c does not reflect the degree to which the optimal stimulus of a taste neuron, for example glucose, is able to be differentiated from other (suboptimal) stimuli. This is, however, reflected in the information about individual stimuli shown in Fig. 5a which illustrates an advantage of the information theoretic approach to neural representation. Consistent with this, but in a visual and less quantitative way, glucose is well separated from other taste and oral stimuli in a multidimensional scale space based on a later sample of 53 orbitofrontal cortex neurons, as shown in Fig. 5d (Kadohisa et al. 2005).

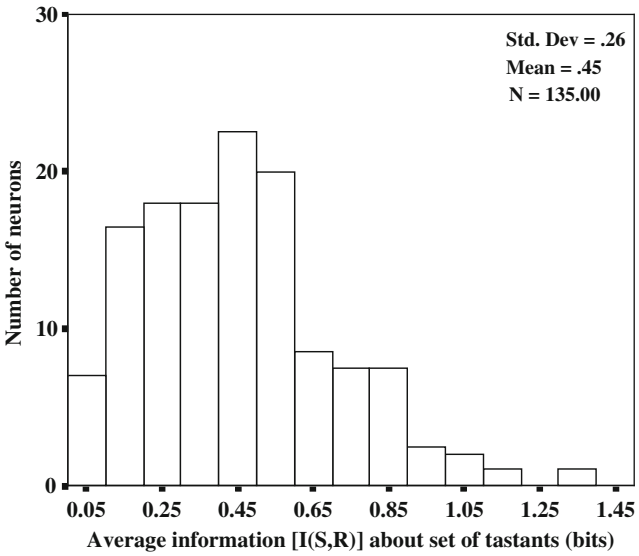

Fig. 6 Histogram showing the average information, $I(S, R)$, about the set of prototypical tastants, glucose, NaCl, HCl, and quinine-HCl

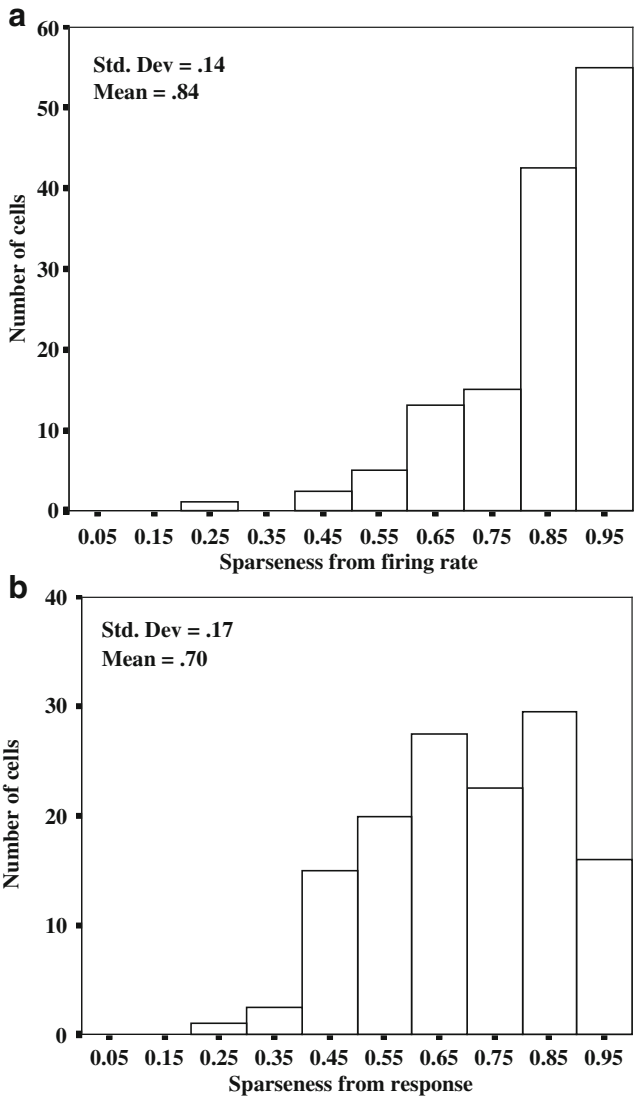

Fig. 7 **a** Histogram of the sparseness values calculated from the evoked firing rates of the neurons to the set of prototypical tastants (glucose, NaCl, HCl, and quinine-HCl). **b** Histogram of the sparseness values calculated from the responses (evoked firing rate minus spontaneous firing rate) of the neurons to the set of prototypical tastants

