

## 3.15 Flavor Processing in the Brain

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### 3.15.1 Abstract

Taste pathways in humans and other primates project from the nucleus of the solitary tract directly to the taste thalamus, and then to the taste insula. The taste cortex in the anterior insula provides separate and combined representations of the taste, temperature, and 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 associative learning with olfactory inputs received from the piriform cortex, and visual inputs from the temporal lobe, to represent food flavor. These neurons encode food reward value in that

they only respond to food when hungry, and in that activations correlate linearly with subjective pleasantness. Cognitive factors, including word-level descriptions, and selective attention to affective value, modulate the representation of the reward value of taste, olfactory and flavor stimuli in the orbitofrontal cortex and a region to which it projects, the anterior cingulate cortex. These food reward representations are important in the control of appetite, and the liking of food. Individual differences in these reward representations may contribute to obesity, and there are age-related differences in these reward representations.

### 3.15.2 Introduction

This chapter describes the taste and olfactory pathways in the brain, and how taste, olfactory, food texture, and related visual inputs are processed in the brain to produce a representation of flavor. It is shown that at stages of processing before the orbitofrontal cortex, the taste or smell are represented unimodally, and that convergence to produce flavor occurs in the orbitofrontal cortex, and a structure to which it connects, the amygdala. Moreover, before the orbitofrontal cortex, the representations are in terms of the identity of the taste or smell, independently of its reward value or pleasantness. Then in the orbitofrontal cortex, a representation of reward value is produced that is related to subjective pleasure, and signals of hunger vs satiety, cognition, and selective attention influence this food reward value-related processing in the orbitofrontal cortex, and beyond to the anterior cingulate cortex.

A concept here is that food reward is a goal that normally drives appetite and eating, and it is therefore important to understand the brain mechanisms involved in food reward, in order to understand the control of appetite and food intake (Rolls, 2014, 2015, 2016a,b, 2018, 2019e).

The description of taste, olfactory, and flavor processing in the brain described here refers to primates including humans, and is therefore relevant to understanding the control of appetite in humans.

This focus is important, because the taste pathways in primates including humans utilize primarily cortical processing, and taste processing in rodents is very different with early taste relays connecting directly to subcortical structures, and a much less clear distinction between the identity of the taste, olfactory, or flavor stimulus, and its reward value and hedonics.

### 3.15.3 Taste and Oral Texture Processing in the Primate Including Human Brain

#### 3.15.3.1 Pathways

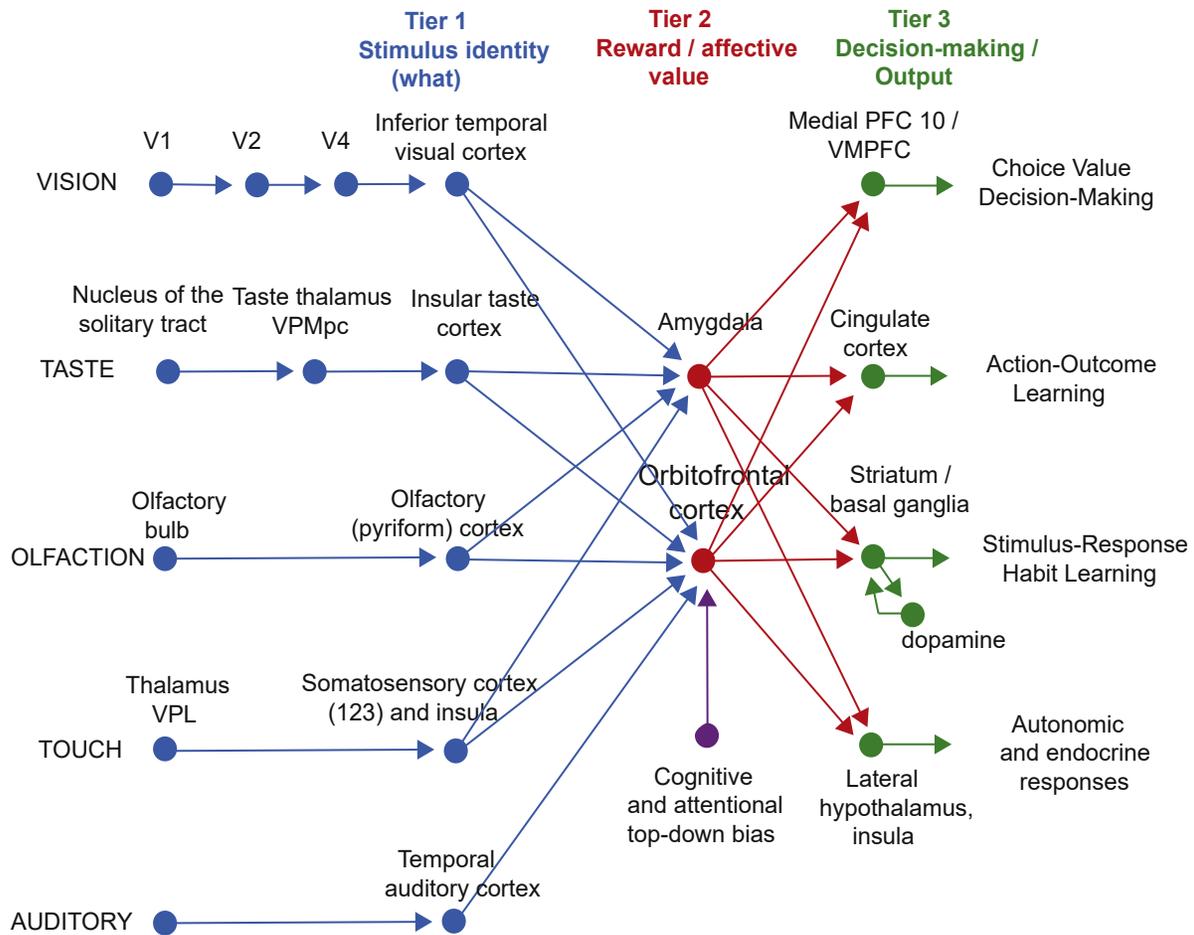
Diagrams of the taste and related olfactory, somatosensory, and visual pathways in primates are shown in Figs. 1 and 2.

Three cranial nerves carry taste information centrally: CN VII (chorda tympani and greater superficial petrosal branches), CN IX (lingual branch) and CN X (superior laryngeal branch). Gustatory axons terminate in the rostral part of the nucleus of the solitary tract (NTS) in the medulla (Beckstead and Norgren, 1979; Fritzsche et al., 2019). In primates, second-order taste neurons project through the central tegmental tract to terminate in the parvocellular division of the ventroposteromedial thalamic nucleus (VPMpc) (Beckstead et al., 1980; Pritchard et al., 1989).

A remarkable difference in primates from the taste system of rodents is this direct projection from the NTS to gustatory thalamus. In rodents, there is an obligatory relay from the NTS to the pontine parabrachial taste nuclei (PBN), which in turn project to the thalamus (Norgren and Leonard, 1973) (Fig. 2B). The pontine taste nuclei also project to the hypothalamus and amygdala in rodents (Norgren, 1976), providing direct access in rodents to these subcortical structures important in motivational behavior (e.g., feeding) and learning (Rolls, 2014). In contrast, in primates there appears to be no such direct pathway from the brainstem taste areas to the hypothalamus and amygdala (Scott and Small, 2009). This fundamental difference in the anatomy of the rodent and primate taste pathways shows that even in a phylogenetically old system such as taste, the way in which the system functions and processes information may be different across mammalian orders. This may result from the great development of the cerebral cortex in primates, and the advantage of using extensive cortical processing from each sensory modality before the representations are integrated in multimodal regions, as suggested below.

In primates, taste neurons in the nucleus of the solitary tract (Scott et al., 1984) do not decrease their responses after feeding to satiety (Scott et al., 1985), a devaluation procedure which reduces the pleasantness and the reward value of the taste of the food to zero (Rolls, 2014, 2016b). Thus in primates, the hedonics of taste are not represented peripherally, and nor are they, as we will see, in the primary taste cortex in the insula (Rolls, 2016a).

In contrast, in rodents, the taste and olfactory systems are modulated peripherally by hunger (in the nucleus of the solitary tract for taste (Scott and Small, 2009) and in the olfactory bulb (Pager et al., 1972; Palouzier-Paulignan et al., 2012)), so that reward is represented peripherally and is entangled with sensory processing, whereas in primates and humans food perception is separated from its reward value, as described below. A perceptual correlate of this is that when humans feed to satiety, the intensity of the flavor changes very little, whereas the pleasantness of the flavor decreases to zero (Rolls et al., 1983d; Rolls and Rolls, 1997), showing that in humans perceptual representations of taste and olfaction are kept separate from hedonic representations. This is adaptive, in that we do not go blind to the sight, taste, and smell of food after eating it to satiety, and can therefore still learn about where food is located in the environment even when we are not hungry (Rolls, 2014). For these reasons, rodents do not provide a good model of taste and olfactory processing in humans, and for the remainder of this chapter the focus on primates and humans, in which the taste and olfactory pathways and processing are similar. The information available from non-human primates



**Figure 1** Schematic diagram showing some of the gustatory, olfactory, visual and somatosensory pathways to the orbitofrontal cortex, and some of the outputs of the orbitofrontal cortex, in primates. The secondary taste cortex, and the secondary olfactory cortex, are within the orbitofrontal cortex. V1 - primary visual cortex. V4 - visual cortical area V4. PreGen Cing – pregenual cingulate cortex. Tier 1: the column of brain regions including and below the inferior temporal visual cortex represents brain regions in which “what” stimulus is present is made explicit in the neuronal representation, but not its reward or affective value. In Tier 2 the reward and hedonic value are represented, in the orbitofrontal cortex and amygdala, and then in the anterior cingulate cortex. In Tier 3 decisions between stimuli of different value are taken, and reward value or goal representations are interfaced to several behavioral output systems (Rolls, 2008a, 2014; Rolls and Deco, 2010). A pathway for top-down attentional and cognitive modulation of emotion is shown in purple. Medial PFC area 10/VMPFC – medial prefrontal cortex area 10/ventromedial prefrontal cortex; VPMpc – ventral posteromedial thalamic nucleus, the thalamic nucleus for taste.

