



# Functions of the anterior insula in taste, autonomic, and related functions



Edmund T. Rolls

Oxford Centre for Computational Neuroscience, Oxford, UK

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## ABSTRACT

The anterior insula contains the primary taste cortex, in which neurons in primates respond to different combinations providing a distributed representation of different prototypical tastes, oral texture including fat texture, and oral temperature. These taste neurons do not represent food reward value, in that feeding to satiety does not reduce their responses to zero, in contrast to the next stage of processing, the orbitofrontal cortex, where food reward value is represented. Corresponding results are found with fMRI in humans. A more ventral part of the anterior insula is implicated using fMRI in autonomic-visceral functions. 'Salient' stimuli, including rewarding, punishing, non-rewarding, and novel stimuli may activate this viscer-autonomic system, via inputs received from regions that represent these stimuli such as the orbitofrontal and anterior cingulate cortex. More posteriorly in the insula, there is an oral somatosensory region, and posterior to this somatosensory regions that respond to touch to the body. These taste and somatosensory representations in the insula provide representations that are about the external world (touch), are intermediate (oral taste and texture), and are about internal signals related to visceral and autonomic function. This functionality needs to be taken into account when considering activations of the insula found in cognitive tasks.

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## 1. Introduction

The anterior insular cortex has been described as a region that represents interoception and is associated with all subjective feelings, and also with attention, cognitive choices and intentions, music, time perception and, unmistakably, awareness of sensations and movements, of visual and auditory percepts, of the visual image of the self, of the reliability of sensory images and subjective expectations, and of the trustworthiness of other individuals (Craig, 2002, 2009, 2011). It has also been suggested that the insula plays a key role in saliency, switching, attention, and control (Menon & Uddin, 2010). It has also been suggested that the mid-insula is the location of the human taste cortex (Craig, 2011; Small, 2010).

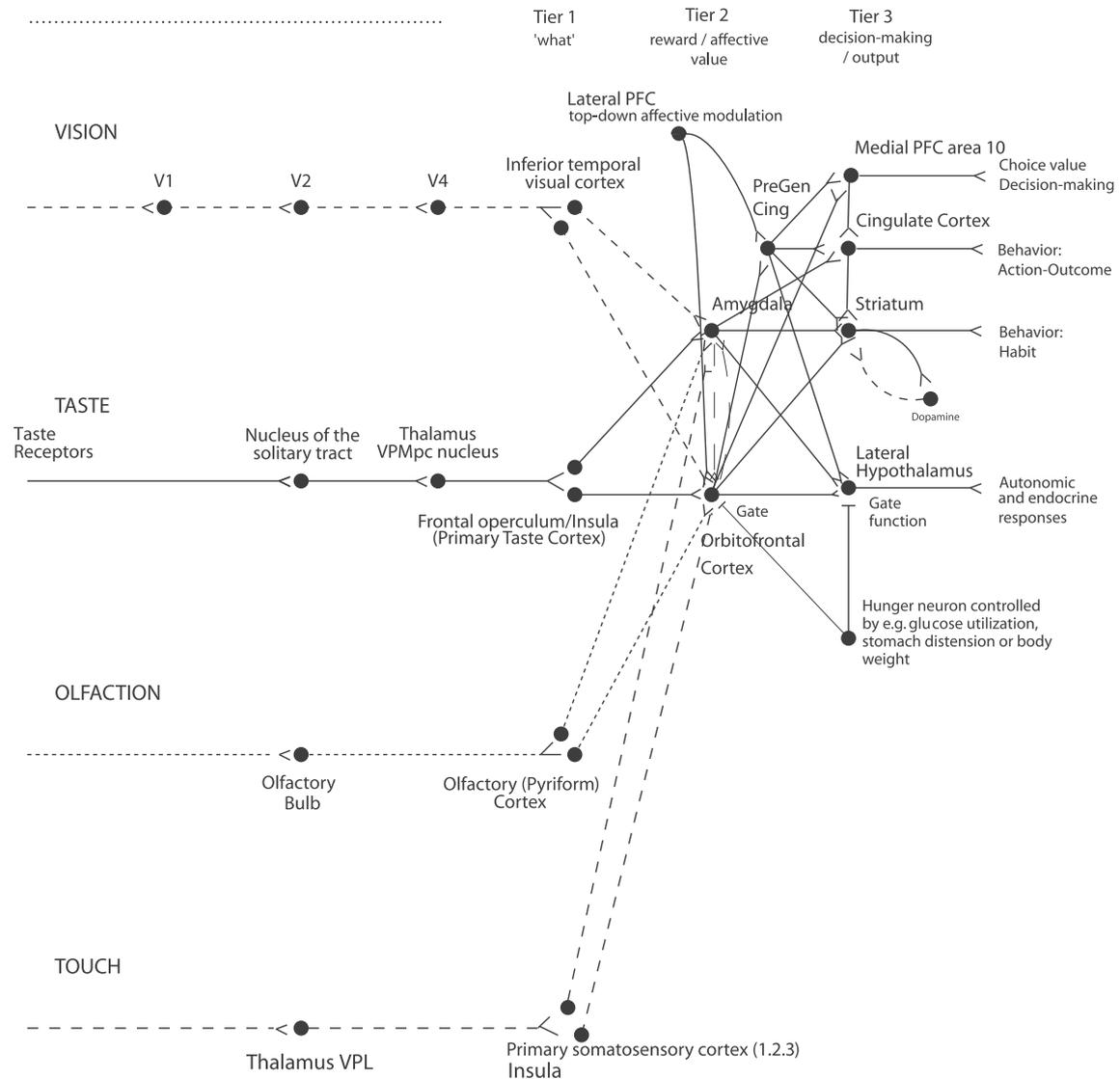
In this paper, evidence on some of the functions of the anterior insular cortex is considered. Part of the focus is on the taste and related viscer-autonomic functions of the anterior insula, for there is considerable evidence on this at the neuronal level in primates, and at the fMRI level in humans. Indeed, the approach taken here is to consider together, side-by-side, the primate neuronal recording and the human functional magnetic resonance imaging

(fMRI) evidence, to build a clear foundation for understanding the processing in this region and the underlying principles in primates including humans. There are a number of differences between rodents and primates including humans in taste and related processing in the insula as follows, which lead to a focus in this paper on processing in primates including humans, with the aim of understanding the principles of operation of the insula in primates including humans.

First, there are major anatomical differences in the neural processing of taste in rodents and primates (Rolls, 2014, 2015c; Rolls & Scott, 2003; Scott & Small, 2009; Small & Scott, 2009). In primates the rostral part of the nucleus of the solitary tract (NTS, the first central taste relay) projects to the taste thalamus and thus to the cortex (Figs. 1 and 2); whereas in rodents the majority of NTS taste neurons project to the pontine parabrachial nucleus (PbN), referred to as the rodent 'pontine taste area' (Cho, Li, & Smith, 2002; Small & Scott, 2009) (Fig. 2). From the PbN the rodent gustatory pathway bifurcates into two pathways: (1) a ventral 'affective' projection to the hypothalamus, central gray, ventral striatum, bed nucleus of the stria terminalis and amygdala; and (2) a dorsal 'sensory' pathway, which first synapses in the thalamus and then the agranular and dysgranular insular gustatory cortex (Norgren, 1974, 1976, 1990; Norgren & Leonard, 1971) (Fig. 2). In

E-mail address: [Edmund.Rolls@oxcns.org](mailto:Edmund.Rolls@oxcns.org)

URL: <http://www.oxcns.org>

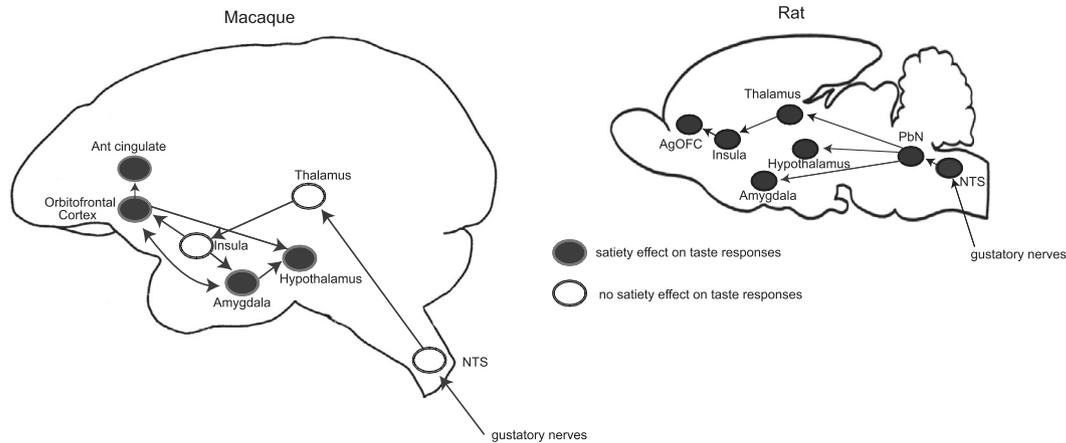


**Fig. 1.** Schematic diagram showing some of the gustatory, olfactory, visual and somatosensory pathways to the orbitofrontal cortex, and some of the outputs of the orbitofrontal cortex, in primates. The secondary taste cortex, and the secondary olfactory cortex, are within the orbitofrontal cortex. V1 – primary visual cortex. V4 – visual cortical area V4. PreGen Cing – pregenual cingulate cortex. “Gate” refers to the finding that inputs such as the taste, smell, and sight of food in some brain regions only produce effects when hunger is present (Rolls, 2014). 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 which are represented in the next tier of brain regions (Tier 2), the orbitofrontal cortex and amygdala, and in the anterior cingulate cortex. In Tier 3 areas beyond these such as medial prefrontal cortex area 10, choices or decisions about reward value are taken (Rolls, 2008b, 2014; Rolls & Deco, 2010). Top-down control of affective response systems by cognition and by selective attention from the dorsolateral prefrontal cortex is also indicated. Medial PFC area 10 – medial prefrontal cortex area 10; VPMpc – ventralposteromedial thalamic nucleus, the thalamic nucleus for taste.

primates (including humans) there is strong evidence to indicate that the PbN gustatory relay is absent (Small & Scott, 2009).