Single Cell Average Information About the Set of Taste Stimuli

In all the data above, the information was calculated for the responses of cells to the individual tastants ($I(s_i)$). Another approach is to calculate the average information reflected in the responses of each neuron about a stimulus set ($I(S,R)$). For the set of six tastants, the average information about which tastant was present, $I(S,R)$, was 0.45 bits (SD=0.26), averaged across neurons (see Fig. 6). This is quite a high value, indicating a robust representation of taste in the orbitofrontal cortex. Robust here

signifies relatively low variability and relatively large differences in firing rate to the different stimuli (so that information can be easily read out). For comparison, the mutual information about a set of 20 faces encoded by inferior temporal cortex neurons was 0.36 bits (Rolls et al. 1997b) and of nine odors by orbitofrontal cortex neurons was 0.09 bits (Rolls et al. 1996a). It was found that if a neuron had a high average information, it was often responsive to several of the taste stimuli, but with clearly different rates to each stimulus. Neurons with a high stimulus-specific information, but to only one stimulus, i.e., neurons with fine tuning as described below, tended to have intermediate values of the average information, as expected. Neurons with rather broad tuning, i.e., rather similar responses to the different stimuli, tended to have low values of the mutual information (see further below).

Breadth of Tuning

A measure of the breadth of tuning of a single neuron to a set of stimuli can be calculated (Smith and Travers 1979) as a coefficient of entropy (H) derived from the proportion of a neuron's total response that is devoted to each of the basic tastants (p_i). A scaling constant (k) is applied such that were the neuron to respond equally to all stimuli, then H=1.0. The coefficient of entropy, H, hence the measure of breadth of tuning is as follows:

$$H = -k\Sigma^{n}_{i=1} p_i \log p_i. \quad (2)$$

Total specificity to only one stimulus would result in a coefficient of entropy of 0.

The mean breadth of tuning (H) for the prototypical tastants (glucose 1.0 M, NaCl, 0.1 M, HCl, 0.01 M, and quinine-HCl 0.001 M) of the population of 135 neurons was 0.77 (SD=0.20). There was a small negative correlation (Pearson correlation coefficient=−0.32) between the average information and the breadth of tuning measure. It is clear that the breadth of tuning measure cannot be confidently used to predict the amount of information in the responses of the population of cells about a stimulus set, as the breadth of tuning does not reflect the reliability/variability of neuronal responses.

Sparseness of the Representation of the Prototypical Tastants

The sparseness, a, of the representation of a set of (taste) stimuli provided by the neurons can be defined and calculated as:

$$a = \left(\sum_{i=1,n}(r_i/n)\right)^2 / \sum_{i=1,n}\left(r_i^2/n\right) \quad (3)$$