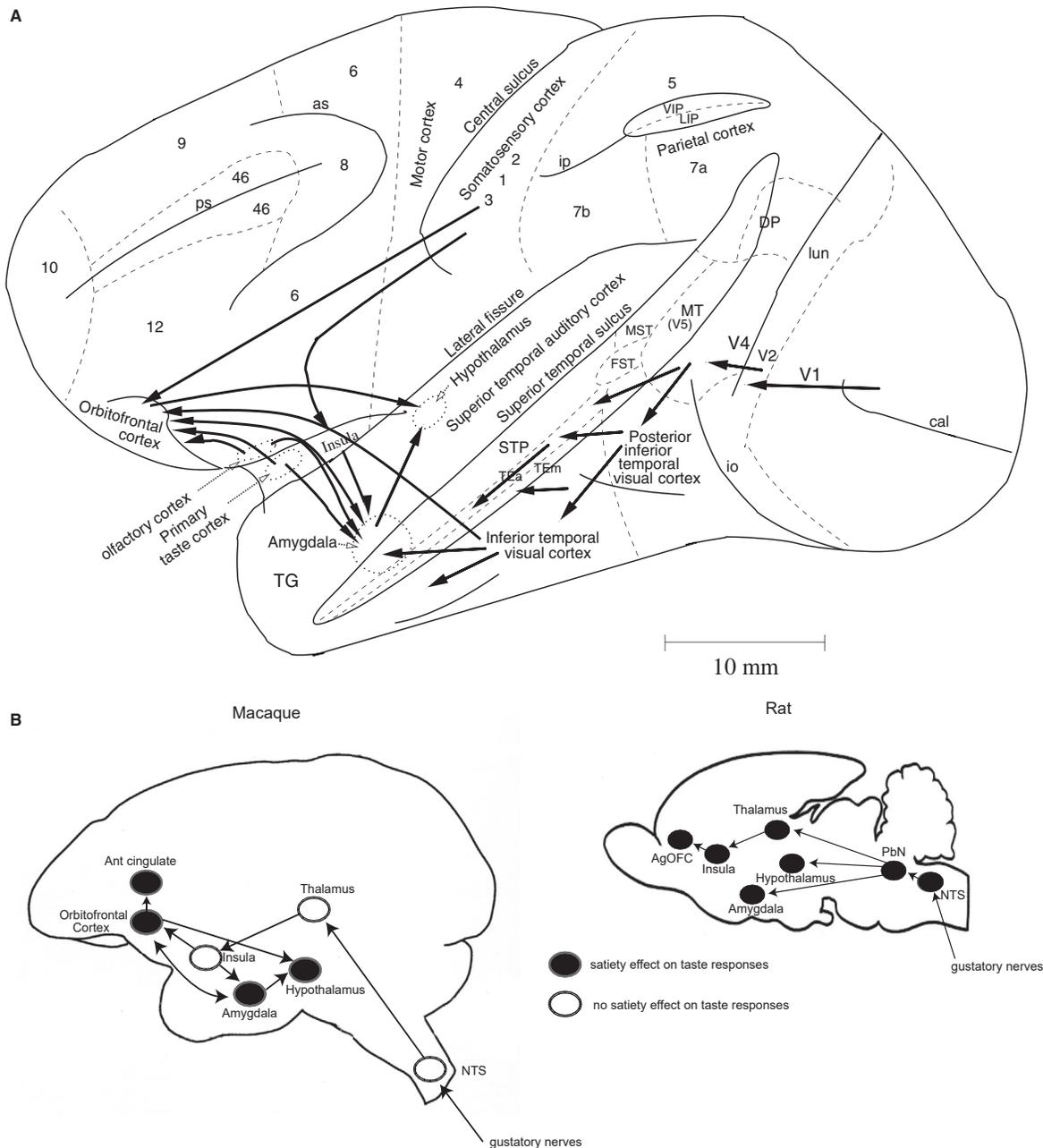
(macaques) provides much more detailed evidence about what is represented than is possible with fMRI in humans, because the responses of single neurons can be measured, and in the following reference is made both to single neuron recording studies in macaques and to complementary human fMRI studies of taste and olfactory processing. Another reason for focusing on research involving primates including humans is that the orbitofrontal cortex is very little developed in rodents (with only an agranular part) (Wise, 2008; Rolls, 2014, 2019c), yet is one of the major brain areas involved in taste and olfactory processing in primates including humans (Rolls, 2014, 2019c,e).

### 3.15.3.2 The Insular Primary Taste Cortex

#### 3.15.3.2.1 Neuronal Responses to Taste

The primary taste cortex in the primate anterior (granular) insula and adjoining frontal operculum (Pritchard et al., 1986) contains not only taste neurons tuned to sweet, salt, bitter, sour (Scott et al., 1986b; Yaxley et al., 1990; Scott and Plata-Salaman, 1999; Rolls and Scott, 2003), and umami as exemplified by monosodium glutamate (Baylis and Rolls, 1991; Rolls et al., 1996b), 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 macaque insular taste cortex neurons do not respond to olfactory stimuli or visual stimuli such as the sight of food (Verhagen et al., 2004).

Neurons in the insular and frontal opercular 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). In



**Figure 2** (A) Some of the pathways involved in processing food-related stimuli are shown on this lateral view of the primate brain (macaque). Connections from the primary taste and olfactory cortices to the orbitofrontal cortex and amygdala are shown. Connections are also shown in the “ventral visual system” from V1 to V2, V4, the inferior temporal visual cortex, etc., with some connections reaching the amygdala and orbitofrontal cortex. In addition, connections from the somatosensory cortical areas 1, 2, and 3 that reach the orbitofrontal cortex directly and via the insular cortex, and that reach the amygdala via the insular cortex, are shown. as, arcuate sulcus; cal, calcarine sulcus; cs, central sulcus; lf, lateral (or Sylvian) fissure; lun, lunate sulcus; ps, principal sulcus; io, inferior occipital sulcus; ip, intraparietal sulcus (which has been opened to reveal some of the areas it contains); sts, superior temporal sulcus (which has been opened to reveal some of the areas it contains). AIT, anterior inferior temporal cortex; FST, visual motion processing area; LIP, lateral intraparietal area; MST, visual motion processing area; MT, visual motion processing area (also called V5); PIT, posterior inferior temporal cortex; STP, superior temporal plane; TA, architectonic area including auditory association cortex; TE, architectonic area including high order visual association cortex, and some of its subareas TEa and TEem; TG, architectonic area in the temporal pole; V1–V4, visual areas V1–V4; VIP, ventral intraparietal area; TEO, architectonic area including posterior visual association cortex. The numerals refer to architectonic areas, and have the following approximate functional equivalence: 1,2,3, somatosensory cortex (posterior to the central sulcus); 4, motor cortex; 5, superior parietal lobule; 7a, inferior parietal lobule, visual part; 7b, inferior parietal lobule, somatosensory part; 6, lateral premotor cortex; 8, frontal eye field; 12, part of orbitofrontal cortex; 46, dorsolateral prefrontal cortex. (B) Taste pathways in the macaque and rat. In the *macaque*, gustatory information reaches the nucleus of the solitary tract (NTS), which projects directly to the taste thalamus (ventral posteromedial nucleus, pars parvocellularis, VPMpc) which then projects to the taste cortex in the anterior insula (Insula). The insular taste cortex then projects to the orbitofrontal cortex and amygdala. The orbitofrontal cortex projects taste information to the anterior cingulate cortex. Both the orbitofrontal cortex

macaques, neural processing peripheral to the primary taste cortex is consistent with this, with taste responses found in the rostral part of the nucleus of the solitary tract (Scott et al., 1986a) that are not influenced by feeding to satiety (Yaxley et al., 1985).

The insular taste cortex in the dorsal anterior insula projects forward to the orbitofrontal cortex (Baylis et al., 1995). Interestingly, neurons in the ventral anterior insula also project to the orbitofrontal cortex (Baylis et al., 1995), these insular neurons probably have visceromotoric functions (Evrard et al., 2014), and this may account for the activation of the insula in emotion-related tasks (Rolls, 2016a).

### 3.15.3.2.2 Activations of the Insular Taste Cortex in Humans

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 (Small et al., 1999; O'Doherty et al., 2001; de Araujo et al., 2003b; Grabenhorst and Rolls, 2008; Small, 2010). This is generally found at MNI coordinates between  $Y = 10$  and  $Y = 20$ . This is illustrated in Fig. 3, which also illustrates activations to taste stimuli in the orbitofrontal cortex, which is probably the secondary taste cortex (Francis et al., 1999; O'Doherty et al., 2001; de Araujo et al., 2003b; Rolls, 2015), and the anterior cingulate cortex. We pioneered the use of a tasteless control with the same ionic constituents as saliva (O'Doherty et al., 2001; de Araujo et al., 2003b), as water can activate some neurons in cortical taste areas (Rolls et al., 1990) and can activate the taste cortex (de Araujo et al., 2003b). The insular primary taste cortex is activated by oral temperature (Guest et al., 2007). In the mid-insular cortex, there is a somatosensory representation of oral texture (de Araujo and Rolls, 2004), which might be unpleasant, and this region can sometimes be activated by taste stimuli as illustrated in Fig. 3. There may thus be an anterior insula representation of taste in humans, and also another more mid-insular region a few mm posterior to the anterior insular taste cortex (de Araujo and Rolls, 2004; de Araujo et al., 2012; Avery et al., 2015; Rolls, 2015, 2016a). If the insular taste cortex in humans is activated by odors (de Araujo et al., 2012), this may be because of taste recalled through backprojection pathways (Rolls, 2016c) from the more anterior agranular insular cortex, which is multimodal (de Araujo et al., 2003c), or from the orbitofrontal cortex.

