Flavor Physiology☆

Edmund T Rolls, Oxford Centre for Computational Neuroscience, Oxford, United Kingdom

Flavor Processing in the Primate Brain

Pathways

This article describes how taste, olfactory, and somatosensory inputs are brought together in the cortex to represent food flavor, and how these representations are influenced by visual and even cognitive inputs. To make the results relevant to understanding these processes and the control of food intake in humans, complementary evidence is provided by neurophysiological studies in nonhuman primates, and by functional neuroimaging studies in humans (Rolls, 2014, 2015a, 2016a).

The taste and related olfactory, somatosensory, and visual pathways in primates are shown in **Fig. 1**. Tier 1 in each modality on primates represents "what" the stimulus is, and its intensity, independently of its reward value. In Tier 2, especially in the orbitofrontal cortex, the representation is of the reward value of the stimulus. In Tier 3, there is an interface to different decision and output systems for different types of behavior (Rolls, 2014, 2015a, 2016a).

Of particular interest is that in primates for taste there is a direct projection from the rostral part of the nucleus of the solitary tract (NTS) to the taste thalamus and thus to the primary taste cortex in the frontal operculum and adjoining insula, with no pontine taste area and associated subcortical projections as in rodents (Rolls, 2014, 2015a,b, 2016a). This emphasis on cortical processing of taste in primates may be related to the great development of the cerebral cortex in primates, with sophisticated processing of each sensory modality before unimodal representations are brought together in multimodal areas to form multimodal representations of objects, such as food.

The Primary Taste Cortex

The primary taste cortex in the primate anterior insula and adjoining frontal operculum contains not only taste neurons tuned to sweet, salt, bitter, sour, and umami as exemplified by monosodium glutamate, but also other neurons that encode oral somatosensory stimuli, including viscosity, fat texture, temperature, and capsaicin (Scott et al., 1986; Yaxley et al., 1990; Scott and Plata-Salaman, 1999; Verhagen et al., 2004; Kadohisa et al., 2005b; Rolls, 2015b). Some neurons in the primary taste cortex respond to particular combinations of taste and oral texture stimuli, but do not respond to olfactory stimuli or visual stimuli such as the sight of food. Neurons in the primary taste cortex do not represent the reward value of taste, that is, the appetite for a food, in that their firing is not decreased to zero by feeding the taste to satiety (Rolls et al., 1988; Yaxley et al., 1988). Corresponding areas are activated by taste and oral texture in humans.

The Secondary Taste Cortex

A secondary cortical taste area in primates was discovered in the orbitofrontal cortex (OFC), extending several millimeters in front of the primary taste cortex (Rolls et al., 1990). In addition to neurons responding to the same taste and oral somatosensory stimuli, including viscosity, fat texture, temperature, and capsaicin, as in the primary taste cortex, some OFC neurons respond to water in the