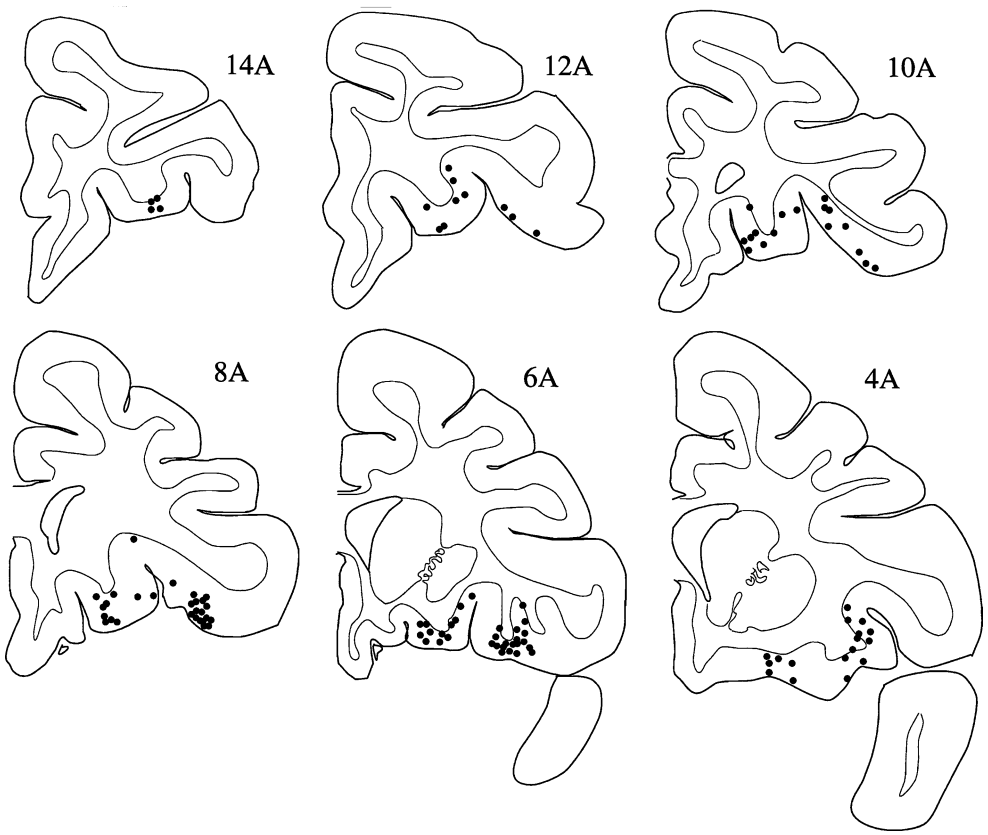

Fig. 8 Location of the orbitofrontal cortex gustatory neurons in the single cell taste information analysis. These neurons were recorded in the studies of Critchley and Rolls (1996a) and Rolls et al. (1996c, 1999)

where r_i is the firing rate to the ith stimulus in the set of n stimuli. The sparseness has a maximal value of 1.0. This is a measure of the extent of the tail of the distribution, in this case of the firing rates of the neuron to each stimulus. A low value indicates that there is a long tail to the distribution, equivalent in this case to only a few neurons with high firing rates. If these neurons were binary (either responding with a high firing rate or not responding), then a value of 0.2 would indicate that 20% of the neurons had high firing rates and 80% had no response. In the more general case of a continuous distribution of firing rates, the sparseness measure, a, still provides a quantitative measure of the length of the tail of the firing rate distribution (Treves and Rolls 1991). This measure of the sparseness of the representation of a set of stimuli by a single neuron has a number of advantages. One is that it is the same measure of sparseness which has proven to be useful and tractable in formal analyses of the capacity of neural networks that use an approach derived from theoretical physics (see Treves 1990; Treves and Rolls 1991; Rolls and Treves 1990). A second is that it can be applied to neurons which have continuously variable (graded) firing rates and not just to firing rates with a binary distribution (e.g., 0 or 100 spikes per second; Treves and Rolls 1991). A third is that it makes no assumption about the form of the firing rate distribution (e.g., binary, ternary, exponential etc.) and can be applied to different firing rate distributions (Treves and Rolls 1991). Fourth, it makes no assumption about the mean and the variance of the firing rate. Fifth, the measure does not make any assumption about the number of stimuli in the set and can be used with different numbers of test stimuli. Its maximal value is always 1.0, corresponding to the situation when a neuron responds equally to all the stimuli in a set of stimuli. The use of this measure of sparseness in neurophysiological investigations has the advantage that the neurophysiological findings then provide one set of the parameters useful in understanding theoretically (Treves and Rolls 1991; Rolls and Treves 1990; Franco et al. 2007) how the system operates.