Second, a functional difference of rodent taste processing from that of primates is that physical and chemical signals of satiety have been shown to reduce the taste responsiveness of neurons in the nucleus of the solitary tract, and the pontine taste area, of the rat, with decreases in the order of 30% (Giza, Deems, Vanderweele, & Scott, 1993; Giza & Scott, 1983, 1987; Glenn & Erickson, 1976; Hajnal, Takenouchi, & Norgren, 1999; Rolls & Scott, 2003; Scott & Small, 2009) (Fig. 2). (Given this evidence, as expected, neuronal responses in many areas of the rat brain including the insula and amygdala are decreased by satiety (de Araujo et al., 2006).) The implication of this whole body of evidence is that in rodents, sensory (perceptual) and reward (hedonic) processing are not independent. In contrast, in primates, the reward value of tastants is represented in the orbitofrontal cortex in that the

responses of orbitofrontal cortex taste neurons are modulated by hunger in just the same way as is the reward value or palatability of a taste, and this is not found in the taste insula (Rolls, 2015c). In particular, it has been shown that orbitofrontal cortex taste neurons stop responding to the taste of a food with which a monkey is fed to satiety, and that this parallels the decline in the acceptability of the food (Critchley & Rolls, 1996a; Rolls, Sienkiewicz, & Yaxley, 1989). In contrast, the representation of taste in the primary taste cortex of non-human primates (Scott, Yaxley, Sienkiewicz, & Rolls, 1986a; Yaxley, Rolls, & Sienkiewicz, 1990) is not modulated by hunger (Rolls, Scott, Sienkiewicz, & Yaxley, 1988; Yaxley, Rolls, & Sienkiewicz, 1988). Thus in the primary taste cortex of non-human primates (and at earlier stages of taste processing including the nucleus of the solitary tract (Yaxley, Rolls, Sienkiewicz, & Scott, 1985)), the reward value of taste is not represented, and instead the identity and intensity of the taste



**Fig. 2.** 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 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 (Passingham & Wise, 2012; Rolls, 2014, 2015c; Small & Scott, 2009; Wise, 2008). 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.

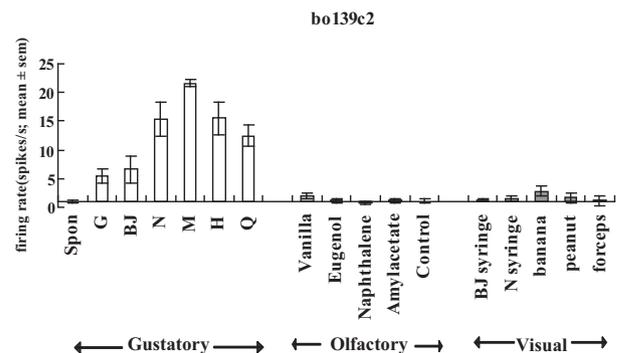
are represented (Rolls, 2014). A perceptual correlate of this is that when humans feed to satiety, the intensity of the flavor changes very little, whereas the pleasantness of the flavor decreases to zero (Rolls, Rolls, & Rowe, 1983), showing that in humans perceptual representations of taste and olfaction 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). Moreover, and consistently, activations in the human insular primary taste cortex are related to the intensity and not to the pleasantness of taste (Grabenhorst & Rolls, 2008; Grabenhorst, Rolls, & Bilderbeck, 2008) (see Figs. 10 and 9).

The importance of cortical processing of taste in primates, first for identity and intensity in the primary taste cortex, and then for reward value in the orbitofrontal cortex, is that both types of representation need to be interfaced to visual and other processing that requires cortical computation. For example, it may have adaptive value to be able to represent exactly what taste is present, and to link it by learning to the sight and location of the source of the taste, even when hunger is not present and reward is not being produced, so that the source of that taste can be found in future, when it may have reward value. In line with cortical processing to dominate the processing of taste in primates, there is no modulation of taste responsiveness at or before the primary taste cortex, and the pathways for taste are directly from the nucleus of the solitary tract in the brainstem to the taste thalamus and then to the taste cortex (Figs. 1 and 2) (Rolls, 2014).

Third, the architectonic division of the rat insula that is involved in taste processing appears to be different from that in primates (Evrard, Logothetis, & Craig, 2014).

Fourth, the prefrontal cortex (and for that matter the temporal lobe visual cortical areas) have also undergone great development in primates, and one part of the prefrontal cortex, the orbitofrontal cortex, is very little developed in rodents, yet is one of the major brain areas involved in taste and olfactory processing, and emotion and motivation, in primates including humans. With this great development of the orbitofrontal cortex in primates, there may

be division of functionality, with the primate taste insula not performing taste-related hedonic functions (Rolls, 2015c). Indeed, it has been argued (on the basis of cytoarchitecture, connections, and functions) that the granular prefrontal cortex is a primate innovation, and the implication of the argument is that any areas that might be termed orbitofrontal cortex in rats (Schoenbaum, Roesch, Stalnaker, & Takahashi, 2009) are homologous only to the agranular parts of the primate orbitofrontal cortex, that is to areas 13a, 14c, and the agranular insular areas Ia (Passingham & Wise, 2012). It follows from that argument that for most areas of the orbitofrontal and medial prefrontal cortex in humans and macaques, special consideration must be given to research in macaques and humans. Indeed, there may be no cortical area in rodents that is homologous to most of the primate including



**Fig. 3.** Responses of an insular taste cortex neuron (bo139c2) with taste responses, to show the lack of response to a range of olfactory and visual stimuli. The mean ( $\pm$  the standard error of the mean, sem) firing rate responses to each stimulus calculated in a 1 s period over 4–6 trials are shown. The spontaneous (Spon) firing rate is shown by the horizontal line. The taste stimuli were 1 M glucose (G), 0.1 M NaCl (N), 0.1 M MSG (M), 0.01 M HCl (H) and 0.001 M QuinineHCl (Q). The visual stimuli were: BJ syringe: the sight of a syringe containing fruit (blackcurrant) juice; N syringe: the sight of a syringe containing 0.1 N NaCl; forceps: control, showing the feeding forceps alone that were used to show and feed banana or peanut.

human orbitofrontal cortex (Passingham & Wise, 2012; Preuss, 1995; Rolls, 2014, 2015c; Wise, 2008).

## 2. Pathways

A diagram of the taste and related olfactory, somatosensory, and visual pathways in primates is shown in Fig. 1. The multimodal convergence that enables single neurons to respond to different combinations of taste, olfactory, texture, temperature, and visual inputs to represent different flavors produced often by new combinations of sensory input is a theme that has been addressed recently, as have the functions of different parts of this system in reward value processing, modulatory effects produced by top-down cognitive descriptors, and decision-making (Rolls, 2015c).

## 3. The anterior insular primary taste cortex

### 3.1. Neuronal responses to taste

Rolls, Scott, and colleagues have shown that the primary taste cortex in the primate anterior insula and adjoining frontal operculum contains not only taste neurons tuned to sweet, salt, bitter, sour (Plata-Salaman, Scott, & Smith-Swintosky, 1992, 1993, 1995, 1996; Rolls & Scott, 2003; Scott, Giza, & Yan, 1998, 1999; Scott & Plata-Salaman, 1999; Scott, Plata-Salaman, Smith, & Giza, 1991; Scott, Plata-Salaman, & Smith-Swintosky, 1994; Scott et al., 1986a; Smith-Swintosky, Plata-Salaman, & Scott, 1991; Yaxley et al., 1990), and umami as exemplified by monosodium glutamate (Baylis & Rolls, 1991; Rolls, Critchley, Wakeman, & Mason, 1996), but also other neurons that encode oral somatosensory stimuli including viscosity, fat texture, temperature, and capsaicin (Verhagen, Kadohisa, & Rolls, 2004). The responses of an insular taste cortex neuron with significantly different responses to different tastes are illustrated in Fig. 3. This neuron had no significant responses to oral viscosity, fat, or temperature. The neuron also had no significant responses to any of the olfactory and visual stimuli tested (see Fig. 3). None of the insular taste cortex neurons had responses to olfactory stimuli, and none could be shown to have responses to visual stimuli that were clearly not just related to mouth movements and the accompanying somatosensory input (Verhagen et al., 2004), in contrast to the orbitofrontal cortex where responses to olfactory and visual stimuli associated with food are common (Critchley & Rolls, 1996a, 1996b; Rolls, 2015c; Rolls, Critchley, Mason, & Wakeman, 1996; Rolls, Critchley, & Treves, 1996; Rolls, Critchley, Verhagen, & Kadohisa, 2010; Thorpe, Rolls, & Maddison, 1983). Water can activate some neurons in cortical taste areas (Rolls, Yaxley, & Sienkiewicz, 1990; Yaxley et al., 1990), and this has also been found in the rodent insula (MacDonald, Meck, & Simon, 2012). Whether this is by mouthfeel relative to saliva, or by ionic content relative to saliva, or by some other mechanism, is not known.

Neurons in the macaque 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) (Fig. 4). This was confirmed in 17 separate experiments on neurons in the insular and frontal opercular primary taste cortex, using anatomical confirmation that these neurons were in the primary taste cortex by the use of X-ray localization and then histological reconstruction. The neurons showed no reduction in their firing to the taste (typically glucose) after it had been fed to satiety (Rolls et al., 1988; Yaxley et al., 1988).