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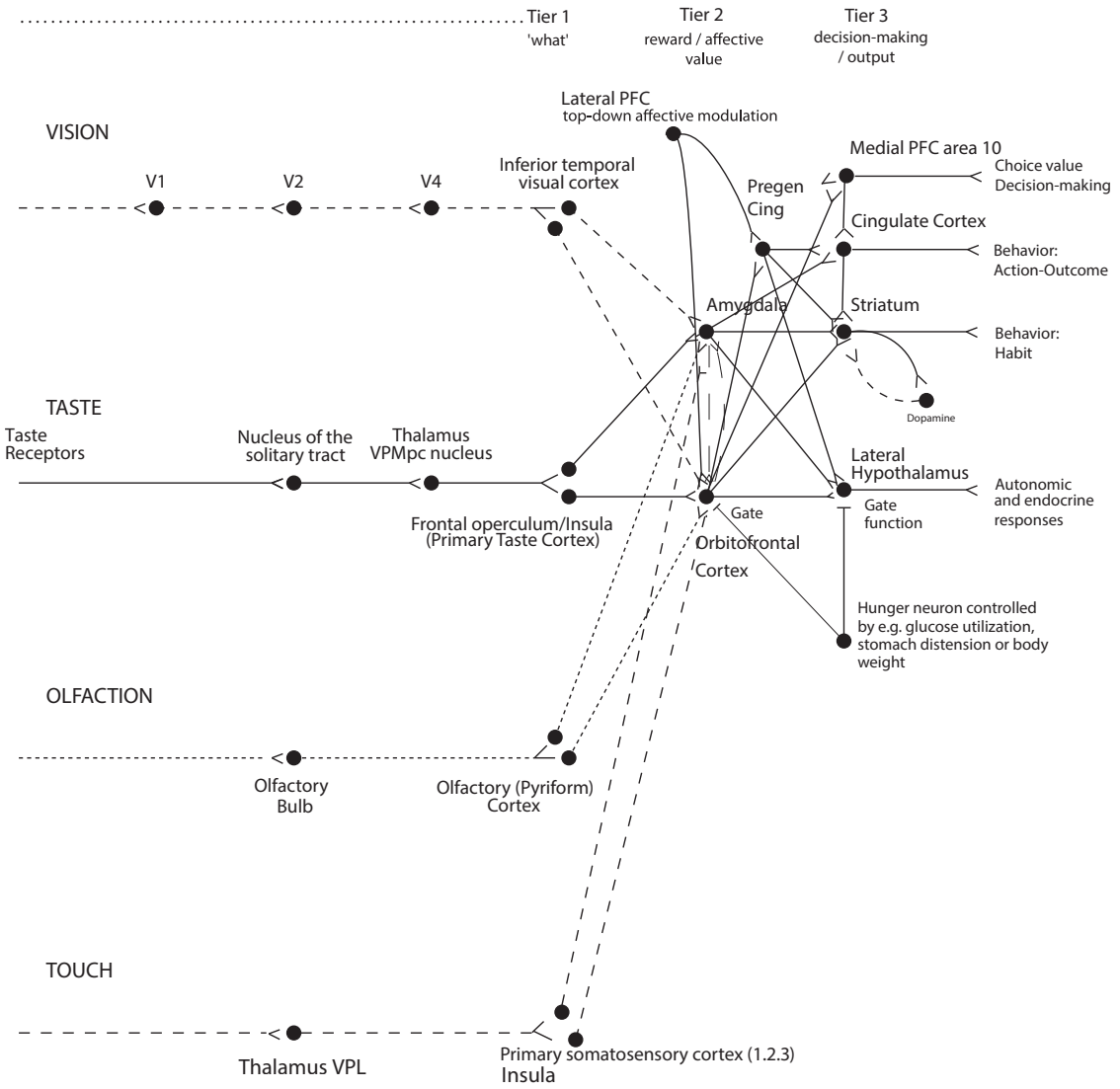

Figure 1 Schematic diagram of the taste and olfactory pathways in primates, showing how they converge with each other and with visual pathways. The gate functions shown refer to the finding that the responses of taste neurons in the orbitofrontal cortex and the lateral hypothalamus are modulated by hunger. *V1, V2, and V4*, visual cortical areas; *VPL*, ventral posterolateral thalamic nucleus; *VPMpc*, ventral posteromedial thalamic nucleus.

mouth, and others to the somatosensory stimuli astringency as exemplified by tannic acid, and to capsaicin (Critchley and Rolls, 1996c; Rolls et al., 2003a; Verhagen et al., 2003; Kadohisa et al., 2004, 2005b). In the OFC, it has been shown in monkeys that responses of the neurons to the taste of glucose decreased to zero while the monkey ate glucose to satiety, during the course of which the feeding behavior of the monkey changed from avid acceptance to active rejection (Rolls et al., 1989). These OFC neurons thus have activity related to the reward value of food.

Representation of Flavor: Convergence of Olfactory and Taste Inputs

At some stage in taste processing, taste representations are brought together with inputs from different modalities, for example, with olfactory inputs to form a representation of flavor (see **Fig. 1**). In the OFC, some neurons are unimodal for taste, olfactory, or visual inputs, but others respond to combinations of these inputs. Some of the multimodal single neurons had corresponding sensitivities in the two modalities, in that they responded best to sweet tastes (e.g., 1 M glucose) and also responded more in a visual discrimination task to the visual stimulus which signified sweet fruit juice than to that which signified saline (Rolls et al., 1996), or responded to sweet taste and in an olfactory discrimination task to fruit odor (Critchley and Rolls, 1996a).