The primary taste cortex in the anterior (granular) insula of humans represents the identity and intensity of taste (Rolls, 2015, 2016a) in that activations there are linearly correlated with the subjective intensity of the taste. In contrast, the orbitofrontal and anterior cingulate cortex represent the reward value of taste, in that activations there correlate with the subjective pleasantness of taste (Grabenhorst and Rolls, 2008; Grabenhorst et al., 2008b; Fig. 3); and in that activations in the orbitofrontal cortex decrease when humans are fed to satiety, but were not found to in the insular taste cortex (Kringelbach et al., 2003). The texture-related unpleasantness of some oral stimuli is represented in frontal opercular areas that are close to the insular taste cortex (Rolls et al., 2015). Indeed, the unpleasantness of the flavor of some foods such as some vegetables in young people appears to be related in part of activation of this region (Rolls et al., 2015).

## 3.15.4 Olfactory Processing in the Primate Including Human Brain

### 3.15.4.1 Olfactory Pathways

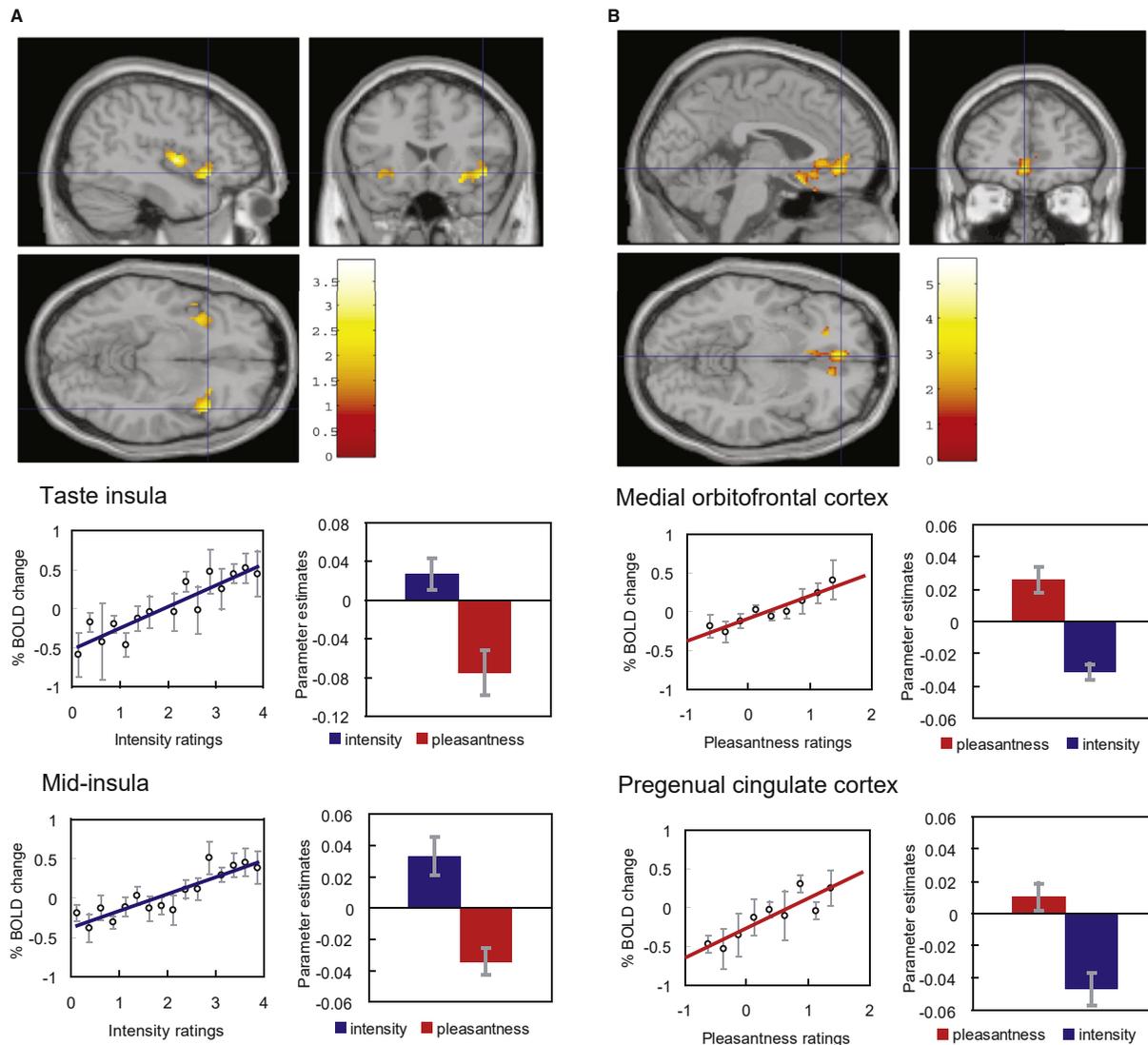
The olfactory nerves project from the olfactory bulb with no thalamic relay to terminate in the pyriform (primary olfactory) cortex (which includes the anterior olfactory nucleus) (Figs. 1 and 2), in the olfactory tubercle (part of the ventral striatum), and even in the entorhinal cortex (Wilson et al., 2014, 2015).

An accessory olfactory vomeronasal system present in rodents and involved in behavioral responses to some pheromones (Isogai et al., 2011) does not appear to be present in humans.

### 3.15.4.2 The Pyriform Olfactory Cortex

In humans, the pyriform (primary olfactory) cortex is activated by olfactory stimuli (Sobel et al., 2000; Rolls et al., 2003a; Howard et al., 2009; Gottfried, 2010, 2015). Activations in the pyriform cortex are correlated with the intensity of odors and not their pleasantness (Rolls et al., 2003a). In addition, feeding to satiety has not been shown to reduce the activations of the pyriform cortex to odors though satiety does reduce activations of the orbitofrontal cortex to food-related odors (O'Doherty et al., 2000; Howard and Kahnt, 2017), and to flavors that include taste and olfactory components (Kringelbach et al., 2003). These findings provide evidence that the human pyriform cortex is involved in representing the intensity and identity of odors, but not their reward value or pleasantness.

and the amygdala project to the hypothalamus (and to the ventral striatum). In macaques, feeding to normal self-induced satiety does not decrease the responses of taste neurons in the NTS or taste insula (and by inference not VPMpc) (see text). In the *rat*, in contrast, the NTS projects to a pontine taste area, the parabrachial nucleus (PbN). The PbN then has projections directly to a number of subcortical structures, including the hypothalamus, amygdala, and ventral striatum, thus bypassing thalamo-cortical processing. The PbN in the *rat* also projects to the taste thalamus (VPMpc), which projects to the *rat* taste insula. The taste insula in the *rat* then projects to an agranular orbitofrontal cortex (AgOFC), which probably corresponds to the most posterior part of the primate OFC, which is agranular. In primates, most of the orbitofrontal cortex is granular cortex, and the *rat* may have no equivalent to this (Wise, 2008; Small and Scott, 2009; Passingham and Wise, 2012; Rolls, 2014, 2015). In the *rat*, satiety signals such as gastric distension and satiety-related hormones decrease neuronal responses in the NTS (see text), and by inference therefore in the other brain areas with taste-related responses, as indicated in the Figure.



**Figure 3** Effect of paying attention to the pleasantness vs the intensity of a taste stimulus, monosodium glutamate. (A, Top) A significant difference related to the taste period was found in the taste insula at  $[42\ 18\ -14]$   $z = 2.42$   $p < 0.05$  (indicated by the cursor) and in the mid insula at  $[40\ -2\ 4]$   $z = 3.03$   $p < 0.025$ . Middle: Taste Insula. Right: The parameter estimates (mean  $\pm$  sem across subjects) for the activation at the specified coordinate for the conditions of paying attention to pleasantness or to intensity. The parameter estimates were significantly different for the taste insula  $t = 4.5$ ,  $df = 10$ ,  $p = 0.001$ . Left: The correlation between the intensity ratings and the activation (% BOLD change) at the specified coordinate ( $r = 0.91$ ,  $df = 14$ ,  $p < 0.001$ ). Bottom: Mid Insula. Right: The parameter estimates (mean  $\pm$  sem across subjects) for the activation at the specified coordinate for the conditions of paying attention to pleasantness or to intensity. The parameter estimates were significantly different for the mid insula  $t = 5.02$ ,  $df = 10$ ,  $p = 0.001$ . Left: The correlation between the intensity ratings and the activation (% BOLD change) at the specified coordinate ( $r = 0.89$ ,  $df = 15$ ,  $p < 0.001$ ). The taste stimulus, monosodium glutamate, was identical on all trials. (B, Top) A significant difference related to the taste period was found in the medial orbitofrontal cortex at  $[-6\ 14\ -20]$   $z = 3.81$   $p < 0.003$  (toward the back of the area of activation shown) and in the pregenual cingulate cortex at  $[-4\ 46\ -8]$   $z = 2.90$   $p < 0.04$  (at the cursor). Middle: Medial orbitofrontal cortex. Right: The parameter estimates (mean  $\pm$  sem across subjects) for the activation at the specified coordinate for the conditions of paying attention to pleasantness or to intensity. The parameter estimates were significantly different for the orbitofrontal cortex  $t = 7.27$ ,  $df = 11$ ,  $p < 10^{-4}$ . Left: The correlation between the pleasantness ratings and the activation (% BOLD change) at the specified coordinate ( $r = 0.94$ ,  $df = 8$ ,  $p < 0.001$ ). Bottom: Pregenual cingulate cortex. Conventions as above. Right: The parameter estimates were significantly different for the pregenual cingulate cortex  $t = 8.70$ ,  $df = 11$ ,  $p < 10^{-5}$ . Left: The correlation between the pleasantness ratings and the activation (% BOLD change) at the specified coordinate ( $r = 0.89$ ,  $df = 8$ ,  $p = 0.001$ ). The taste stimulus, 0.1 M monosodium glutamate, was identical on all trials. After [Grabenhorst and Rolls, 2008](#).