The sparseness values for the population of neurons are shown in Fig. 7a. In addition, a second sparseness measure, calculated from the responses and not the evoked firing rates of the neurons, is illustrated in Fig. 7b. The sparseness values from both the firing rates and the responses were high (0.84 and 0.70, respectively). This is indicative of a distributed representation of the stimuli. A distributed encoding of tastes enables fine discriminations to be made of the tastants while at the same time being conservative and resistant to degradations of the neural code. Interestingly, the sparseness of the representation provided by inferior temporal cortex neurons about faces and objects is approximately 0.7 (Rolls et al. 1997b; Franco et al. 2007) and by orbitofrontal cortex neurons of odors is 0.93 (Critchley and Rolls 1996c).

The locations of the orbitofrontal cortex neurons in the single cell taste information study just described are shown in Fig. 8.

Multiple Cell Information Analysis for Taste: Methods

A multiple cell information measure, the average amount of information that is obtained about which stimulus was shown from a single presentation of a stimulus from the responses of all the cells, enabled measurement of how the information increases as a function of the number of neurons considered. If the information increases linearly with the number of cells, then the information encoded by each cell is independent of that encoded by the other cells. For at least small numbers of neurons, and with relatively large stimulus sets, this is the case for the inferior temporal visual cortex and is a very powerful type of encoding in that the number of stimuli represented increases exponentially with the number of neurons in the set (Abbott et al.

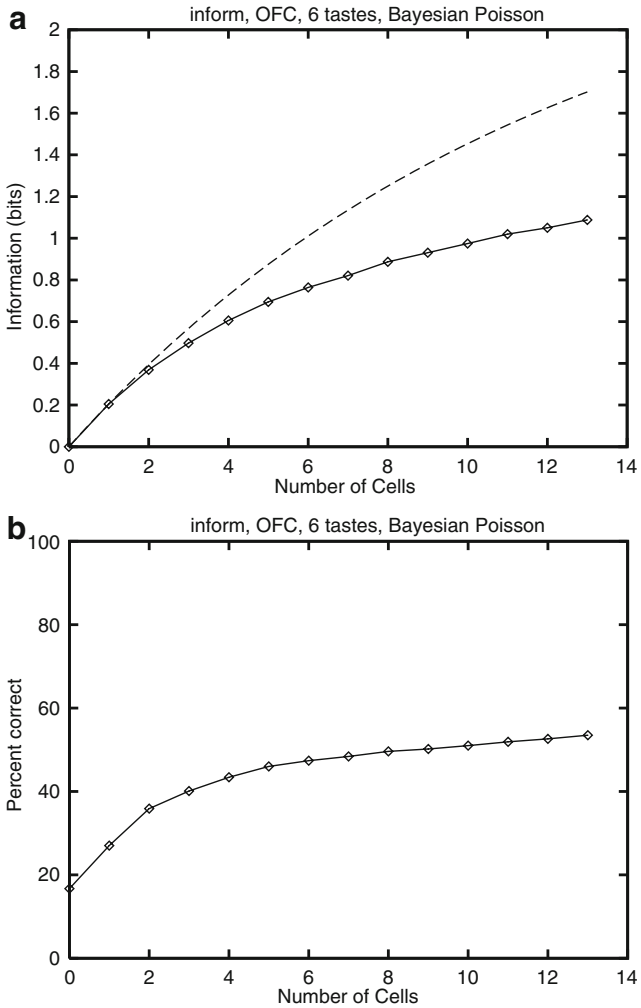

Fig. 9 Multiple cell taste information analysis for orbitofrontal cortex for six taste stimuli

1996; Rolls et al. 1997a; Rolls 2008a). If the information saturates at one cell, then the information encoded by the set of cells is redundant with respect to each other (Rolls 2008a).