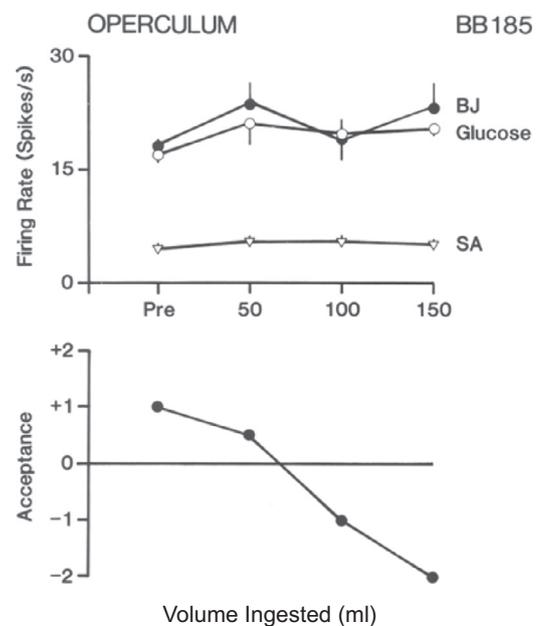
In macaques, neural processing peripheral to the primary taste cortex is consistent with this, with taste responses found in the

rostral part of the nucleus of the solitary tract (Scott, Yaxley, Sienkiewicz, & Rolls, 1986b) that are not influenced by feeding to satiety (Yaxley et al., 1985), and also taste-responsive neurons in the taste nucleus of the thalamus, VPMpc (Pritchard, Hamilton, & Norgren, 1989) (which projects to the primary taste cortex in the anterior insula (Pritchard, Hamilton, Morse, & Norgren, 1986)).

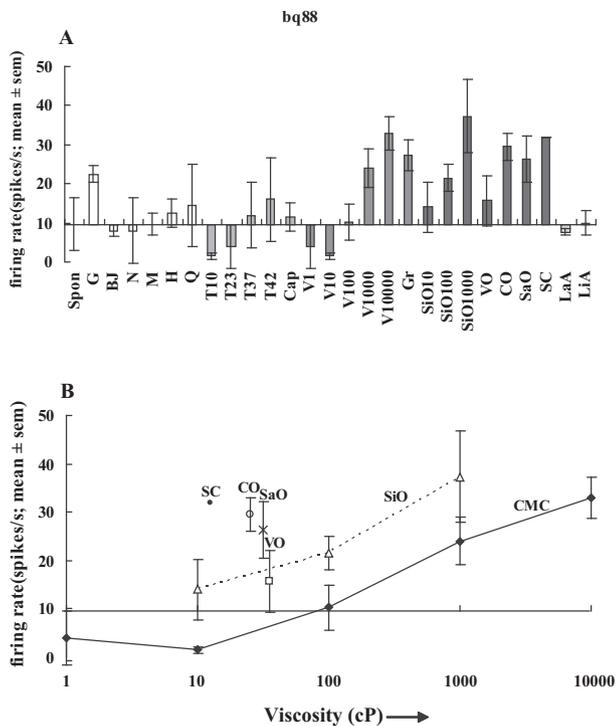
### 3.2. Neuronal responses to oral (food) texture and temperature

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

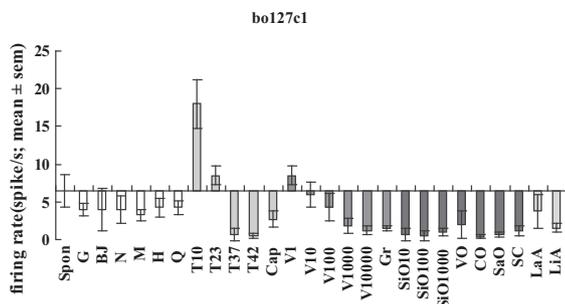
Fig. 5 shows a neuron (bq88) that responded more to the set of oils than to the members of the viscosity series. Indeed, the response to the 10, 100, and 1000 cP oils was greater than to the corresponding carboxymethylcellulose (CMC) viscosity stimuli. (Within the CMC viscosity series, there were significant differences to the different viscosities, and this neuron was classified as being fat-responsive, but also as being influenced by the CMC viscosity stimuli. CMC is a non-fat food thickening agent.) The neuron did respond to single cream (SC, 18% fat, viscosity: 12 cP), a fat in water emulsion. Interestingly, the neuron did not respond to the fatty acids lauric acid (LaA) and linoleic acid (LiA), indicating that the responses to fat were based on its texture, and not on any fatty acids that might possibly be present if fat is lipolysed at all in the mouth by any salivary lipase that might be present (Rolls, 2015c; Verhagen et al., 2004). Further evidence that the neuronal response was not based on fatty acids is that the neuron responded to the silicone oils (which contain no fat or fatty acids, but have a similar texture to the fatty oils such as vegetable oil, coconut oil (CO), and safflower oil (SaO)) (Rolls, 2015c; Verhagen et al., 2004).



**Fig. 4.** No effect of feeding to satiety with glucose solution on the responses (firing rate  $\pm$  s.e.m.) of a neuron in the primary taste cortex in the insular/frontal opercular area to the taste of glucose (open circles) and of blackcurrant fruit 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. (After (Yaxley et al., 1988) and (Rolls et al., 1988).)



**Fig. 5.** A. Responses of an insular taste cortex neuron (bq88) with larger responses to fatty oils and other oils than to a viscosity stimulus carboxymethyl cellulose. The mean ( $\pm$ the standard error of the mean, sem) firing rate responses to each stimulus calculated in a 1 s period over 4–6 trials are shown here and elsewhere unless otherwise indicated. The spontaneous (Spon) firing rate is shown by the horizontal line. The taste stimuli were 1 M glucose (G), 0.1 M NaCl (N), 0.1 M MSG (M), 0.01 M HCl (H) and 0.001 M QuinineHCl (Q); the temperature stimuli were T10, T23, T37 and T42 where the number indicates the temperature in  $^{\circ}$ C; the viscosity stimuli were V1, V10, V100, V1000 and V10000 where the numeral indicates the viscosity in cP at 23  $^{\circ}$ C; fat texture stimuli were SiO10, SiO100, SiO1000 (silicone oil with the viscosity indicated), vegetable oil (VO), coconut oil (CO) and safflower oil (SaO). BJ is fruit (blackcurrant) juice; Cap is 10  $\mu$ M capsaicin; LaA is 0.1 mM lauric acid; LiA is 0.1 mM linoleic acid; Gr is a gritty stimulus. B. The firing rate ( $\pm$ sem) to different viscosities of carboxymethylcellulose (CMC) shown as a graph, with the responses to the oils shown at their viscosity. The horizontal line shows the spontaneous activity ( $\pm$ sem). (After Verhagen et al., 2004.)



**Fig. 6.** The responses of an insular taste cortex neuron responding primarily to an oral stimulus with a temperature of 10  $^{\circ}$ C (T10, cold). Conventions as in Fig. 5.

Fig. 6 shows a neuron with differential responses to different temperatures. The neuron responded primarily to the 10  $^{\circ}$ C stimulus (T10, cold) from the temperature series, with a small decrease of firing rate to 37  $^{\circ}$ C (T37, body temperature) and 42  $^{\circ}$ C (T42, warm) (this decrease being a response produced by many of the oral stimuli). The neuron did have a differential response to the set of taste stimuli (which included water, V1 = T23, to which the neuron had a small increase of firing rate). This neuron also had a differentially decreasing response as a function of viscosity (Verhagen et al., 2004).

Of the orally responsive neurons, some (53%) represented the viscosity, tested using carboxymethyl-cellulose in the range 1–10,000 cP. Other neurons (8%) responded to fat in the mouth by encoding its texture (as shown by similar neuronal responses to non-fat oils), and 8% responded to gritty texture. Some neurons (35%) responded to the temperature of the liquid in the mouth. Some neurons responded to capsaicin, and others to fatty acids. Some neurons (56%) had taste responses. Some (50%) of these neurons were unimodal, responding to one of these types of stimulus, and the others combined responsiveness to these types of stimulus, with 23% responding for example to both taste and temperature (Verhagen et al., 2004). None of these orally responsive neurons responded to odor or to the sight of food.

Some of these types of information may be transmitted to the insular taste cortex via the taste nerves and taste thalamus, for there is some evidence that some taste fibers in rodents may respond to trigeminal (somatosensory) stimuli (S. Simon, Duke University, personal communication, 2014). The insular taste cortex provides a route for this information to reach the orbitofrontal cortex and amygdala.