### 3.15.5 The Orbitofrontal Cortex, Which Contains the Secondary Taste and Secondary Olfactory Cortex

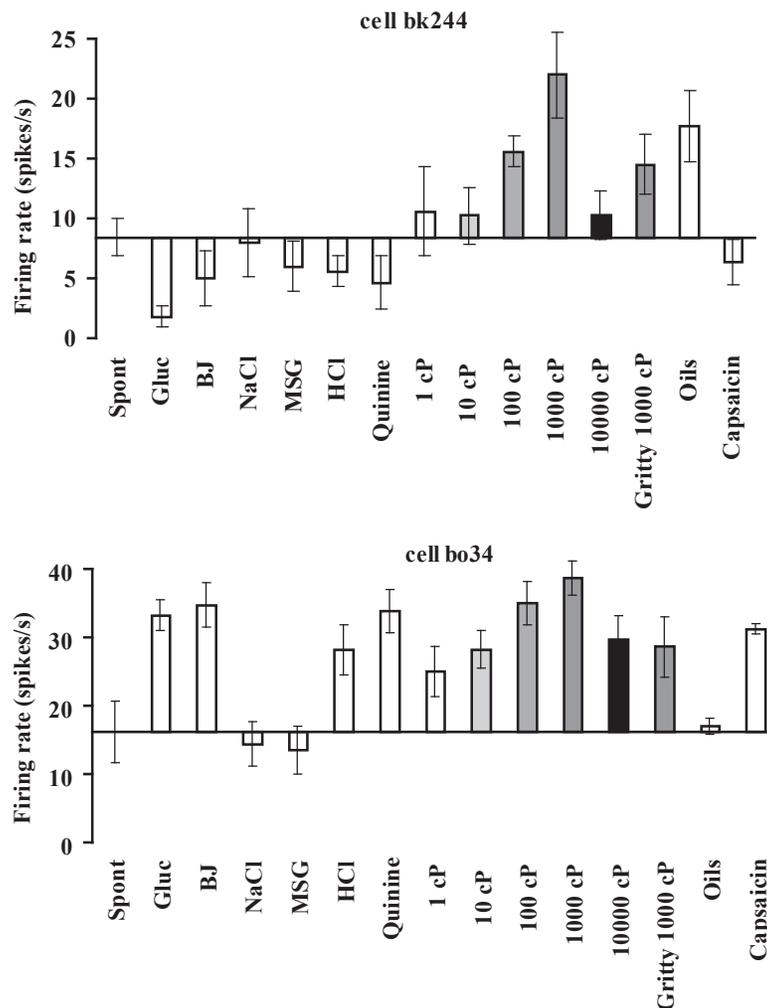
As illustrated in [Figs. 1](#) and [2](#), the orbitofrontal cortex receives taste and olfactory inputs, and also visual and somatosensory inputs ([Rolls, 2014, 2019c](#)). It plays key roles in taste, olfactory, and flavor processing in humans, as described next.

### 3.15.5.1 Neuronal Responses in the Orbitofrontal Cortex to Taste

A secondary cortical taste area in primates was discovered by Rolls and colleagues (Thorpe et al., 1983; Rolls et al., 1989, 1990) in the orbitofrontal cortex, extending several mm in front of the primary taste cortex (Figs. 1 and 2). This is defined as a secondary cortical taste area, for it receives direct inputs from the primary taste cortex, as shown by a combined neurophysiological and anatomical pathway tracing investigation (Baylis et al., 1995).

Different neurons in this region respond not only to each of the four classical prototypical tastes sweet, salt, bitter and sour (Rolls et al., 1990, 2003b; Verhagen et al., 2003; Kadohisa et al., 2005b), but also to umami tastants such as glutamate (which is present in many natural foods such as tomatoes, mushrooms and human milk) (Baylis and Rolls, 1991) and inosine monophosphate (which is present in meat and some fish such as tuna) (Rolls et al., 1996b). 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 channels, 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 (Rolls et al., 1990), and others to somatosensory stimuli including astringency as exemplified by tannic acid (Critchley and Rolls, 1996c), and capsaicin (Rolls et al., 2003b; Kadohisa et al., 2004).

Some of the coding principles are illustrated by the two neurons shown in Fig. 4. The two neurons each have their independent tuning to the set of stimuli. It is this independent tuning or coding with sparse distributed representations that underlies the ability



**Figure 4** Independent coding of food-related stimuli shown by the responses of two orbitofrontal cortex neurons to taste and oral somatosensory inputs. *Above.* Firing rates (mean  $\pm$  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 (carboxymethylcellulose 1–10,000 centiPoise), to the gritty stimulus (1000 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. *Below.* Firing rates (mean  $\pm$  sem) of viscosity-sensitive neuron bo34 which had responses to some taste stimuli and 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. 2003.

of the brain to represent the exact nature of a stimulus or event, and this applies to taste in addition to other sensory modalities including smell (Rolls et al., 1996a, 2010d; Rolls and Treves, 2011; Rolls, 2015, 2016c). This tuning also provides a foundation for the implementation of sensory-specific satiety (Rolls, 2014, 2015). Taste responses are found in a large mediolateral extent of the orbitofrontal cortex (Critchley and Rolls, 1996c; Pritchard et al., 2005; Rolls, 2008b, 2015; Rolls and Grabenhorst, 2008).

The majority of these orbitofrontal cortex neurons have their responses to taste and/or olfactory stimuli modulated by hunger (Critchley and Rolls, 1996b), as illustrated in Fig. 5, and described in more detail in Section “Reward Value in the Orbitofrontal Cortex”.

### 3.15.5.2 Activations of the Orbitofrontal Cortex in Humans to Taste Stimuli

Different regions of the human orbitofrontal cortex can be activated by pleasant (sucrose or glucose) or by aversive (e.g., quinine or sodium chloride) taste stimuli (Zald et al., 1998; O’Doherty et al., 2001; Zald et al., 2002). 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., 2003a; Rolls, 2009a).

### 3.15.5.3 Neuronal Responses to Odors in the Primate Orbitofrontal Cortex

Some primate orbitofrontal cortex neurons respond well to olfactory stimuli (Critchley and Rolls, 1996a; Rolls et al., 1996c, 2010d). For many of these neurons, the response is related to tastes (Critchley and Rolls, 1996a) and can be learned by olfactory to taste association learning (Rolls et al., 1996c), providing evidence that the orbitofrontal cortex can remap odors from the olfactory gene-specified representation (Buck and Axel, 1991; Mombaerts, 2006) into a representation where the “meaning” in terms of the association of the odor with other stimuli is paramount. Flavors are built by learning in the orbitofrontal cortex as combinations of taste and olfactory inputs, with oral texture also often being a component (Rolls et al., 1996c). The olfactory to taste association learning is though slow, taking 30–60 trials to reverse, so that flavor representations are somewhat stable (Rolls et al., 1996c). The representation of information by primate orbitofrontal cortex neurons (Rolls et al., 1996a) is approximately independent by different neurons, in that the information increases approximately linearly with the number of neurons (Rolls et al., 2010d).

Many primate olfactory orbitofrontal neurons encode the reward value of odor, not only in that their responses often reflect the taste primary reinforcer with which an odor is associated (Critchley and Rolls, 1996a; Rolls et al., 1996c), but also in that their activity is decreased in a sensory-specific satiety way by feeding a particular food to satiety (Critchley and Rolls, 1996b) (Section “Reward value in the orbitofrontal cortex”).

### 3.15.5.4 Olfactory Representations in the Human Orbitofrontal Cortex

In humans, there is strong and consistent activation of the orbitofrontal cortex by olfactory stimuli (Zatorre et al., 1992; Francis et al., 1999; Rolls et al., 2003a). This region represents the reward value and pleasantness of odor, as shown by a sensory-specific satiety experiment with banana vs vanilla odor (O’Doherty et al., 2000), and these reward-specific activations have been confirmed by Gottfried et al. (personal communication, Gottfried, 2015; Howard et al., 2015; Howard and Kahnt, 2017), who also showed that activations in the pyriform (primary olfactory) cortex were not decreased by odor devaluation by satiety. Further, pleasant odors tend to activate the medial, and unpleasant odors the more lateral, orbitofrontal cortex (Rolls et al., 2003a), 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; Grabenhorst and Rolls, 2011; Rolls, 2014, 2019c). The primary olfactory (pyriform) cortex represents the identity and intensity of odor in that activations there correlate with the subjective intensity of the odor, and the orbitofrontal and anterior cingulate cortex represent the reward value of odor, in that activations there correlate with the subjective pleasantness (medially) or unpleasantness (laterally) of odor (Rolls et al., 2003a, 2008, 2009; Grabenhorst et al., 2007; Rolls and Grabenhorst, 2008; Grabenhorst and Rolls, 2011; Rolls, 2014, 2015).