Procedures for calculating the multiple cell information measure are given by Rolls et al. (1997a). The multiple cell information measure is the mutual information $I(S,\mathbf{R})$, that is, the average amount of information that is obtained from a single presentation of a stimulus about the set of stimuli S from the responses of all the cells. For multiple cell analysis, the set of responses, **R**, consists of response vectors comprising the responses from each cell.

Ideally, we would like to calculate

$$I(S,\mathbf{R}) = \sum_{s \in S} P(s) I(s,\mathbf{R}). \tag{4}$$

However, the information cannot be measured directly from the probability table $P(\mathbf{r},s)$ embodying the relationship between a stimulus s and the response rate vector **r** provided by the firing of the set of neurons to a presentation of that stimulus. This is because the dimensionality of the response vectors is too large to be adequately sampled by trials. Therefore, a decoding procedure is used in which the stimulus **s′** that gave rise to the particular firing rate response vector on each trial is estimated. This involves for example maximum likelihood estimation or dot product decoding. For example, given a response vector **r** to a single presentation of a stimulus, its similarity to the average response vector of each neuron to each stimulus is used to estimate using a dot product comparison which stimulus was presented. The probabilities of it being each of the stimuli can be estimated in this way. Details are provided by Rolls et al. (1997a). A probability table is then constructed of the real stimuli s and the decoded stimuli s'. From this probability table, the mutual information is calculated as:

$$I(S,S') = \sum_{s,s'} P(s,s') \log_2 \frac{P(s,s')}{P(s)P(s')}. \tag{5}$$

Multiple Cell Information Analysis for Taste: Results

Figure 9 shows the multiple cell information analysis for 13 taste neurons from the orbitofrontal cortex in macaque bk (the multiple cell information analysis can only be performed within a single animal for the effects of correlations in neuronal responses would be obscured if the neurons were from different individuals). Six taste stimuli were used: 0.1 M NaCl, 0.01 M HCl, 1 M glucose, 0.001 M quinine-HCl, 0.1 M MSG, and water. Figure 9a shows the multiple cell information as a function of the number of neurons. The dashed line shows what would be predicted if the neuronal responses were independent. Adding neurons clearly provides more information, but the information does not increase to the 2.58 bits that would be necessary to discriminate the stimuli perfectly, and consistent with this, the percent correct discrimination as a function of the number of neurons shown in Fig. 9b does not reach 100%. Furthermore, the neurons do not provide independent information, that is, there is some redundancy. This is shown by the finding that the information plot lies below what would be expected for independent information (the dashed