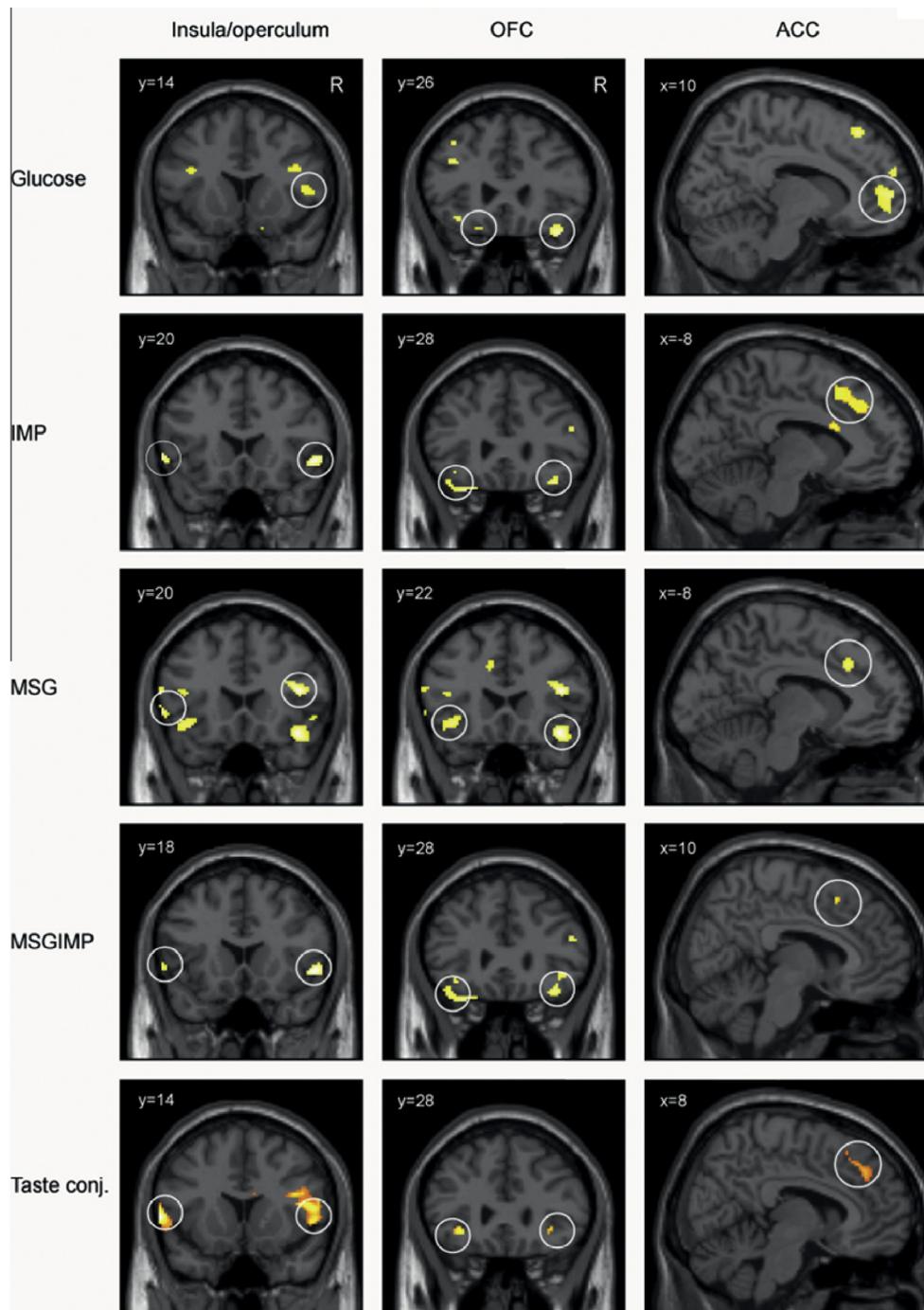
The location of the insular/opercular taste cortex is in the dorsal one third of the anterior part of the macaque insula and adjoining frontal operculum, as shown by the histologically reconstructed recording sites of these taste neurons (Kadohisa, Rolls, & Verhagen, 2005; Rolls et al., 1988; Scott et al., 1986a; Verhagen et al., 2004; Yaxley et al., 1988, 1990). This is the primary taste cortex, in that this region receives from the thalamic taste nucleus (VPMpc) (Pritchard et al., 1986). Moreover, this insular/opercular region projects heavily to orbitofrontal cortex regions in which taste neurons are recorded as shown by retrograde anatomical labelling (Baylis, Rolls, & Baylis, 1995), thereby defining the orbitofrontal cortex as a secondary taste cortical region. Very interestingly, neurons in the anterior insula that were ventral to the insular taste cortex also projected directly to the same orbitofrontal cortex taste area, and this more ventral anterior insular cortex is probably visceral cortex, given the evidence from rats for visceral/autonomic connections of the anterior insula (Allen, Saper, Hurley, & Cechetto, 1991), and also from humans that is described in Section 4. Consistent with this, food-related taste (Rolls et al., 1989), visual, and olfactory neurons (Critchley & Rolls, 1996a) in the orbitofrontal cortex have their responses modulated down to zero after feeding to satiety, which is only achieved in the presence of signals from the viscera (Gibbs, Maddison, & Rolls, 1981).

This evidence provided by the responses of single neurons is essential for providing information about exactly what is represented, and how it is represented, in a cortical area, and these investigations in macaques thus provide an important complement to evidence from functional neuroimaging in humans (Rolls, 2016).

### 3.3. Activations of the insular taste cortex in humans

#### 3.3.1. Taste stimuli

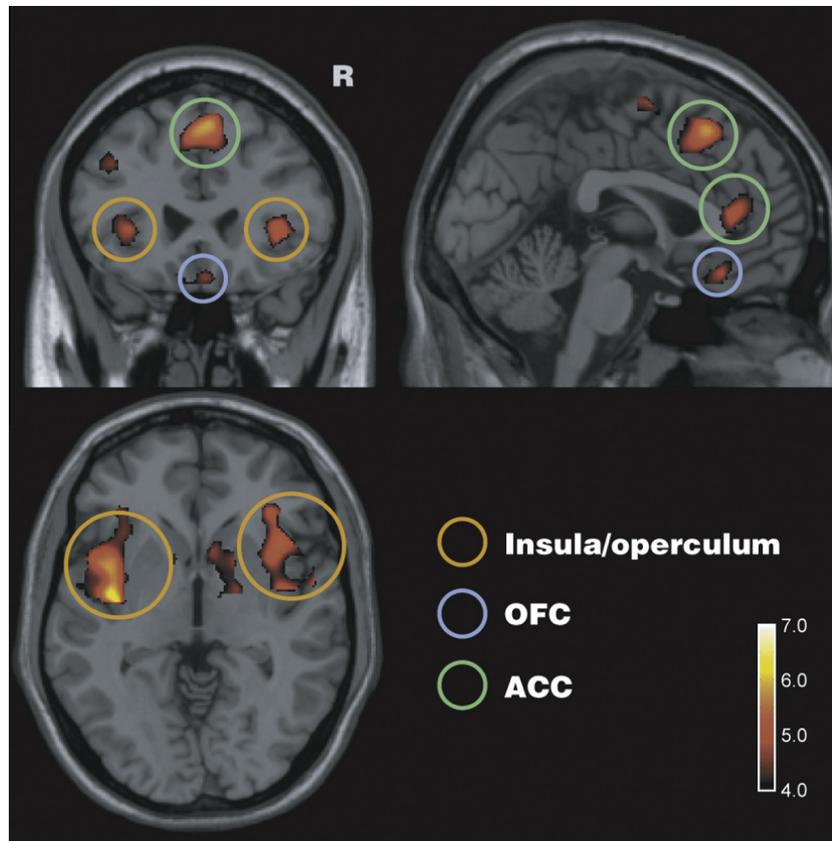
In humans it has been shown in neuroimaging studies using functional Magnetic Resonance Imaging (fMRI) that taste activates an area of the anterior insula/frontal operculum, which is probably the primary taste cortex (de Araujo, Kringelbach, Rolls, & McGlone, 2003; O'Doherty, Rolls, Francis, Bowtell, & McGlone, 2001; Small, 2010; Small et al., 1999). This is generally found at MNI coordinates between  $Y = 10$  and  $Y = 20$ . This is illustrated in Fig. 7 (de Araujo, Kringelbach, Rolls, & Hobden, 2003), which also illustrates activations to taste stimuli in the orbitofrontal cortex, which is probably the secondary taste cortex (de Araujo, Kringelbach, Rolls, & McGlone, 2003; Francis et al., 1999; O'Doherty et al., 2001; Rolls, 2005, 2008a). As illustrated in Fig. 7, this orbitofrontal cortex taste region is just anterior to the primary taste cortex in the anterior insula. Fig. 7 also illustrates activation of the anterior



**Fig. 7.** Activation of the human primary taste cortex in the insula/frontal operculum; the orbitofrontal cortex (OFC); and the anterior cingulate cortex (ACC) by taste. Coronal slices are shown. The stimuli used included glucose, two umami taste stimuli (monosodium glutamate (MSG) and inosine monophosphate (IMP)), and a mixture of the two umami stimuli. Taste conj. Refers to a conjunction analysis over all the taste stimuli. (Reproduced from [de Araujo, Kringelbach, Rolls, & Hobden, 2003](#).)

cingulate cortex to taste, with the pleasant taste of glucose activating the pregenual cingulate cortex, and the less pleasant taste of monosodium glutamate activating a more dorsal part of the anterior cingulate cortex ([de Araujo, Kringelbach, Rolls, & Hobden, 2003](#)), consistent with the hedonic map found in this region ([Grabenhorst & Rolls, 2011](#)). We pioneered the use of a tasteless control with the same ionic constituents as saliva ([de Araujo, Kringelbach, Rolls, & McGlone, 2003](#); [O'Doherty et al., 2001](#)), as water can activate some neurons in cortical taste areas ([Rolls et al., 1990](#); [Yaxley et al., 1990](#)) and can activate the taste cortex ([de Araujo, Kringelbach, Rolls, & McGlone, 2003](#)). The use of a

tasteless control solution, and of a pure taste stimulus (sweet, salt, bitter, sour, umami) with no olfactory or texture component, is essential when defining a cortical taste areas. (Stimuli such as fruit juice or chocolate may be useful for other purposes, but should not be relied on as stimuli to identify taste cortical areas.) Indeed, consistent with this, water – a tasteless control activates the anterior taste cortex ( $Y = 22$ ) in a region activated by a prototypical tastant glucose ([de Araujo, Kringelbach, Rolls, & McGlone, 2003](#)) (see [Fig. 8](#)). Interestingly, satiation with water did not reduce the activation to water in the mouth in the anterior insular taste cortex ([de Araujo, Kringelbach, Rolls, & McGlone, 2003](#)). The findings



**Fig. 8.** Areas activated by water in the mouth. Conjunction analysis revealing the main effects of taste across the comparisons (water-control) AND (glucose-control) AND (salt-control). Significant activations were found in the insular, opercular, anterior cingulate and orbitofrontal cortices. This shows that water in the mouth minus a tasteless control activated the same taste areas activated by the taste of glucose and the taste of salt. (After de Araujo, Kringelbach, Rolls, & McGlone, 2003.)