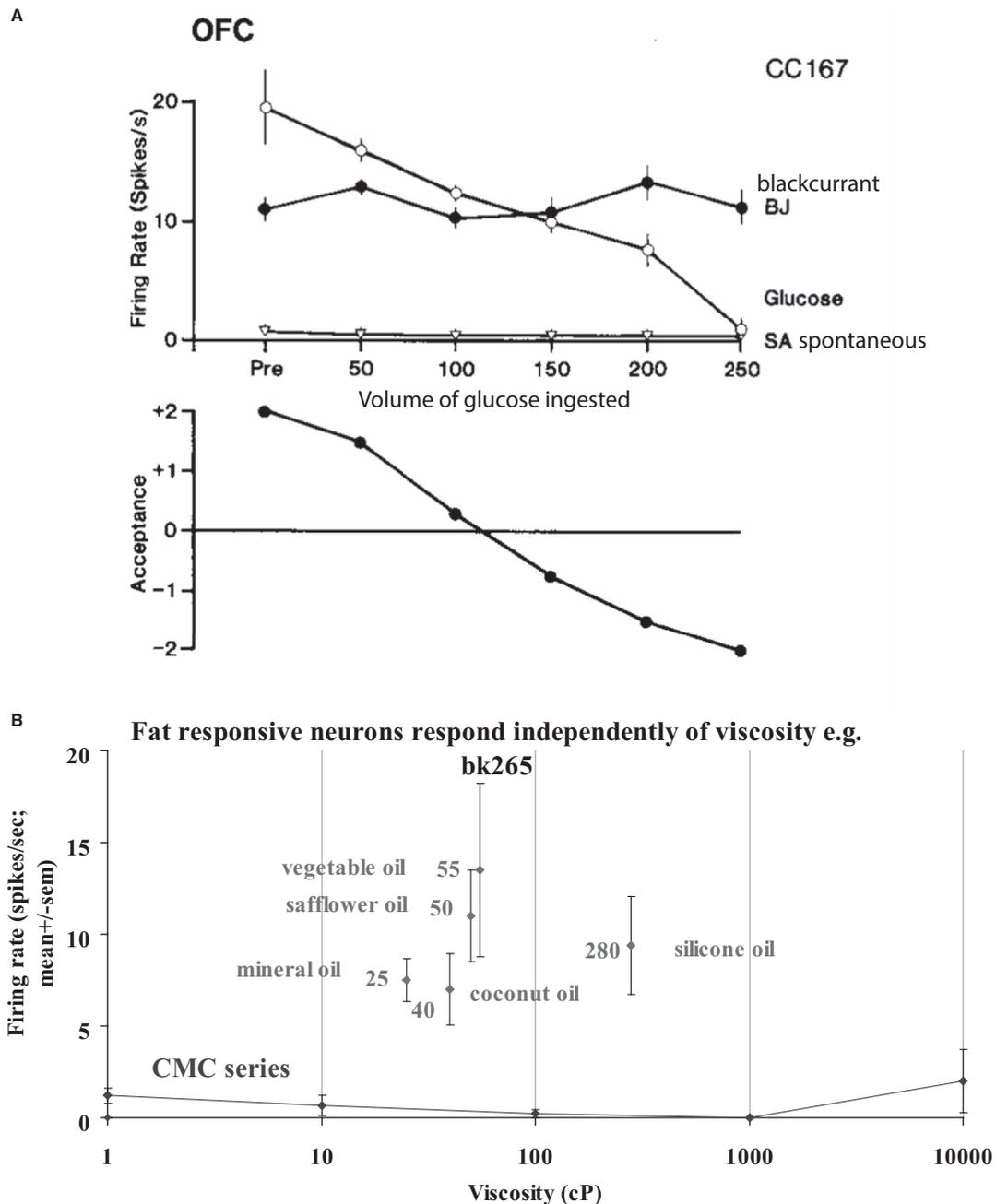
### 3.15.5.5 The Texture of Food, Including Fat Texture

#### 3.15.5.5.1 Viscosity, Particulate Quality, and Astringency

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 centiPoise), and other neurons independently encode the particulate quality of food in the mouth (Rolls et al., 2003b). Somatosensory signals that transmit information about capsaicin (chilli) and astringency are also reflected in neuronal activity in these cortical areas (Critchley and Rolls, 1996c; Kadohisa et al., 2004, 2005b).

#### 3.15.5.5.2 Oral Fat Texture

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) have found a population of neurons that responds when fat is in the mouth. The fat-related responses of these neurons are produced at least in part by the texture of the food rather than by receptors sensitive to certain chemicals, in that such neurons typically respond not only to foods such as cream and milk containing fat, but also to paraffin oil (which is a pure hydrocarbon) and to silicone oil ((Si(CH<sub>3</sub>)<sub>2</sub>O)<sub>n</sub>). Moreover, the texture channels through which these fat-sensitive neurons are activated are separate from viscosity sensitive



**Figure 5** The effect of feeding to satiety with glucose solution on the responses (firing rate  $\pm$  s.e.m.) of a neuron in the orbitofrontal (secondary taste) cortex to the taste of glucose (open circles) and of blackcurrant juice (BJ). The spontaneous firing rate is also indicated (SA). Below the neuronal response data, the behavioral measure of the acceptance or rejection of the solution on a scale from +2 (strong acceptance) to -2 (strong rejection) is shown. The solution used to feed to satiety was 20% glucose. The monkey was fed 50 mL of the solution at each stage of the experiment as indicated along the abscissa, until he was satiated as shown by whether he accepted or rejected the solution. Pre is the firing rate of the neuron before the satiety experiment started. (B) 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 ( $\text{Si}(\text{CH}_3)_2\text{O}_n$ ) and paraffin (mineral) oil (hydrocarbon). Some of these neurons have taste inputs. (A) Reproduced from Rolls, E.T., Sienkiewicz, Z.J., Yaxley, S. 1989. Hunger modulates the responses to gustatory stimuli of single neurons in the caudolateral orbitofrontal cortex of the macaque monkey. *J. Neurosci.* 1(1), 53–60, Copyright 1989 Society for Neuroscience. (B) After Verhagen et al. (2003).

channels, in that the responses of these neurons cannot be predicted by the viscosity of the oral stimuli, as illustrated in Fig. 5B (Verhagen et al., 2003; Rolls, 2011). The responses of these oral fat-encoding neurons are not related to free fatty acids such as linoleic or lauric acid (Verhagen et al., 2003; Kadohisa et al., 2005b; Rolls, 2011), and the fat responsiveness of these primate

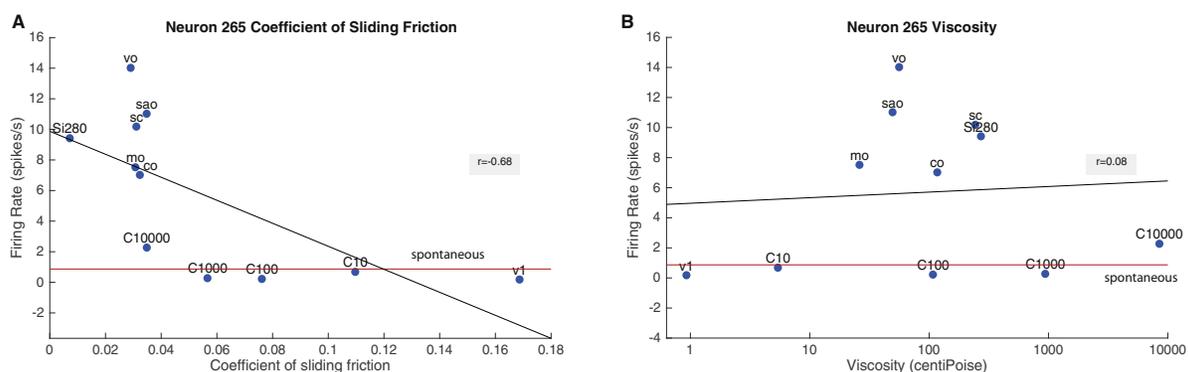
orbitofrontal cortex neurons is therefore not related to fatty acid sensing (Gilbertson et al., 1997; Gilbertson, 1998), but instead to oral texture sensing (Rolls, 2011) (The hypothesis is that in rodents, with relatively high concentrations of lingual lipase, a fatty acid responsive “taste” receptor might provide evidence about the presence of fat in the mouth (Gilbertson et al., 1997; Gilbertson, 1998). There is less lingual lipase in primates, and the neuronal responses to fat placed in the mouth in macaques are fast (Verhagen et al., 2003, 2004) so that the intervention of digestion by a salivary enzyme is unlikely to be the main mechanism that detects fat in the mouth. Moreover, oils that have the same texture as fat but that contain no fat, such as silicone and paraffin oil, activate the neurons in macaques that respond to fat in the mouth). This has important implications for the development of foods with the mouth feel of fat, but low energy content (Rolls, 2011). A few neurons do have responses to linoleic and/or lauric acid, but these neurons do not respond to fat in the mouth, and may reflect the bad taste that rancid fats may have because of their free fatty acids (Verhagen et al., 2003; Rolls, 2011). Some of the fat texture-related orbitofrontal cortex neurons do though have 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).

We have analyzed the physical properties that are being sensed by the fat-sensitive neurons. We have found that the firing rate responses of these fat-responsive neurons in the macaque orbitofrontal cortex and insular taste cortex are correlated with the coefficient of sliding friction, and not with viscosity which reflects food thickness (Rolls et al., 2018; Rolls, 2019a). Some neurons had responses that were non-linear in their responses to the coefficient of sliding friction, responding selectively only when the coefficient was very low. An example is shown in Fig. 6. Other neurons had responses that increased linearly with decreases in the coefficient of sliding friction. We hypothesize that the high fat selectivity of the neurons is being computed in the cortex. Indeed there was a tendency for there to be more of the non-linear highly selective fat-selective neurons in the orbitofrontal cortex than the insular taste cortex. Further neurons had their responses decreased linearly by increases in the coefficient of sliding friction. A different population of non fat-sensitive neurons encoded viscosity and not the coefficient of sliding friction. Neuronal population analyses confirmed that fat-responsive neurons conveyed information about the coefficient of sliding friction but not about viscosity. Conversely the viscosity-sensitive neuronal population conveyed information about viscosity, but not about the coefficient of sliding friction. This new understanding of the representation of oral fat in the cerebral cortex and amygdala opens the way for the systematic development of foods with the pleasant mouth-feel of fat, together with ideal nutritional content, and has great potential to contribute to healthy eating and a healthy body weight.

Feeding to satiety with fat (e.g., cream) decreases the responses of these fat-responsive neurons to zero on the food eaten to satiety, providing evidence that they encode the reward value of fat in the mouth, 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).

### 3.15.5.5.3 Oral Temperature

In addition, we have shown that some neurons in the insular cortex, orbitofrontal cortex, and amygdala 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, 2005a, 2005b; Verhagen et al., 2004). Somatosensory signals that transmit information about capsaicin (chilli) are also reflected in neuronal activity in these brain areas (Kadohisa et al., 2004, 2005b). Activations in the human orbitofrontal and insular taste cortex also reflect oral temperature (Guest et al., 2007).