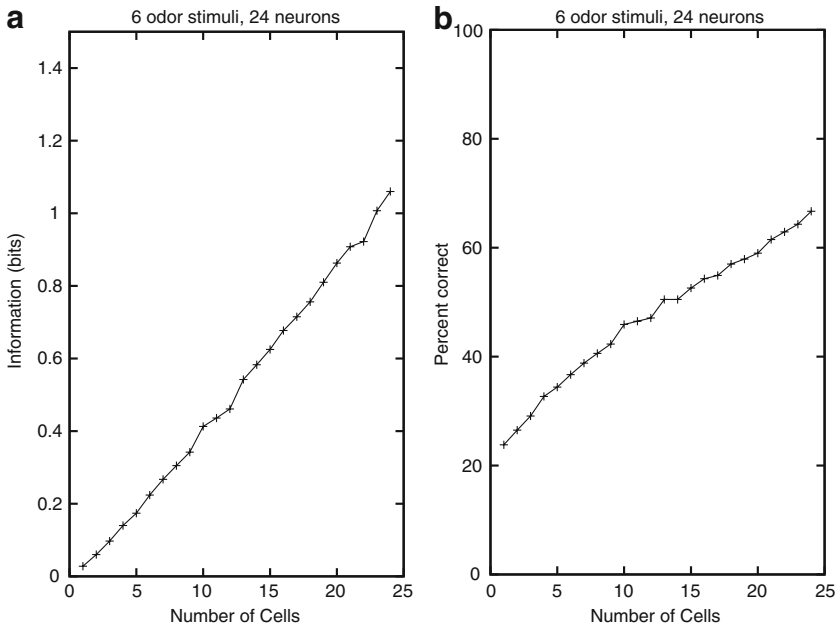

Fig. 10 Multiple cell olfactory information

line in Fig. 9a). The less than perfect discrimination between this set of taste stimuli is consistent with the evidence that the orbitofrontal cortex specializes in the representation of the affective quality of tastes rather than their identity (Kadohisa et al. 2005; Rolls 2005). Consistent with this, in analyses in progress, we are finding that the multiple cell information for the primary taste cortex, where the identity of tastes is represented (Rolls 2008b; Rolls and Grabenhorst 2008), does rise further as the number of neurons in the sample increases. Another factor in the less than independent encoding is that the taste space is inherently limited by the relatively small number of taste receptor channels (which include sweet, salt, bitter, sour, and umami) so that greater redundancy in the representation may be expected than in some other sensory modalities (Rolls 2008a).

Odor

Multiple Cell Information Analysis for Odor

A single cells analysis of the representation of information about a set of nine odor stimuli (eugenol, hexylamine, phenylethanol, butyric acid, naphthalene, caprylic acid, citral, amy1 acetate, and vanillin) has shown that the average information about the stimulus set provided by each of the 38 neurons was 0.09 bits (Rolls et al. 1996a). This is low when compared with the information values for the responses of temporal lobe face-selective neurons but may reflect the nature of olfactory processing and variability in the olfactory responses.

We now describe a new, multiple cell information analysis of this data set which aims to show how the information increases when more neurons are considered and whether the neurons encode information independently.

The neurophysiological methods have been described previously (Rolls et al. 1996a), and the multiple cell information theoretic analysis methods used were as described above for the taste multiple cell information analyses.

Figure 10 shows the multiple cell odor information analysis for the orbitofrontal cortex (calculated over the six odors for which there were sufficient trials and excluding two odors for which taste associations had been established; Rolls et al. 1996b). It is clear that the information increases approximately linearly with the number of neurons. The indication thus is that although the information encoded by each neuron is relatively small, the total information from the population increases in a way that enables a population of such neurons to discriminate the set of stimuli, though more than the 24 neurons in this sample of neurons would be needed.

This principle of independent encoding is useful given that the stimulus space is large, with hundreds of olfactory receptor genes, and nonlinear combinations of the effects of these expanding the space even further (Zou and Buck 2006), as is usual in sensory systems and as can be implemented by competitive learning (Rolls 2008a). The independent encoding allows the number of stimuli that can be encoded to increase exponentially with the number of neurons, given that information is a logarithmic measure (Abbott et al. 1996; Rolls et al. 1997a; Rolls 2008a).

Synthesis

These investigations show that a principle of brain function is that representations of the reward/hedonic value and pleasantness of sensory including food-related stimuli are formed separately from representations of what the stimuli are and their intensity. The pleasantness/reward value is represented in areas such as the orbitofrontal cortex and pregenual cingulate cortex, and it is here that satiety signals modulate the representations of food to make them implement reward in that they only occur when hunger is present. The satiety signals that help in this modulation may reach the orbitofrontal cortex from the visceral insula and/or hypothalamus, and in turn, the orbitofrontal cortex projects to the hypothalamus where neurons are found that respond to the sight, smell, and taste of food if hunger is present (Rolls 2007a; Rolls and Grabenhorst 2008). The insula itself has a number of partially segregated and partially overlapping representations, including for taste and odor in the agranular insula, for taste in the anterior insula, for oral somatosensory responses to example texture in the midinsula, and a visceral representation, and a body somatosensory representation more posteriorly. We have seen above some of the principles that help make the food pleasant, including particular combinations of taste, olfactory, texture, visual, and cognitive inputs. In addition, we have gained insight into how information is encoded by neurons, and by populations of neurons, in the taste and olfactory systems.

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