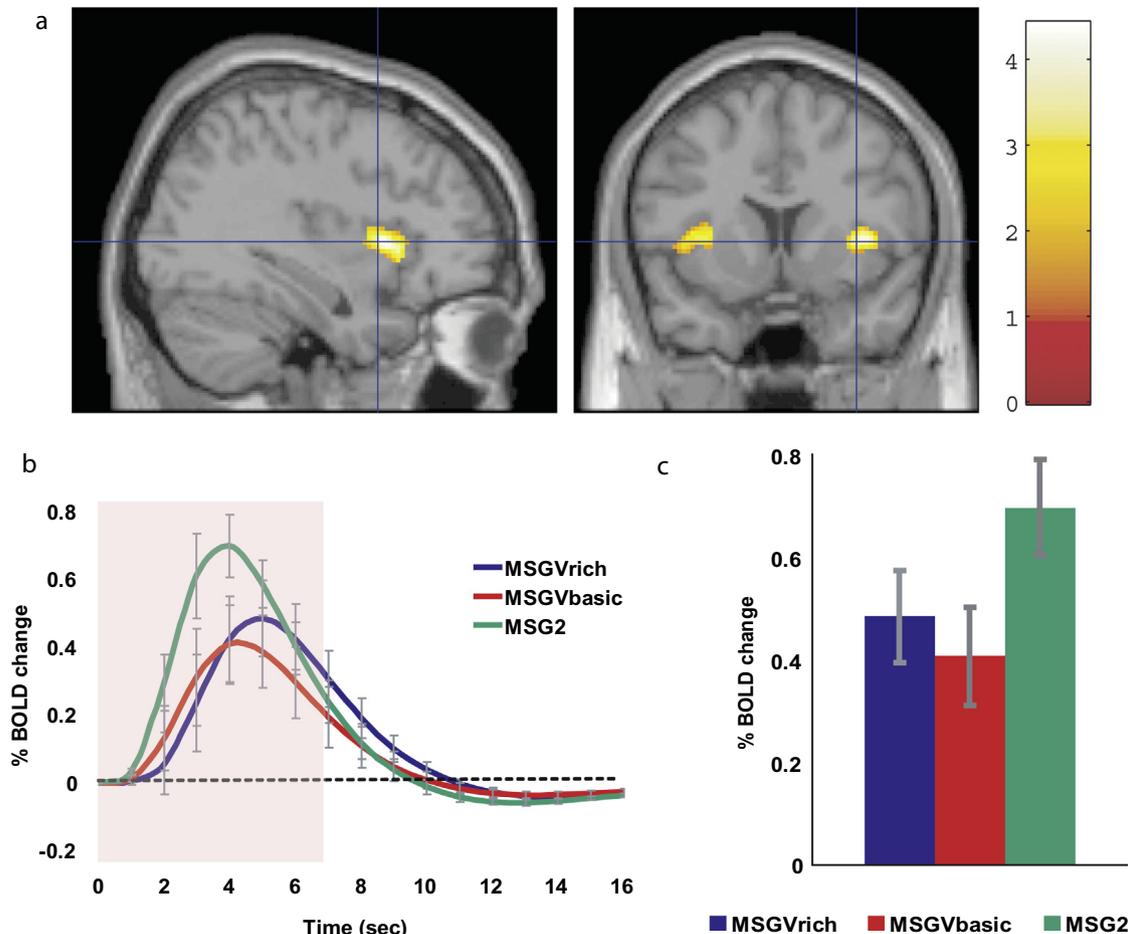
indicate strongly that water is not an appropriate control for taste-related activations in the taste cortex as taste-related activations might well be missed, and that a tasteless solution should be used as a control comparison condition. Another study which identified the taste cortex in the anterior insula using a rigorous conjunction of 0.1 M MSG with two different cognitive labels vs a tasteless control produced activations with a peak at [34164] (Fig. 9a) (Grabenhorst et al., 2008). Moreover, cognitive labels describing the 0.1 M MSG with vegetable flavor added on different trials as 'rich and delicious flavor' (MSGVrich) or 'boiled vegetable water' (MSGVbasic) did not produce significantly different activations in this insular taste cortex, but a higher concentration of MSG, 0.4 M, did produce a larger activation, showing that the insular taste cortex does reflect the concentration of a tastant, but not the effects of cognitive labels which alter its pleasantness (Fig. 9b and c) (Grabenhorst et al., 2008).

There is also some evidence for activation by prototypical taste stimuli more posteriorly, in a mid-insular region. For example, O'Doherty et al. (2001) found activation in a region at  $Y = 2$  to glucose and  $Y = -3$  to salt taste stimuli. The two separate activations for the anterior and mid-insular regions are illustrated in their Figs. 3 and 4. Grabenhorst and Rolls (2008) using the pure taste stimulus monosodium glutamate also found activation in both the anterior taste insula at  $Y = 18$ , and in a mid-insular region at  $Y = -2$ , with both sites illustrated in Fig. 10. Water in the mouth can also activate a mid-insular/opercular region ( $Y = -2$ ) [-60 -218], and in this region satiation with water did reduce activation to water in the mouth, which might be interpreted as something related to mouthfeel (de Araujo, Kringelbach, Rolls, & McGlone, 2003). (The mouth does feel dry after water deprivation (Rolls et al., 1980).) Small (2010) also described evidence for

activation in a mid-insular region, but care must be taken in the interpretation because some of the studies cited did not use prototypical taste stimuli (but instead complex stimuli with olfactory and texture components such as chocolate), and did not use a tasteless control.

### 3.3.2. Oral texture and temperature

In the insular cortex posterior to the taste cortex in the anterior insula, there is a somatosensory representation of oral texture (de Araujo & Rolls, 2004). 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 represents oral somatosensory stimuli (de Araujo & 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 & 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 (Grabenhorst, Rolls, Parris, & D'Souza, 2010; Rolls, 2009b, 2010b) (Fig. 11). 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, 2012). 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 & Rolls, 2014). On the other hand, activations in a frontal opercular/insular region at  $Y = 12$  and  $Y = 18$  (and in an agranular (far anterior) insular



**Fig. 9.** Insular taste cortex. a. A conjunction analysis of the activations produced by the taste of MSG with two different cognitive labels shows the location of the insular primary taste cortex [34 164]. Subtraction of the tasteless control was performed. b. The timecourse of the BOLD signals for the conditions with cognitive labels describing the 0.1 M MSG with vegetable flavor added on different trials as 'rich and delicious flavor' (MSGVrich) or 'boiled vegetable water' (MSGVbasic) did not produce significantly different activations in this insular taste cortex, but a higher concentration of MSG, 0.4 M, did produce a larger activation, showing that the insular taste cortex does reflect the concentration of a tastant, but not the effects of cognitive labels which alter its pleasantness. c. The peak values of the BOLD signal (mean across subjects  $\pm$  sem) were not different in this region for the flavor stimulus under the different labels (MSGVrich vs MSGVbasic), but the effect of the more concentrated solution of 0.4 M MSG (MSG2) was significantly larger. (From Grabenhorst et al., 2008.)

region at  $Y = 24$ ), are activated in relation to the unpleasantness of fat texture and flavor (Fig. 11) (Grabenhorst et al., 2010), providing further evidence that some oral stimuli with an unpleasant mouth feel can activate this frontal opercular region. Further evidence for this is that in young participants (22 years), who rate vegetable juice (V8) as unpleasant, a similar frontal opercular activation is produced by this stimulus, and not by orange juice (Rolls, Kellerhals, & Nichols, 2015).

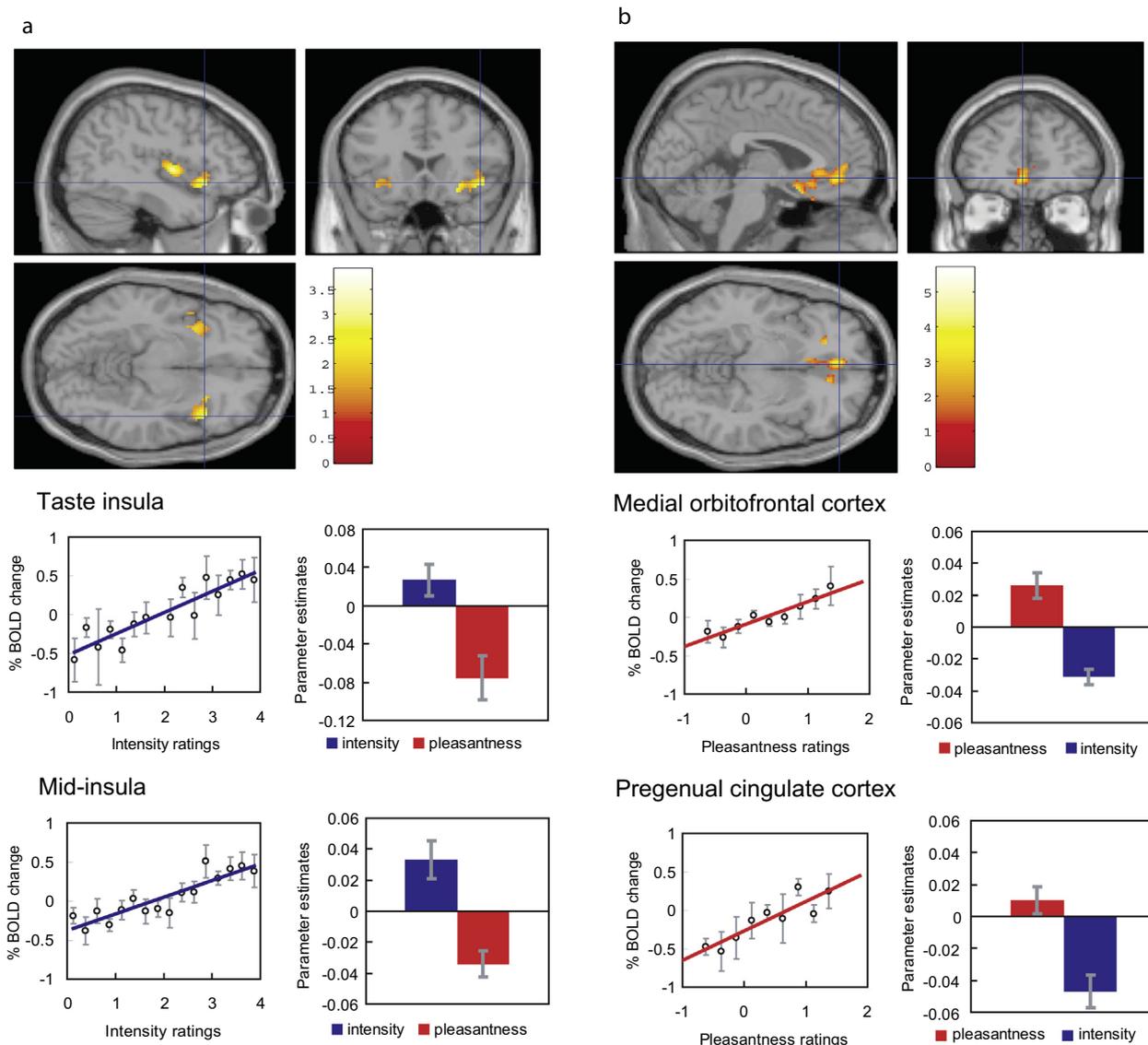
The human insular taste cortex is activated by oral temperature, in both the anterior and mid insular cortical regions (Guest et al., 2007).