**Figure 6** An orbitofrontal cortex (secondary taste cortex) neuron with responses non-linearly correlated with decreases in the coefficient of sliding friction (A). The neuron responds almost not at all until the coefficient of sliding friction falls below 0.04. The neuron is thus very selective for fat texture, because of its non-linear response in relation to the coefficient of sliding friction. The linear regression line has a correlation of  $r = -0.68$  ( $p = 0.02$ ). (B) There is a much weaker relation to viscosity ( $r = 0.08$ ,  $p = 0.82$ ), with the oils producing a larger response than predicted linearly. Further, a regression line through the non-oil stimuli would have a lower slope. C10–C10000: carboxymethyl cellulose with the nominal viscosity of 10, 100, 1000 and 10,000 cP. v1: water (1 cP). co: coconut oil; mo: mineral oil; sao: safflower oil; vo: vegetable oil; sc: single cream. Si280: silicone oil with the viscosity indicated. Li: linoleic acid; La: lauric acid. The horizontal line indicates the spontaneous firing rate. The Pearson correlation between the firing rate of each neuron and (A) the coefficient of sliding friction, and (B) the viscosity, was calculated to show to what extent the firing of a neuron reflected one or other of these measures. After Rolls et al., 2018.

#### 3.15.5.4 Activations in Humans to Oral 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 may not be primarily 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 pregenual 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). We have shown that the pleasantness and reward value of fat texture is represented in the mid-orbitofrontal and anterior cingulate cortex, where activations are correlated with the subjective pleasantness of oral fat texture (Rolls, 2009a; Grabenhorst et al., 2010a). This provides a foundation for future studies of whether activations in the fat reward system are heightened in people who tend to become obese (Rolls, 2012a). Interestingly, high fat stimuli with a pleasant flavor increase the coupling of activations between the orbitofrontal cortex and somatosensory cortex, suggesting a role for the somatosensory cortex in processing the sensory properties of food in the mouth (Grabenhorst and Rolls, 2014).

#### 3.15.5.6 Convergence of Taste, Olfactory, Oral Texture, and Visual Inputs in the Orbitofrontal Cortex to Produce Flavor

##### 3.15.5.6.1 Neuronal Activity

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, 1996a; Rolls et al., 1996a). 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 et al., 1996c). Olfactory-to-taste associative learning by these orbitofrontal cortex neurons may take 30–40 trials to reverse in an olfactory-to-taste discrimination task, and this slow learning may help to make a flavor stable (Rolls et al., 1996c). Olfactory neurons are found in a considerable anterior-posterior extent of the primate orbitofrontal cortex, extending far into areas 11 and 14 (Rolls and Baylis, 1994; Critchley and Rolls, 1996a,b; Rolls et al., 1996c; Rolls et al., 1996a), and are not restricted to a posterior region as some have thought (Gottfried and Zald, 2005).

Visual-to-taste association learning and its reversal by neurons in the orbitofrontal cortex can take place in as little as one trial (Thorpe et al., 1983; Rolls et al., 1996c; Deco and Rolls, 2005). This has clear adaptive value in enabling particular foods with a good or bad taste to be learned and recognized quickly, important in foraging and in food selection for ingestion. The visual inputs reach the orbitofrontal cortex from the inferior temporal visual cortex, where neurons respond to visual objects independently of their reward value (e.g., taste) as shown by satiety and reversal learning tests (Rolls et al., 1977; Rolls, 2008a, 2012b). The visual-to-taste associations are thus learned in the orbitofrontal cortex (Rolls, 2014). These visual-taste neurons thus respond to expected value (Rolls, 2014).

Different neurons in the orbitofrontal cortex respond when a visually signaled expected taste reward is not obtained, that is, to negative reward prediction error (Thorpe et al., 1983; Rolls and Grabenhorst, 2008; Rolls, 2014). There is evidence that dopamine neurons in the ventral tegmentum respond to positive reward prediction error (Schultz, 2007), and as such, they do not respond to taste reward (Rolls, 2014). The inputs to the dopamine neurons may originate from structures such as the orbitofrontal cortex, where expected value, reward outcome (e.g., taste), and negative reward prediction error are represented (Rolls, 2014).

##### 3.15.5.6.2 Taste-Olfactory Convergence Shown by Activations in Humans

Taste and olfactory conjunction analyses, and the measurement of supradditive effects that provide evidence for convergence and interactions in fMRI investigations, showed convergence for taste (sucrose) and odor (strawberry) in the orbitofrontal and anterior cingulate cortex, and activations in these regions were correlated with the pleasantness ratings given by the participants (de Araujo et al., 2003c; Small et al., 2004; 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 (Rolls, 2014, 2015). The first region where the effects of this olfactory-taste convergence are found is in an agranular part of what cytoarchitecturally is the insula (Ia) that is topologically found in the posterior orbitofrontal cortex, though it is anterior to the insular taste cortex, and posterior to the granular orbitofrontal cortex (de Araujo et al., 2003c; Rolls, 2015, 2016a).

McCabe and Rolls (2007) have shown that the convergence of taste and olfactory information in the orbitofrontal cortex 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; and that these combinations are formed in the brain far beyond the taste or olfactory receptors (Rolls, 2009a).

O'Doherty et al. (2002) showed that visual stimuli associated with the taste of glucose activate the orbitofrontal cortex and some connected areas, consistent with the primate neurophysiology. Simmons et al. (2005) found that showing pictures of foods, compared to pictures of places, 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).

#### 3.15.5.7 Reward Value of Taste, Olfactory and Flavor Stimuli in the Orbitofrontal Cortex

The visual and olfactory as well as the taste inputs represent the reward value of the food in the orbitofrontal cortex, as shown by sensory-specific satiety effects (Critchley and Rolls, 1996b) (see Fig. 5A). So does their combination, flavor (Critchley and Rolls, 1996b; de Araujo et al., 2003c; Kringsbach et al., 2003).

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, 2014, 2015). 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 Edmund Rolls' 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 by neurons 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; Rolls, 2015). Consistent changes are found in humans (Kringelbach et al., 2003), and this study provided evidence that the subjective pleasantness of the flavor of food, and sensory-specific satiety, are represented in the human orbitofrontal cortex.

This evidence shows that the reduced acceptance and reward value 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 (Rolls and Rolls, 1977, 1997; Rolls et al., 1981a,b, 1982, 1983a,b, 1984; Hetherington, 2007), are produced in the primate orbitofrontal cortex, but not at earlier stages of processing including the insular-opercular primary taste cortex (Rolls et al., 1988; Yaxley et al., 1988) and the nucleus of the solitary tract (Yaxley et al., 1985), where the responses reflect factors such as the intensity of the taste, which is little affected by satiety (Rolls et al., 1983d; Rolls and Grabenhorst, 2008). In addition to providing an implementation of sensory-specific satiety (probably by adaptation of the synaptic afferents to orbitofrontal cortex 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, insular visceral cortex, 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, 2014, 2015, 2019e).

### 3.15.5.8 The Neuroeconomics of Food Reward Value in the Orbitofrontal Cortex

The reward value representations in the primate orbitofrontal cortex of taste, olfactory, and flavor stimuli are appropriate for economic decision-making in a number of ways (Rolls, 2014, 2015). First, the responses of orbitofrontal cortex neurons reflect the quality of the commodity or "good" (e.g., the sight or taste of food) multiplied by the amount available (Padoa-Schioppa and Assad, 2006; Padoa-Schioppa, 2011; Padoa-Schioppa and Conen, 2017). In humans, activations in the orbitofrontal cortex reflect the "subjective value" of foods (where "subjective value" in economics refers strictly to what is chosen by a subject rather than to conscious subjective pleasantness (Rolls, 2014, 2015)), measured in a task in which the value is measured by choices between different foods and different amounts of money (Plassmann et al., 2007). Moreover these neurons reflect (in primates; the situation may be different in rodents) the value of reward stimuli, and not actions made to obtain them (Thorpe et al., 1983; Rolls et al., 1990; Verhagen et al., 2003; Padoa-Schioppa and Assad, 2006; Rolls, 2014).

### 3.15.5.9 Representations in the Orbitofrontal Cortex of Reward Value on a Common Scale but Not in a Common Currency

For decision-making, it is important that representations of reward value are on a common scale (so that they can be compared), but are not in a common currency of general reward value, for the specific reward must be represented to guide actions (Rolls, 2014, 2015, 2019e). To investigate whether specific reward representations are on a common scale of reward value, we performed an fMRI study in which we were able to show that even fundamentally different primary rewards, taste in the mouth and warmth on the hand, produced activations in the human orbitofrontal cortex that were scaled to the same range (Grabenhorst et al., 2010b). Further fMRI studies are consistent with this (Levy and Glimcher, 2012). These reward value representations in the orbitofrontal cortex are thus in a form suitable for making decisions about whether to for example choose and eat a particular food, with the decision-making mechanisms now starting to be understood (Rolls and Deco, 2010; Rolls et al., 2010a,b,c; Grabenhorst and Rolls, 2011; Rolls, 2014, 2015, 2016c).

## 3.15.6 The Amygdala

The amygdala is a structure in the temporal lobe with somewhat similar connections to the orbitofrontal cortex (see Fig. 1). The amygdala has been present in evolution for much longer than the primate orbitofrontal cortex, and appears to differ from the orbitofrontal cortex in that it cannot implement one-trial, rule-based, visual discrimination reversal when the taste or flavor associated with the visual stimulus is reversed (Rolls, 2014). The primate amygdala contains neurons that respond to taste and oral texture (Sanghera et al., 1979; Scott et al., 1993; Kadohisa et al., 2005a,b). Some neurons respond to visual stimuli associated with reinforcers such as taste, but do not reflect the reinforcing properties very specifically, do not rapidly learn and reverse visual-to-taste associations, and are much less affected by reward devaluation by feeding to satiety than are orbitofrontal cortex neurons (Sanghera et al., 1979; Yan and Scott, 1996; Kadohisa et al., 2005a,b; Wilson and Rolls, 2005; Rolls, 2014). The primate orbitofrontal cortex appears to be much more closely involved in flexible (rapidly learned, and affected by reward devaluation) reward representations than is the primate amygdala (Rolls, 2014).