Olfactory inputs become associated with taste inputs to represent flavor by olfactory-to-taste association learning. This has been shown by reversing the taste with which an odor is associated, and this has been found to produce slow changes of the odor to which a neuron responds, taking typically 40 trials in primates, as illustrated in (Fig. 2; Critchley and Rolls, 1996a). Thus flavor, represented by taste–olfactory convergence, is relatively stable. Thus for some neurons in the OFC the neuronal response to the odor depends on the taste with which it is associated and does not depend primarily on the physicochemical structure of the odor. These findings demonstrate directly a coding principle in primate olfaction whereby the responses of some OFC olfactory neurons are modified by, and depend upon, the taste with which the odor is associated. This convergence can be detected in human functional magnetic resonance imaging (fMRI) studies by supralinear responses to a flavor compound (such as sweet taste and strawberry odor), compared to the sum of the components presented separately (de Araujo et al., 2003). Supradditive interactions between congruent taste and smell stimuli in areas including the caudal OFC and anterior cingulate cortex (ACC) have been confirmed (Small et al., 2004).

In humans, in addition to activation of the pyriform (olfactory) cortex, there is strong and consistent activation of the OFC by olfactory stimuli. In an investigation of where the pleasantness of olfactory stimuli might be represented in humans, O'Doherty et al. (2000) showed that the activation of an area of the OFC by banana odor was decreased (relative to a control vanilla odor) after bananas were eaten to satiety. Thus activity in a part of the human OFC olfactory area is related to sensory-specific satiety, and this is one brain region where the pleasantness of odor is represented.

An important issue is whether there are separate regions of the brain, discriminable with fMRI, that represent pleasant and unpleasant odors. To investigate this, we measured the brain activations produced by three pleasant and three unpleasant odors