### 3.3.3. Hedonics and reward value

One point of interest still is whether the human insular taste cortex contains a hedonic representation of taste, with responses to taste decreasing to zero after feeding to natural self-induced satiety. The evidence in macaques is quite clear. In the insular and frontal opercular taste cortex, neuronal responses to the taste fed to satiety do not decrease at all after satiety (Rolls et al., 1988; Yaxley et al., 1988) (Fig. 4). In contrast, in the macaque orbitofrontal cortex throughout its mediolateral extent, almost all neurons show a decrease to zero of the response to taste, that is, the neurons do not alter from their spontaneous firing rate after feeding to satiety (Critchley & Rolls, 1996a; Pritchard et al., 2008; Rolls,

2015c; Rolls et al., 1989) (Fig. 12). In the human orbitofrontal cortex, we found a large decrease in the BOLD signal to a complex food (tomato juice vs chocolate) fed to satiety, but not in the insula (Kringelbach, O'Doherty, Rolls, & Andrews, 2003). Moreover, this was a sensory-specific decrease in the BOLD signal, a useful indication that this was a response related to real satiety, which is to a considerable extent sensory-specific, and not for every food. Moreover, this sensory-specific decrease was related to the decrease in the subjective pleasantness of the food eaten to satiety (see Fig. 13). Further, we are looking for a brain region not just where there may be small changes, perhaps significant, to the response to a taste fed to satiety, but a region where the response decreases to zero, for this is what happens to the pleasantness of food after it is fed to satiety, with little effect on its intensity (Rolls, 2014; Rolls & Grabenhorst, 2008; Rolls et al., 1983).

Further evidence on hedonics, in this case using the prototypical taste monosodium glutamate, is shown in Fig. 10. In this study on selective attention to the intensity or pleasantness of the taste, it was found not only that attention to intensity but not pleasantness modulate the BOLD signal in the anterior and mid-insular taste cortical areas, but of particular importance in the present context, that the BOLD activations in both the anterior and mid-insular taste cortical areas were linearly related to the intensity but not the pleasantness of the tastes (see Fig. 10) (Grabenhorst & Rolls,

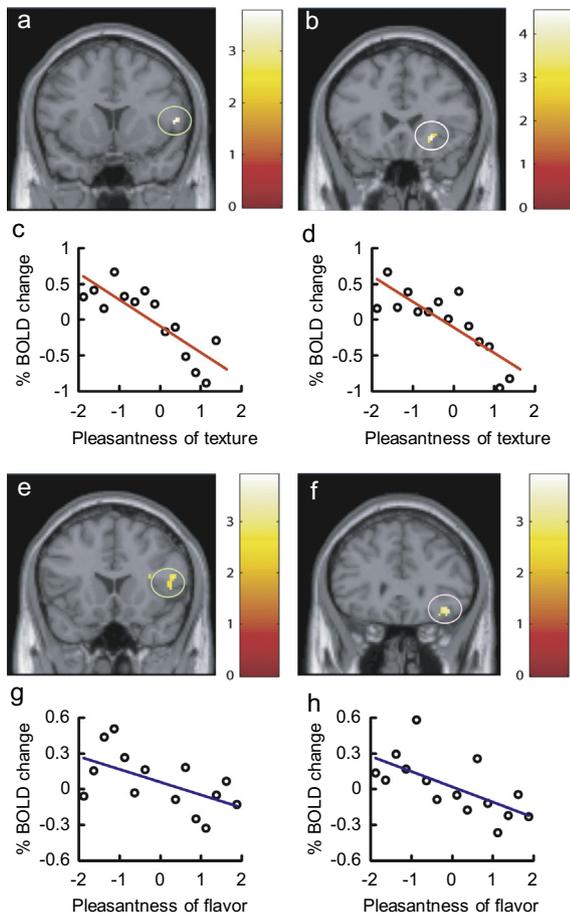


**Fig. 10.** Effect of paying attention to the pleasantness vs the intensity of a taste stimulus, monosodium glutamate. **a.** Top: A significant difference related to the taste period was found in the taste insula at  $[42\ 18\ -14]\ z = 2.42\ p < 0.05$  (indicated by the cursor) and in the mid insula 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 ( $r = 0.91$ ,  $df = 14$ ,  $p \ll 0.001$ ). 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 ( $r = 0.89$ ,  $df = 15$ ,  $p \ll 0.001$ ). 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 ( $r = 0.94$ ,  $df = 8$ ,  $p \ll 0.001$ ). 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 & Rolls, 2008).)

2008). The converse was found for the orbitofrontal cortex, in which attention to pleasantness but not intensity modulated the BOLD signal in the orbitofrontal cortex, and that the BOLD activations in the orbitofrontal cortex but not the anterior and mid-insular taste cortical areas were linearly related to the pleasantness of the tastes (Grabenhorst & Rolls, 2008). This double dissociation provides evidence that the orbitofrontal cortex taste areas are more involved in the reward value/subjective hedonic evaluation and representation of taste stimuli in humans as well

as macaques, and that the insular taste cortex is more involved in the representation of what the stimulus is and its intensity.

Against this background, there are suggestions that the human insular taste cortex has decreased responses after feeding to satiety, and represents taste hedonics (de Araujo, Geha, & Small, 2012; Small, 2010; Small, Zatorre, Dagher, Evans, & Jones-Gotman, 2001; Sun et al., 2014). Let us evaluate these suggestions. First, taste stimuli were not used in most of these investigations, and thus inferences about whether taste representations

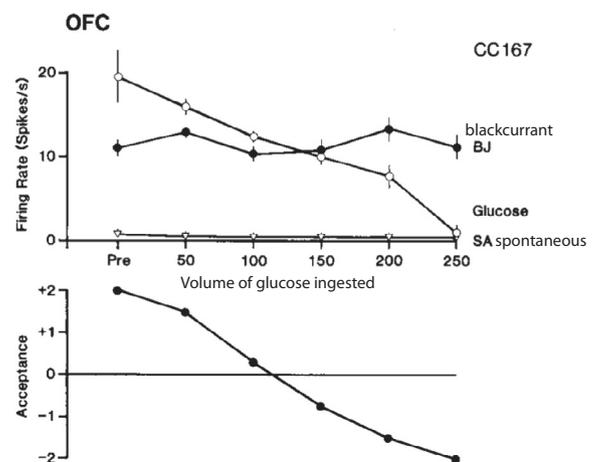


**Fig. 11.** Brain regions in which the activations were negatively correlated with the pleasantness of fat texture: Frontal operculum/overlying cortex ([56 128]  $z = 3.34$   $p = 0.017$ ) (a, c) and far anterior, agranular insular cortex ([2624–6]  $z = 3.70$   $p = 0.011$ ) (b, d). Negative correlations between activity and the pleasantness of flavor (strawberry vs vanilla) were found in the frontal operculum/overlying cortex ([50 18 16]  $z = 4.17$   $p < 0.001$ ) (e, g) and the lateral posterior orbitofrontal cortex ([32 32–18]  $z = 3.64$   $p < 0.001$ ) (f, h). (After Grabenhorst et al., 2010.)

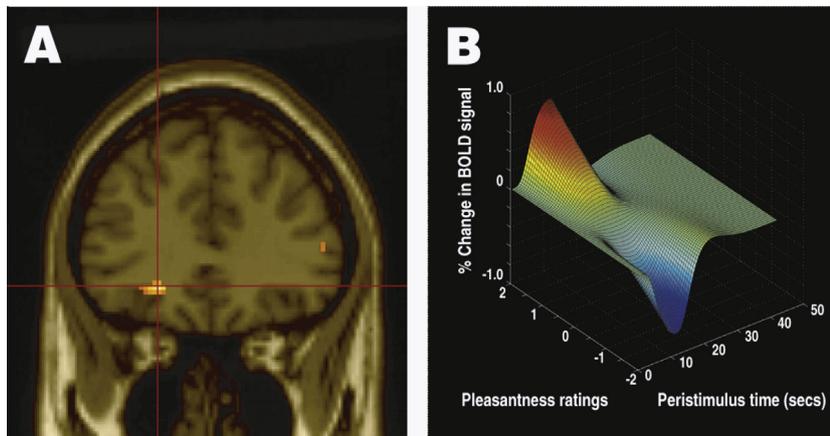
in the insula are subject to devaluation to zero by feeding to satiety are weak. Another weakness is that water was used as a control in some of the studies, again making inferences about taste representations weak (see below). Another important factor is that it is useful in such studies to allow subjects to eat to self-determined satiety, rather than to use a fixed food load, to ensure that normal physiological satiety is being investigated. (This has always been the case in our studies in macaques (Critchley & Rolls, 1996a; Rolls et al., 1988, 1989; Yaxley et al., 1988) and humans (de Araujo, Kringelbach, Rolls, & McGlone, 2003; Kringelbach, O'Doherty, Rolls, & Andrews, 2003).) Also, because of sensory-specific satiety, the test stimulus should always be that on which the subjects were satiated, for otherwise the value of the test stimulus may not be zero after the feeding. It is also important to measure whether the effects of satiety in a given brain region are as large as they are in brain regions where satiety does reduce responsiveness to a food that has been eaten to satiety, such as the orbitofrontal cortex (Kringelbach, O'Doherty, Rolls, & Andrews, 2003). In one investigation, chocolate was used (and a water control) (Small et al., 2001), and in another, milkshake (Sun et al., 2014) (and a food load other than that being tested), so that there were major somatosensory components. Somatosensory components of complex foods, including oral viscosity, are represented in the anterior insula and the adjoining frontal operculum (at  $Y = 14$ ) at which taste responses (to sucrose)