Fat texture, oral viscosity, and temperature, for some neurons in combination with taste, and also the sight and smell of food, are represented in the macaque amygdala (Rolls and Scott, 2003; Kadohisa et al., 2005a,b). Interestingly, the responses of these amygdala neurons do not correlate well with the preferences of the macaques for the oral stimuli (Kadohisa et al., 2005b), and feeding to satiety does not produce the large reduction in the responses of amygdala neurons to food (Yan and Scott, 1996; Rolls and Scott, 2003) that is typical of orbitofrontal cortex neurons.

We found activation of the human amygdala by the taste of glucose (Francis et al., 1999). 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, 2002) also showed that the human amygdala responds to aversive (e.g., quinine) and to sucrose taste stimuli.

Rolls (2014, 2019e) has compared and contrasted the functions of the orbitofrontal cortex and the amygdala.

### 3.15.7 The Anterior Cingulate Cortex: A Tertiary Taste Cortical Area

The orbitofrontal cortex, including the extensive areas where taste neurons noted above are found, projects to the pregenual cingulate cortex area 32 (Carmichael and Price, 1996) (see Figs. 1 and 2). In human imaging studies it has been shown that reward-related stimuli, such as the taste of sucrose and the texture of oral fat, activate the pregenual cingulate cortex (de Araujo and Rolls, 2004; Rolls and Grabenhorst, 2008; Rolls, 2009b; Grabenhorst and Rolls, 2011). In recordings made in the primate pregenual cingulate cortex, we (Rolls, Gabbott, Verhagen and Kadohisa) (Rolls, 2008b) showed that neurons can respond to taste and related food texture stimuli such as glucose, fruit juice and cream, to monosodium glutamate, and to quinine, and that such neurons show a sensory-specific decrease in the response to the taste of glucose after feeding to satiety with glucose (Rolls, 2008b). Our hypothesis is that the outcomes, the rewards and punishers, are represented in the anterior cingulate cortex because it is involved in action-outcome learning (Rolls, 2008b, 2009b; Grabenhorst and Rolls, 2011; Rushworth et al., 2011; Rolls, 2014, 2019e,f,d).

### 3.15.8 Hypothalamus

The orbitofrontal cortex and amygdala project to the hypothalamus, which is implicated in the control of food intake (Rolls, 2014). The primate lateral hypothalamus contains taste-responsive neurons, which only respond to food when hunger is present, and indeed reflect sensory-specific satiety (Rolls, 1981; Rolls et al., 1986). The lateral hypothalamus also contains neurons that respond to the sight of food, and they also only respond to food when hunger is present, that is, when the food is rewarding (Burton et al., 1976; Mora et al., 1976; Rolls et al., 1976, 1979, 1986; Rolls, 1981, 2014). The traditional view of the hypothalamus is that it integrates many of the hormonal and nutritional signals that control appetite (Suzuki et al., 2010; Woods, 2013; Morton et al., 2014) (see section "The Amygdala"), but this neurophysiological evidence shows that the hypothalamus is also involved in the reward signals from taste, olfaction, and vision that need to be interfaced to hunger and satiety signals (Rolls, 2014).

### 3.15.9 Striatum

The primate ventral striatum and adjoining part of the head of the caudate nucleus receive connections from the orbitofrontal cortex and amygdala (Haber and Knutson, 2010; Rolls, 2014). Consistent with this, some neurons in these striatal regions respond to the taste, flavor, and/or sight of food (Rolls et al., 1983; Williams et al., 1993; Rolls, 2014; Strait et al., 2015).

These taste and related inputs to the basal ganglia may be involved in stimulus-response habit formation, with the taste and other reinforcers helping to stamp in the connections between environmental stimuli and behavioral responses that co-occur just prior to receiving a reinforcer such as the taste, flavor, or sight of food (Rolls, 2014). Perhaps as part of this functionality, incentive stimuli such as the food can have effects on behavior that are mediated through the striatum (Everitt and Robbins, 2013; Smith and Robbins, 2013). The hypothesis that there is less D2 receptor binding in the dorsal striatum of the obese and that this system contributes to human obesity (Volkow et al., 2013) has been questioned (Cosgrove et al., 2015). There are smaller BOLD responses in the dorsal striatum to palatable food with increasing body mass index, with the reduced striatal response being interpreted as a consequence of the reduced incentive value of food in the overweight. There is in contrast a positive relation of D2/D3 receptor binding to body mass index, and this is not associated with the change in the BOLD response (Cosgrove et al., 2015).

The striatum receives a dopaminergic input that it has been suggested is a positive reward prediction error signal (Schultz, 2013), though there may be too much diversity in the activity of dopamine neurons for this to apply in a simple way (Bromberg-Martin et al., 2010; Rolls, 2014). Moreover, there is no evidence that the dopamine neurons encode a specific reward signal (for example for the taste of food vs the texture of fat) in the way that is required to account for the control of goal-directed rewarded behavior and that is present in the primate orbitofrontal cortex (Rolls, 2014). Further, the activity of ventral striatal neurons appears to be more influenced by orbitofrontal cortex types of signal rather than by positive reward prediction error signals (Strait et al., 2015). The role of the striatum and of dopamine in the control of behavior is considered in more detail elsewhere (Rolls, 2014).

### 3.15.10 Further Imaging Studies on Reward Value Representations of Taste, Smell, and Flavor in Humans

#### 3.15.10.1 Top-Down Cognitive Effects on Taste, Olfactory, and Flavor Processing

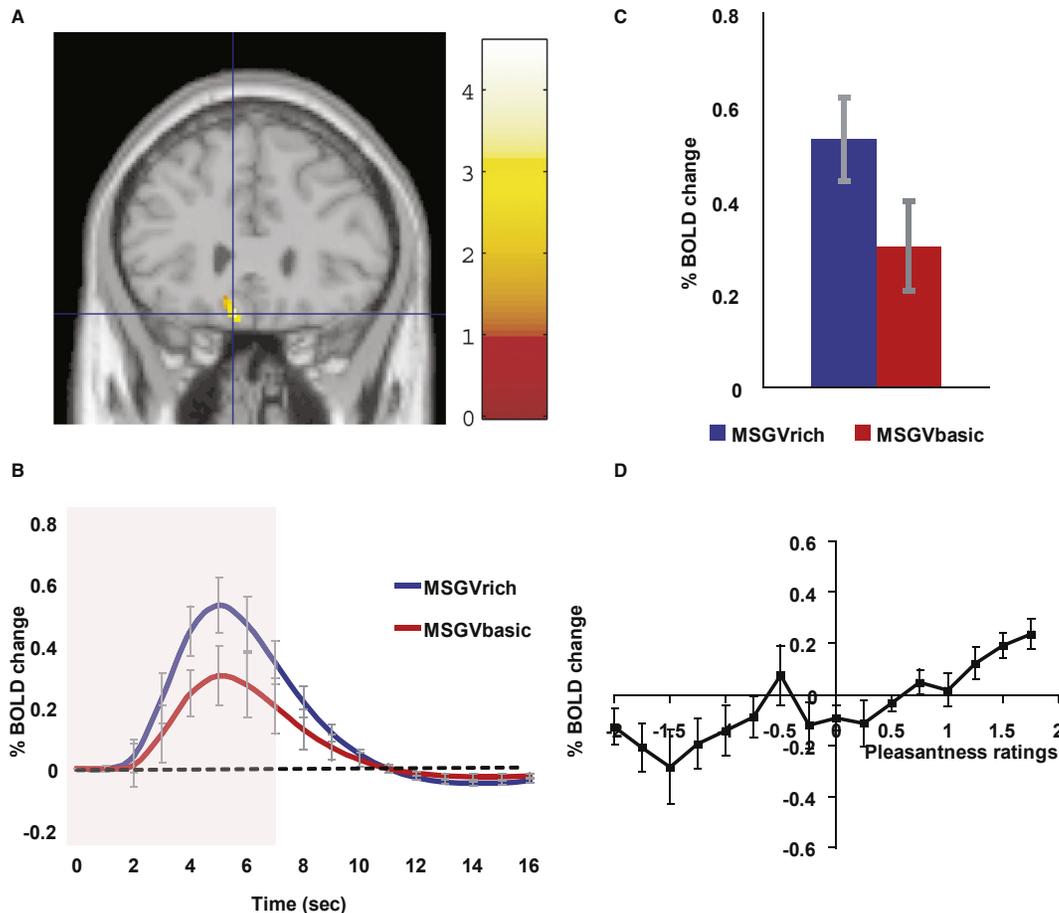
To what extent does cognition influence the hedonics of food-related stimuli, and how far down into the sensory system does the cognitive influence reach? We measured the activation to a standard test odor (isovaleric acid combined with cheddar cheese odor, presented

orthonasally using an olfactometer) that 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 standard test odor, isovaleric acid, as significantly more pleasant when labeled “Cheddar Cheese” than when labeled “Body odor”, and these effects reflected activations in the medial orbitofrontal cortex and pregenual cingulate cortex (de Araujo et al., 2005). 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 and hedonic processing (in the orbitofrontal cortex, see Fig. 1), 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, where the cognitive word level descriptor was for example “rich delicious flavor” and activations to flavor were increased in the orbitofrontal cortex and regions to which it projects including the pregenual cingulate cortex and ventral striatum, but were not influenced in the insular primary taste cortex where activations reflected the intensity (concentration) of the stimuli (Grabenhorst et al., 2008b) (see Fig. 7). Cognitive factors can also influence the release of the hunger-related hormone ghrelin (Crum et al., 2011). If self control of reward-related processing is required, the dorsolateral prefrontal cortex may be involved in the attentional and related aspects of the processing (Hare et al., 2009; Rolls, 2014).