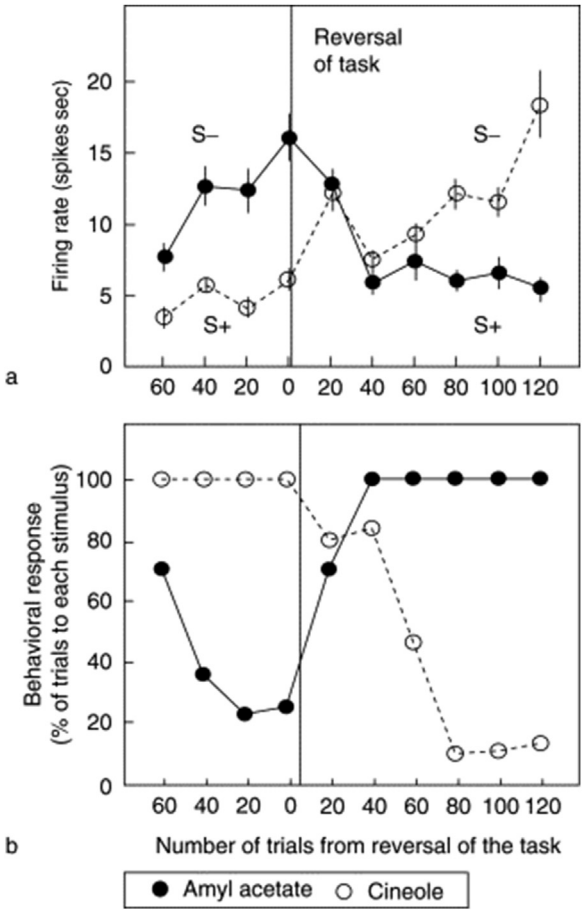

Figure 2 Orbitofrontal cortex: olfactory to taste association reversal. (A) The activity of a single orbitofrontal olfactory neuron during the performance of a two-odor olfactory discrimination task and its reversal is shown. Each point represents the mean poststimulus activity of the neuron in a 500 ms period on approximately 10 trials of the different odorants. The standard errors of these responses are shown. The odorants were amyl acetate (*closed circle*) (initially S−, that is, associated with the taste of saline) and cineole (*open circle*) (initially S+, that is, associated with the taste of glucose). After 80 trials of the task, the reward associations of the stimuli were reversed. This neuron reversed its responses to the odorants following the task reversal. (B) The behavioral responses of the monkey during the performance of the olfactory discrimination task. The number of lick responses to each odorant is plotted as a percentage of the number of trials for that odorant in a block of 20 trials of the task. Reproduced from Rolls, E.T., Critchley, H., Mason, R., Wakeman, E.A., 1996. Orbitofrontal cortex neurons: role in olfactory and visual association learning. J. Neurophysiol. 75, 1970–1981.

(Rolls et al., 2003b). The pleasant odors chosen were linalyl acetate (floral, sweet), geranyl acetate (floral), and α-ionone (woody, slightly food-related). (Chiral substances were used as racemates.) The unpleasant odors chosen were hexanoic acid, octanol, and isovaleric acid. We found that they activated dissociable parts of the human brain. Pleasant but not unpleasant odors were found to activate a medial region of the rostral OFC. Further, there was a correlation between the subjective pleasantness ratings of the six odors and activation of a medial region of the rostral OFC. In contrast, a correlation between the subjective unpleasantness ratings of the six odors was found in regions of the left and more lateral OFC.

Representation of Flavor: Convergence of Visual Inputs With Taste, Olfactory, and Oral Texture Inputs

Visual stimuli such as the sight of food can produce responses in some OFC neurons that have taste or olfactory inputs (Thorpe et al., 1983). The visual inputs are associated by learning with the taste inputs to a neuron, and this learning can be very fast, in as little as one trial (Thorpe et al., 1983; Rolls et al., 1996). This enables prediction of the taste associated with ingestion of what is seen, and thus in the visual selection of foods. This representation also provides a way for the sight of a food to influence the flavor of a food. Oral temperature, which can also affect the palatability of a food, also influences the responses of OFC neurons, and indeed some of these neurons are tuned to oral temperature (Kadohisa et al., 2004).

Representation of the Pleasantness and Reward Value of Flavor in the Brain

The responses of OFC neurons to the taste, olfactory, visual, and/or oral texture components of food flavor all show a reduction that is correlated with the decrease in the reward value of food (Rolls et al., 1989; Critchley and Rolls, 1996b). This reflects probably an influence of satiety signals, including gastric distension, on the responses of these neurons. An additional effect is a sensory-specific reduction in the responses of these neurons after feeding to satiety with a food, and this is likely to be computed in the orbitofrontal cortex, and to be important in which foods are eaten in a meal and in the control of food intake (Rolls et al., 1989; Critchley and Rolls, 1996b; Rolls, 2014, 2016a,b).

To assess how satiety influences the brain activations to a whole food which produces taste, olfactory, and texture stimulation, we measured brain activation by whole foods before and after the food is eaten to satiety. The aim was to show, using a food that has olfactory, taste, and texture components, the extent of the region that shows decreases when the food becomes less pleasant, in order to identify the different brain areas where the pleasantness of the odor, taste, and texture of food is represented. The foods eaten to satiety were either chocolate milk or tomato juice. A decrease in activation by the food eaten to satiety relative to the other food was found in the OFC but not in the primary taste cortex. This study provided evidence that the pleasantness of the flavor of food, and sensory-specific satiety, are represented in the OFC (Kringelbach et al., 2003).