were found, and in the mid insula ( $Y = -8$  to  $-12$ ), in which activations were correlated with viscosity but much less with taste (de Araujo & Rolls, 2004). In addition, there is a frontal opercular area ([56 128]) lateral to the insular taste cortex where activations reflect a factor of oral including fat texture that relates to its unpleasantness (Grabenhorst et al., 2010). This was revealed with complex flavor stimuli that included high dairy fat vs low fat components, and two flavors, vanilla (pleasant) and strawberry (which was unpleasant) (Fig. 8). A similar lateral opercular cortex ( $[-58 22 14]$ ) region has activations correlated with the unpleasantness of a complex texture/flavor stimulus, vegetable juice (V8) (Rolls, Kellerhals, et al., 2015). There is also an agranular insular area ([26 24–6]) anterior to the anterior insular taste cortex where activations reflect a factor of oral including fat texture that relates to its unpleasantness (Grabenhorst et al., 2010). In contrast, the pleasantness of fat texture was represented in the mid-orbitofrontal cortex and pregenual cingulate cortex (Grabenhorst et al., 2010). A similar agranular insular area ([36 26 4]) is activated by vegetable juice (V8) which is unpleasant to young people (age 22) (Rolls, Kellerhals, et al., 2015), though the main areas with correlations with unpleasantness are the lateral orbitofrontal cortex and anterior cingulate cortex dorsal to the corpus callosum (Grabenhorst & Rolls, 2011; Rolls, Kellerhals, et al., 2015).

In summary, the anterior ( $Y = 10$  to  $Y = 20$ ) and mid ( $Y \sim 0$ ) insular taste cortical areas in humans have activations related mainly to the intensity and not the pleasantness or unpleasantness of taste, while a part of the lateral frontal opercular cortex and agranular insular cortex anterior to the anterior taste cortex can have activations to oral stimuli with unpleasant textures or flavors. The main representation of the pleasantness of taste, oral texture, odor, and flavor is in the mid and medial orbitofrontal cortex and pregenual cingulate cortex; whereas the main representation of the unpleasantness of taste, oral texture, olfactory, and flavor is in the lateral orbitofrontal cortex and anterior cingulate cortex above the corpus callosum (Grabenhorst & Rolls, 2011; Rolls, 2014, 2015c).



**Fig. 12.** 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. (Reproduced from Rolls, Sienkiewicz, & Yaxley, 1989.)



**Fig. 13.** Areas of the human orbitofrontal cortex with activations correlating with pleasantness ratings for food in the mouth. (A) Coronal section through the region of the orbitofrontal cortex from the random effects group analysis showing the peak in the left orbitofrontal cortex (Talairach co-ordinates  $X, Y, Z = -22, 34, -8$ ,  $z$ -score = 4.06), in which the BOLD signal in the voxels shown in yellow was significantly correlated with the subjects' subjective pleasantness ratings of the foods throughout an experiment in which the subjects were hungry and found the food pleasant, and were then fed to satiety with the food, after which the pleasantness of the food decreased to neutral or slightly unpleasant. The design was a sensory-specific satiety design, and the pleasantness of the food not eaten in the meal, and the BOLD activation in the orbitofrontal cortex, were not altered by eating the other food to satiety. The two foods were tomato juice and chocolate milk. (B) Plot of the magnitude of the fitted haemodynamic response from a representative single subject against the subjective pleasantness ratings (on a scale from  $-2$  to  $+2$ ) and peristimulus time in seconds. (After [Kringelbach, O'Doherty, Rolls, & Andrews, 2003](#).)

Consistent with this in chocolate cravers there was enhanced activation to chocolate in areas such as the orbitofrontal and cingulate cortex, but not the insular taste cortex ([Rolls & McCabe, 2007](#)); and age differences in the pleasantness of different flavors are represented in brain areas such as the orbitofrontal and anterior cingulate cortices, but not in the insular taste cortex ([Rolls, Kellerhals, et al., 2015](#)). The implication is that the hedonics of different foods, and preferences for them, are implemented in the orbitofrontal and anterior cingulate cortex and related areas, and not in the insular taste cortical areas, in which activations are more related to the intensity and identity of taste, and not their hedonic and reward value properties ([Rolls, 2014, 2015c](#)).

### 3.3.4. 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 (see [Fig. 10](#)), whereas selective attention to intensity modulates activations in areas such as the primary taste cortex ([Grabenhorst & Rolls, 2008; Rolls, Grabenhorst, Margot, da Silva, & Velazco, 2008](#)). Thus, depending on the context in which tastes and odors are presented and whether affect is relevant, the brain responds to a taste, odor or flavor differently. These findings show that when attention is paid to affective value, the brain systems engaged to represent the stimulus are different from those engaged when attention is directed to the physical properties of a stimulus such as its intensity.

The source of the top-down modulation by attention of the orbitofrontal cortex appears to be the lateral prefrontal cortex, as shown by PPI (psychophysiological interaction) analyses ([Grabenhorst & Rolls, 2010](#)), and by Granger causality analyses ([Ge, Feng, Grabenhorst, & Rolls, 2012; Luo, Ge, Grabenhorst, Feng, & Rolls, 2013](#)). The mechanism probably involves a weak top-down biased competition effect on the taste and olfactory processing ([Deco & Rolls, 2005; Desimone & Duncan, 1995; Rolls, 2008b, 2013](#)). Because whole streams of cortical processing are influenced (orbitofrontal and cingulate cortex, and even their coupling to the primary taste cortex, by pleasantness-related processing; and insular taste cortex and the mid-insula by intensity-related processing ([Grabenhorst & Rolls, 2010; Luo](#)

[et al., 2013](#))), the process has been described as a biased activation model of attention ([Grabenhorst & Rolls, 2010; Rolls, 2013](#)).

This differential biasing by prefrontal cortex attentional mechanisms ([Ge et al., 2012; Grabenhorst & Rolls, 2010](#)) 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 & Rolls, 2008, 2011; Rolls, 2012; Rolls et al., 2008](#)). 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 and perfumery products.

### 3.3.5. Olfactory–visual–taste convergence

In macaques, as shown above, there is little response of neurons in the insular taste cortex to olfactory and visual stimuli ([Verhagen et al., 2004](#)), and the orbitofrontal cortex does respond to olfactory and visual stimuli ([Critchley & Rolls, 1996a, 1996b; Rolls & Baylis, 1994](#)), and indeed learns associations of visual or olfactory stimuli to taste stimuli ([Rolls, 2014, 2015c; Rolls, Critchley, Mason, et al., 1996; Thorpe et al., 1983](#)). With human fMRI, we found some effects of olfactory (retronasal strawberry) as well as taste (sucrose) in a region that is at the anterior end of and anterior to the main anterior insular taste cortex area at  $Y = 10-20$  ([de Araujo, Rolls, Kringelbach, McClone, & Phillips, 2003](#)), with evidence for convergence shown by interaction of the components in the orbitofrontal cortex. Some studies in humans have reported activations in the insula to the sight of food, with activations in the mid-insular but not anterior insular taste area modulated by peripheral glucose ([Simmons et al., 2013](#)). Olfactory stimuli may also activate the human insular cortex ([de Araujo et al., 2012; Small et al., 2004](#)). One possibility is that in humans visual and olfactory cues can elicit strong memories of tastes, and that it is the recollection of taste, and perhaps the associated autonomic responses produced by the visual, olfactory, or recalled taste, that accounts for activations to these stimuli in the anterior insular cortex ([Rolls, 2014, 2015c](#)). Another possibility is that some of the 'insular' activations are in a region that is often classified as caudolateral orbitofrontal cortex. For example, we found that a

set of three unpleasant odors produced activation at  $[-3727-8]$  (Rolls, Kringelbach, & de Araujo, 2003), which can be thought of as a caudolateral orbitofrontal cortex region, or as a part of the agranular insular cortex where there is a transition to what is at least topologically orbitofrontal cortex.

For comparison with the insula, 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, Rolls, et al., 2003; Small & Prescott, 2005; Small et al., 2004). Further, 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; and that these combinations are formed in the brain far beyond the taste or olfactory receptors, and even beyond primary taste and olfactory cortical areas (Rolls, 2009b).

O'Doherty, Deichmann, Critchley, and Dolan (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, Martin, and Barsalou (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). These results provide evidence on the neural substrate for the convergence of taste, olfactory, and visual stimuli to produce flavor in humans, and where the pleasantness of flavor is represented in the human brain, in the orbitofrontal and pregenual cingulate cortex.

Other functions of the anterior insula are considered in the following sections of the paper.

#### 4. An autonomic/visceral representation in the anterior/ventral insula

Parts of the insula receive visceral afferent inputs, and in turn are connected to efferent systems involved in the elicitation of autonomic responses (Al Omran & Aziz, 2014; Allen et al., 1991; Craig, 2002, 2009). In humans, a part of the anterior insula has activations related to visceral signals (Al Omran & Aziz, 2014; Critchley, 2005; Critchley & Harrison, 2013; Critchley, Wiens, Rotshtein, Ohman, & Dolan, 2004). For example, Critchley et al. (2004) observed enhanced activation in the anterior insular cortex (e.g.  $[34204]$ ) when subjects judged the timing of their own heartbeats, with the activations predicting the subjects' accuracy. Furthermore, local gray matter volume in a similar region  $[332813]$  correlated with both interoceptive accuracy and subjective ratings of visceral awareness. In another study, heartbeat monitoring engaged a ventral anterior insular/inferior frontal operculum region  $[4624-4]$ . In addition, this interoception-related region also was engaged when participants rated their own emotion during emotional video clips, and activity here correlated with the trial-by-trial intensity of participants' emotional experience (Zaki, Davis, & Ochsner, 2012). Further, using a paradigm that orientates attention either to the participants' own internal bodily state or to their own emotion state during fMRI scanning, bilateral anterior insular cortex activations  $[34264]$

were found to be related to both the cognitive evaluation of bodily state and appraisal of self-emotion (Terasawa, Shibata, Moriguchi, & Umeda, 2013).