### 3.15.10.2 Effects of Top-Down Selective Attention to Affective Value Versus Intensity on Representations of Taste, Olfactory, and Flavor Processing

We have found that with taste, flavor, and olfactory food-related stimuli, selective attention to pleasantness modulates representations in the orbitofrontal cortex, whereas selective attention to intensity modulates activations in areas such as the primary taste cortex (see Fig. 3) (Grabenhorst and Rolls, 2008, 2010; Rolls et al., 2008; Ge et al., 2012; Luo et al., 2013; Rolls, 2013).



**Figure 7** Cognitive modulation of flavor reward processing in the brain. (A) The medial orbitofrontal cortex was more strongly activated when a flavor stimulus was labeled “rich and delicious flavor” (MSGVrich) than when it was labeled “boiled vegetable water” (MSGVbasic) [−8 28 −20]. (The flavor stimulus, MSGV, was the taste 0.1 M MSG + 0.005 M inosine 5′monophosphate combined with a consonant 0.4% vegetable odor). (B) The timecourse of the BOLD signals for the two conditions. (C) The peak values of the BOLD signal (mean across subjects  $\pm$  sem) were significantly different ( $t = 3.06$ ,  $df = 11$ ,  $p = 0.01$ ). (D) The BOLD signal in the medial orbitofrontal cortex was correlated with the subjective pleasantness ratings of taste and flavor, as shown by the SPM analysis, and as illustrated (mean across subjects  $\pm$  sem,  $r = 0.86$ ,  $p < 0.001$ ). After Grabenhorst et al., 2008b.

This differential biasing of brain regions engaged in processing a sensory stimulus depending on whether the cognitive demand is for affect-related vs more sensory-related processing may be an important aspect of cognition and attention which have implications for how strongly the reward system is driven by food, and thus for eating and the control of appetite (Grabenhorst and Rolls, 2008, 2011; Rolls et al., 2008; Rolls, 2012a, 2014). The top-down modulations of processing have many implications for investigations of taste, olfactory, and other sensory processing, and for the development of new food products.

### 3.15.10.3 Individual Differences in the Flavor Reward System

An important hypothesis is that different humans may have reward systems that differ in how strongly their reward systems are activated, driven by the sensory and cognitive factors that make taste, olfactory, and flavor stimuli attractive. In a test of this, we showed that activations to the sight and flavor of chocolate in the orbitofrontal and pregenual cingulate cortex were much higher in chocolate cravers than non-cravers (Rolls and McCabe, 2007), though there were no differences at the level of the insular taste cortex. This provides evidence that differences in specific reward systems, and not necessarily in earlier sensory processing, can lead to individual differences in behavior to taste, olfactory, and flavor stimuli. This is consistent with the hypothesis that part of the way in which evolution results in effective specific reward systems is by utilizing natural variation in these reward systems, and selecting for reward systems that lead to reproductive success (Rolls, 2014). This concept that individual differences in responsiveness to food reward are reflected in brain activations in regions related to the control food intake (Beaver et al., 2006; Rolls and McCabe, 2007) may provide a way for understanding and helping to control food intake and obesity (Rolls, 2012a, 2014).

### 3.15.10.4 Age-Related Differences in Food Flavor Reward Representations

There are age-related differences in the acceptability of different foods. For example children may not take readily to a wide range of vegetables, yet find sweet foods palatable (Birch, 1999; Hetherington et al., 2011). Adults may find a wide range of foods pleasant. As people age, smell and even taste may become less sensitive and this may contribute to the changes in eating that can occur in aging (Jacobson et al., 2010). In an examination of the neural mechanisms underlying these age-related differences in the acceptability of different flavors and foods with three age groups (21, 41, and 61 years) we found that orange was liked by all age groups, while vegetable juice was disliked by the Young, but liked by the Elderly (Rolls et al., 2015). In the insular primary taste cortex, the activations to these stimuli were similar in the 3 age groups, indicating that the differences in liking for these stimuli between the 3 groups were not represented in this first stage of cortical taste processing. In the supracallosal anterior cingulate cortex, where unpleasant stimuli are represented, there was a greater activation to the vegetable than to the orange stimuli in the Young but not in the Elderly. In the amygdala (and orbitofrontal cortex), where the activations were correlated with the pleasantness of the stimuli, there was a smaller activation to the vegetable than to the orange stimuli in the Young but not in the Elderly. Thus age differences in the activations to different flavors can in some brain areas where olfactory, taste, and flavor stimuli are represented in terms of their hedonic value, be related to, and probably cause, the differences in pleasantness of foods as they differ for people of different ages (Rolls et al., 2015).

### 3.15.10.5 Beyond Reward Value to Decision-Making

Representations of the reward value of food, and their subjective correlate the pleasantness of food, are fundamental in determining appetite and processes such as food-related economic decision-making (Padoa-Schioppa, 2011; Padoa-Schioppa and Cai, 2011; Rolls, 2014). But after the reward evaluation, a decision has to be made about whether to seek for and consume the reward. We are now starting to understand how the brain takes decisions as described in *The Noisy Brain: Stochastic Dynamics as a Principle of Brain Function* (Rolls and Deco, 2010) and *Emotion and Decision-Making Explained* (Rolls, 2014), and this has implications for whether a reward of a particular value will be selected (Rolls, 2008a, 2014; Rolls and Grabenhorst, 2008; Rolls and Deco, 2010; Grabenhorst and Rolls, 2011; Deco et al., 2013).

A tier of processing beyond the orbitofrontal cortex, in the medial prefrontal cortex area 10 (or ventromedial prefrontal cortex), becomes engaged when choices are made between odor stimuli based on their pleasantness (Grabenhorst et al., 2008a; Rolls et al., 2010a,b,c) (tier 3 in Fig. 1). For example, activations in this area are larger when humans make a decision about which of two odors they prefer, compared to only rating the odors on a continuous scale of reward value (Grabenhorst et al., 2008a).

### 3.15.11 Future Developments, and Questions for Future Research

The evidence described here provides a foundation for understanding taste and olfactory processing in humans that is based on neuroimaging in humans, and the much more detailed evidence about what is represented in the brain at each stage of processing that is provided by neuronal recordings in non-human primates (Rolls, 2015, 2016a,b, 2019e). Key issues for future research include the following:

- A. One key issue for future research is the mechanisms by which hunger and satiety signals influence taste, olfactory and flavor processing in the ways described here. Some of the mechanisms are described elsewhere (Rolls, 2016b).

- B. Another key issue is how disorders in these mechanisms, and individual differences in the reward-related processing of taste, olfactory, and flavor stimuli, may contribute to disorders such as obesity (Rolls, 2016b).
- C. Individual differences in impulsivity may be important in overeating, and may reflect less strong inhibition of behavior by reward error/correction systems in the lateral orbitofrontal cortex that restrain behavior (Rolls, 2014, 2019e; Doty, 2015). The influence of this system on eating behavior is of interest, as is how alcohol affecting this system to increase impulsivity (Lopez-Caneda et al., 2014) may increase eating.
- D. To what extent does the explicit, reasoning, system (Rolls, 2014, 2018) provide top-down cognitive and attentional modulation of food reward information processing in the human brain, and to what extent can this influence feeding behavior and obesity?
- E. How are decisions taken about actions such as whether to eat by decision-making systems in the brain based on reward value (Rolls, 2014, 2015, 2019e)?
- F. Many different factors acting separately may contribute to overeating and obesity (Rolls, 2016b). To what extent when *all* of the different factors are taken into account can this help in the control of the amount of food eaten, and the prevention and control of obesity?

When food enters the gastro-intestinal (GI) tract it activates a wide range of gut receptors including gut taste receptors, which stimulate locally the release of peptides such as CCK, PYY, ghrelin and GLP-1 from endocrine cells (Margolskee et al., 2007; Kokrashvili et al., 2009a,b; Depoortere, 2014), which play a crucial role in the regulation of food intake (Hussain and Bloom, 2013; Parker et al., 2014; Price and Bloom, 2014). The gut sensing mechanisms, and their role in conditioned appetite, are reviewed elsewhere (Sclafani, 2013; Ackroff and Sclafani, 2014; Kadohisa, 2015). Many of these studies have been on conditioned preferences produced by food in the GI tract. However, we should note that in these studies, the food entering the gut does not provide the reward signal that humans and animals work for (cf. Han et al., 2018). Placing food into the gut does not act as a reward to promote eating, except in very much larger quantities such as a drop of a sweet taste on the tongue (Nicolaidis and Rowland, 1976, 1977). What gut stimulation by food can do is to act as an unconditioned stimulus that can modulate the reward value produced by the taste of a food such as a sweet taste when hungry.

It will be of interest in future research to analyze in addition how visceral signals can produce conditioned satiety for the flavor with which they are paired. It would be of interest to develop our understanding of conditioned satiety, for this may be relevant to food intake control and its disorders. Disorders of olfactory and taste processing are often found in neurological disease, and it is important to be able to detect and assess these disorders (Wilson et al., 2014; Doty, 2015; Rolls, 2019b). Patients with damage to the orbitofrontal cortex may complain about olfactory or taste disorders, and be less aware of other significant changes in their behavior which it may be important to assess (Rolls, 2019c,e).

## Acknowledgments

This research was supported by the Medical Research Council. The participation of many colleagues in the studies cited is sincerely acknowledged. They include Ivan de Araujo, Gordon Baylis, Leslie Baylis, Hugo Critchley, Paul Gabbott, Fabian Grabenhorst, Mikiko Kadohisa, Michele Kellerhals, Morten Kringelbach, Christian Margot, Ciara McCabe, Francis McGlone, Tom Mills, Tom Nichols, Ian Norton, John O'Doherty, Barbara Rolls, Juliet Rolls, Thomas Scott, Zenon Sienkiewicz, Simon Thorpe, Maria Ines Velasco, Justus Verhagen, and Simon Yaxley.

## Disclosure Statement

The author is not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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