Cognitive Effects on Representations of Food

Brie can smell pleasant. However, the same odor taken out of the context of cheese might be unpleasant. There is evidence that the sight (including color) of a food or wine can influence its flavor. However, what about a more cognitive influence, such as a word? Can this influence the perception and hedonics of food-related stimuli, and if so, how far back down into the sensory system does the cognitive influence reach? To address this, we performed a fMRI investigation in which the delivery of a standard test odor (isovaleric acid combined with cheddar cheese flavor, presented orthonasally using an olfactometer) was paired with a descriptor word on a screen, which on different trials was "cheddar cheese" or "body odor." The subjects rated the pleasantness and the intensity of the odor on every trial. α-Ionone (pleasant, labeled "flowers") and octanol (unpleasant, labeled "burned plastic") were used as reference pleasant and unpleasant stimuli for the psychophysics and neuroimaging. Subjects rated the affective value of the test odor as significantly more unpleasant when labeled "body odor" than when labeled "cheddar cheese". We found that the medial OFC/rostral ACC was significantly more activated by the test stimulus labeled "cheddar cheese" than when labeled "body odor," and that these activations were correlated with the pleasantness ratings (see **Fig. 3**; de Araujo et al., 2005). This cognitive modulation was also found in the medial amygdala olfactory area, and this extended toward the olfactory tubercle. Thus cognitive modulation extends into the olfactory system as far down as the secondary olfactory cortex, in the orbitofrontal cortex, and may even influence some parts of the primary olfactory areas, such as the olfactory tubercle. Corresponding cognitive modulation of taste and flavor representations in the orbitofrontal cortex has also been discovered (Grabenhorst et al., 2008). The implication is that cognitive factors can have profound effects on our responses to the hedonic and sensory properties of food, in that these effects are manifest quite far back into sensory processing, so that at least hedonic representations of odors are affected, and even perceptual representations may be modulated.

Selective Attention to the Pleasantness or Intensity of Flavor

Selective attention can also influence the representations of flavor in the brain. In particular, selective attention to the pleasantness of flavor increases activations to a flavor in the orbitofrontal and anterior congulate cortices, and selective attention to the intensity