In summary, a part of the far anterior insula has activations related to visceral function. From the above coordinates ( $Y$  in the range 20–28) this appears to be in a region anterior to the anterior insular taste cortex ( $Y = 10$  to  $Y = 20$ ), in a region that we have referred to as agranular insular cortex where activations can be found to some multimodal unpleasant oral stimuli (see Section 3).

Some investigations have also reported activations that may be related to interoception in the mid-insula, in tasks in which the subjects are asked to focus attention on the sensations from for example the heart, stomach, and bladder (Avery et al., 2015; Simmons et al., 2013). Overlap in the mid-insula with a region activated by sweet taste – water was reported (Avery et al., 2015), but, probably because they did not use a tasteless control instead of water which has been shown to activate taste cortical areas (de Araujo, Kringelbach, Rolls, & McGlone, 2003), did not obtain data on activations to taste in the main insular taste area at  $Y = 20$  to  $Y = 10$ , making the results difficult to interpret. The mid-insula region close to  $Y = 0$  can be activated by distension of a balloon in the stomach but is not activated (in fact, is deactivated) by the normal gastric distension and other signals produced by the infusion of nutrient into the stomach (Geeraerts et al., 2011), so this mid-insular region, frequently referred to as part of the 'visceral pain matrix' (Geeraerts et al., 2011), may be related to aversive stimulation, rather than to normal physiological gastrointestinal visceral signaling.

Parts of the insula can be activated by visual stimuli related to disgust, such as a face expression of disgust (Phillips et al., 2004; Surguladze et al., 2010) (e.g. at  $Y = 22$  and  $Y = -11$ ), and this could reflect the fact that parts of the far anterior insula (e.g.  $Y = 22$ ) located probably mainly anterior to the insular taste cortex are part of the visceral efferent system involved in autonomic responses (Critchley, 2005; Critchley & Harrison, 2013; Rolls, 2014) (see above). (A disgust face expression is characterised by an open gaping mouth, consistent with rejection of an aversive oral stimulus from the mouth, such as a stimulus that might induce vomiting (Ekman, 1982; Ekman, Levenson, & Friesen, 1983; Rolls, 2011).) This visceromotoric part of the insula may not compute emotions, but may be activated as part of the efferent pathway by brain regions such as the orbitofrontal cortex when these brain regions produce autonomic responses to emotion-provoking including aversive stimuli (Rolls, 2014). Similarly, the activated state of the anterior insula in depression may be related to the visceral/autonomic changes that are typically present in depression (Rolls, 2015b). Further, damage to the human insula does not impair emotional feelings (Damasio, Damasio, & Tranel, 2013), and nor does peripheral autonomic failure (Heims, Critchley, Dolan, Mathias, & Cipolotti, 2004), consistent with the evidence that feedback from the viscera etc is not crucial for the experience of emotion (Rolls, 2014).

#### 5. Saliency

It has been suggested that the anterior insula is a key part of a "saliency network" implemented by the insula and the anterior cingulate cortex (Menon & Uddin, 2010). The disparate functions ascribed to the insula are conceptualized by a few basic mechanisms: (1) bottom-up detection of salient events, (2) switching between other large-scale networks to facilitate access to attention and working memory resources when a salient event is detected, (3) interaction of the anterior and posterior insula to modulate autonomic reactivity to salient stimuli, and (4) strong functional coupling with the anterior cingulate cortex that facilitates rapid

access to the motor system (Menon & Uddin, 2010). In this manner, with the insula as its integral hub, the salience network is described as assisting target brain regions in the generation of appropriate behavioral responses to salient stimuli. Menon and Uddin (2010) postulate that the insula is sensitive to salient events, and that its core function is to mark such events for additional processing and initiate appropriate control signals. They postulate that the core function of the anterior insula is to first identify stimuli from the continuous stream of sensory stimuli that impact the senses. Once such a stimulus is detected, the anterior insula facilitates task-related information processing by initiating appropriate transient control signals to engage brain areas mediating attentional, working memory, and higher order cognitive processes while disengaging the default mode network. These switching mechanisms are said to help focus attention on external stimuli, as a result of which they take on added significance or saliency (Menon & Uddin, 2010).

This so-called ‘saliency network’ showed increased coupling ( $p \sim 10^{-5}$ ) between the anterior cingulate cortex and anterior insular cortex in a resting-state voxel-level brain-wide functional connectivity investigation in 249 ADHD patients with attention deficit hyperactivity disorder when compared to 253 typically developing control children (Ji et al., submitted for publication; Rolls, Ji, et al., 2015). The peak voxel for the anterior insula was at  $[-24, 28, 6]$ , showing that this is the far anterior insula where the insula transitions into the lateral orbitofrontal cortex, though the extent of the increased functional connectivity was evident from  $Y = 32$  (which is lateral orbitofrontal cortex) to  $Y = 0$ . The peak voxel for the anterior cingulate cortex region was at  $[-12, 44, 10]$ , which is pregenual cingulate cortex. The results are interpreted in terms of connections between a system involved in rewards, punishers, and actions, the anterior cingulate cortex, and a system involved in autonomic output, the anterior insular cortex, as a result of which autonomic activity may be different in patients with ADHD. Indeed, the anterior cingulate cortex is itself implicated in autonomic function (Critchley, 2005; Critchley & Harrison, 2013; Vogt, 2009), and perhaps provides a route for cognitive function, including evidence about rewards and punishers being received (Grabenhorst & Rolls, 2011; Rolls, 2009a, 2014), to influence autonomic output, in part via the insula (Critchley, 2005; Mesulam & Mufson, 1982; Mufson & Mesulam, 1982; Vogt, 2009). Consistent with this, there is altered autonomic function in ADHD (Musser, Galloway-Long, Frick, & Nigg, 2013).

In another example, we found in the stop-signal task analyzed in 1709 participants that there was higher activation in both the anterior insula (with peaks at  $Y = 8$  and  $Y = 12$ ) and the anterior cingulate cortex on trials on which the participants failed to stop the trial correctly compared to trials when they did stop correctly (Deng et al., 2015). Further, significant functional connectivity was found in the task between the anterior cingulate cortex and the anterior insula. The activation of the anterior insula was interpreted as due to visceral/autonomic activity related to emotional responses occurring to the failure on the incorrect trials. In comparison, the lateral orbitofrontal cortex (with peaks at  $Y = 50$  and  $Y = 52$ ) was activated more on trials when the change of behavior to inhibit a response was performed correctly, and the interpretation was that the lateral orbitofrontal cortex is important for the computations involved in the change of the behavior (Deng et al., 2015). Consistent with this, a very similar lateral orbitofrontal cortex region was activated on the reversal trials of a visual discrimination reversal task, when non-reward was received and behavior must change (Kringelbach & Rolls, 2003). Thus in this behavioral inhibition task, the stop-signal task, the anterior insula activation was related to the emotional/autonomic responses on failure trials, and the lateral orbitofrontal cortex to the computations required to change (i.e. switch) the behavior (Deng et al., 2015; Rolls, 2014).

Thus at present a more parsimonious view might be taken than that the anterior insula is a key part of a ‘saliency network’ that can switch brain processing. The simpler view is that the insula receives inputs from cortical areas such as the orbitofrontal cortex and anterior cingulate cortex that are involved in reward and punishment related processing, and that the anterior insula is part of a route by which such stimuli can elicit autonomic and related responses to such stimuli (Rolls, 2014). (Further, both the anterior insula and the anterior cingulate cortex are activated by visceral signals (Al Omran & Aziz, 2014).) This more parsimonious view at least needs to be excluded by appropriate controls in which autonomic and related output is measured in studies that suggest cognitive computations (i.e. functions) are performed by the anterior insula, which is implicated as shown in this paper in oral sensory and viscer-autonomic functions.

## 6. Somatosensory representations in the mid/posterior insular cortex

The mid and posterior insular cortex contain somatosensory areas (Kaas, 2012; Mufson & Mesulam, 1984). Effects found in these areas are briefly described for comparison with the effects found in the anterior insula.

In a mid/posterior insular area at  $Y = -2$  to  $Y = -22$  we found activations to touch on the forearm or hand (McCabe, Rolls, Bilderbeck, & McGlone, 2008). Interestingly, similar activations were not produced in these areas to the sight of touch, though they were in many other somatosensory areas such as S1 and parietal cortex area 7, and in areas with hedonic representations such as the orbitofrontal cortex and anterior cingulate cortex (McCabe et al., 2008). We therefore hypothesized that the greater sensitivity of the insular touch representation compared to other somatosensory areas enabled the insular somatosensory cortex to provide a representation that it was oneself being touched, and not someone else which ‘mirror touch’ systems in other cortical areas might confuse (McCabe et al., 2008). In a sense, this is consistent with the fact that when the insular taste cortex is activated, we know that it is we who have the taste; and we do not experience taste when we see other people eating, though we might have autonomic responses if we see another person eating. (However, under conditions of slow and social touch being seen to the arm, some insular activation has been found (Morrison, Bjornsdotter, & Olausson, 2011), so it is not the case that insular areas are totally unaffected by the sight of touch.) Consistent with the view just described (McCabe et al., 2008; Rolls, 2010a, 2015a), a study by Blakemore, Bristow, Bird, Frith, and Ward (2005) showed that a synesthetic subject who felt touch whilst just observing touch had anterior insula activation whereas the control non-synesthetic subjects who did not feel touch as they observed touch did not have insular activation, again evidence for the insula being involved in recognition of touch to one’s own body.

In conclusion, in this paper some of the rules of the cortical processing performed by the insular cortex and how it is related to and differs from processing in connected cortical areas in primates including humans have been described. The discoveries provide an important foundation for understanding the brain mechanisms underlying the control of food intake, emotion, and value-related decision-making.

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