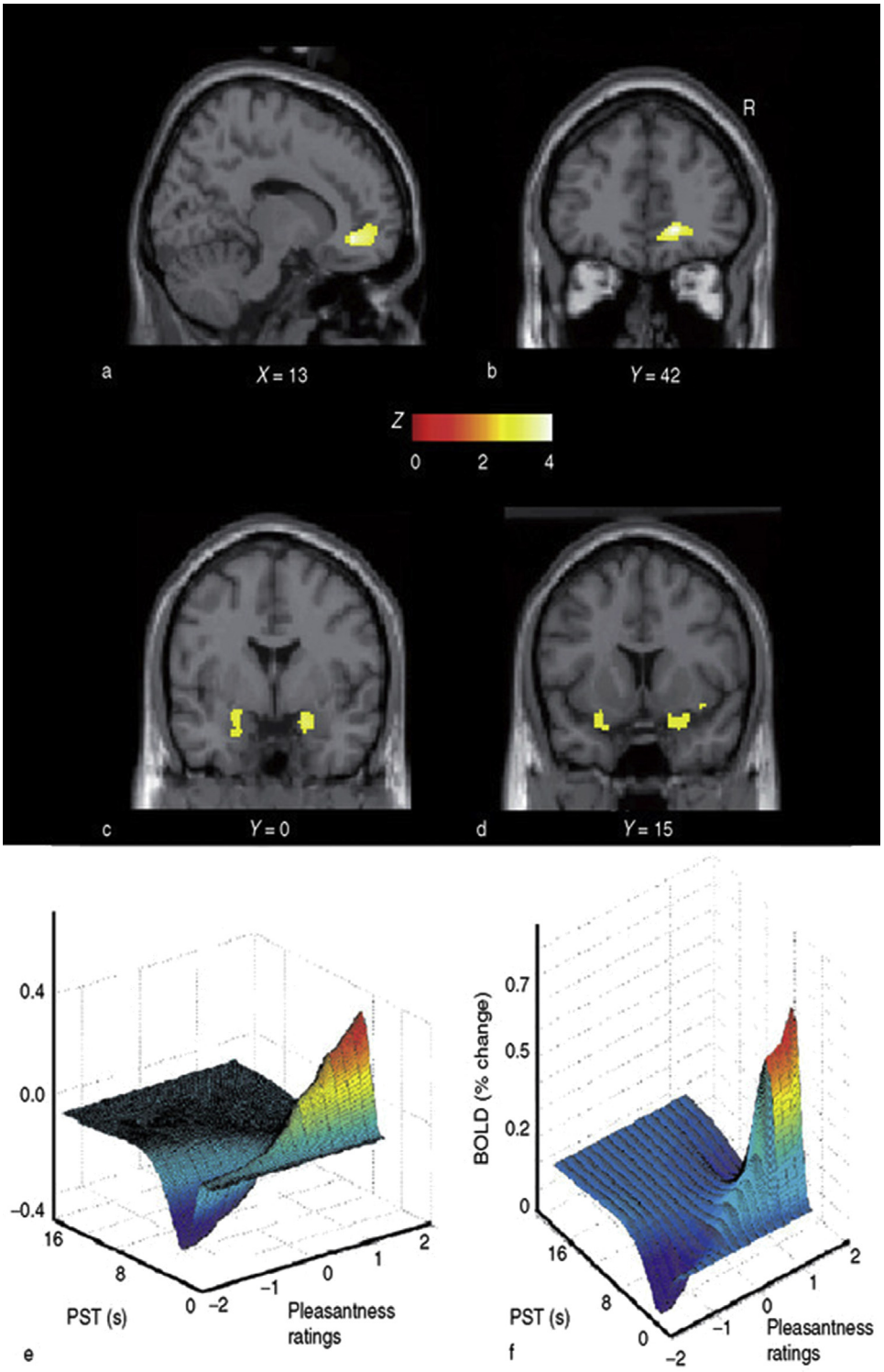

Figure 3 Cognitive influences on olfactory representations in the human brain. Group (random) effects analysis showing the brain regions where the BOLD signal was correlated with pleasantness ratings given to the test odor. The pleasantness ratings were being modulated by the word labels. (A) Activations in the rostral anterior cingulate cortex, in the region adjoining the medial OFC, shown in a sagittal slice. (B) The same activation shown coronally. (C) Bilateral activations in the amygdala. (D) These activations extended anteriorly to the primary olfactory cortex. The image was thresholded at $P < .0001$ uncorrected in order to show the extent of the activation. (E) Parametric plots of the data averaged across all subjects, showing that the percentage BOLD change (fitted) correlates with the pleasantness ratings in the region shown in (A) and (B). The parametric plots were very similar for the primary olfactory region shown in (D). *PST*, poststimulus time (in seconds). (F) Parametric plots for the amygdala region shown in (C). Adapted from de Araujo, I.E.T., Rolls, E.T., Velazco, M.I., et al., 2005 Cognitive modulation of olfactory processing. Neuron 46, 671–679.

of a flavor can increase activations in the primary taste cortex and primary olfactory cortex (Grabenhorst and Rolls, 2008; Rolls et al., 2008). These discoveries have important implications for sensory testing of flavor, for different brain systems are engaged depending on the instructions (Rolls, 2014, 2015a, 2016a).

The Amygdala

These oral sensory properties of food, and also the sight and smell of food, are also represented in the primate amygdala (Kadohisa et al., 2005a). Interestingly, the responses of these amygdala neurons do not correlate well with the preferences of the macaques for the oral stimuli, and feeding to satiety does not produce the large reduction in the responses of amygdala neurons to food that is typical of OFC neurons. 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.

Conclusions

Food flavors, and their subjective complements, including the consonance of food taste and olfactory components, are represented in primates, including humans, only after several stages of analysis (Rolls, 2014, 2015a, 2016a). First the representation of the taste of the food (its identity and intensity) is made explicit in the primary taste cortex. In the pyriform (primary) olfactory cortex, the intensity of an odor, and not its pleasantness or taste, is represented. The OFC is where multimodal representations of food are built, which include taste, texture, olfactory, oral temperature, and visual components.

Although representations of the taste and texture of food are found in the primate (including human) amygdala, the primate OFC is more closely related to the changing affective value of food than the amygdala is, in that the OFC shows responses that decrease to zero as the reward decreases to zero with satiety, and in that the OFC tracks (and probably computes) the changing reward value of stimuli as they are altered by stimulus–reinforcer association learning and reversal (Rolls, 2014, 2015a, 2016a).

It is thus becoming possible to start to understand how smell, taste, and other stimuli combine to represent flavor in the brain.

Although functional neuroimaging with its spatial resolution of several millimeters shows that some of these representations are close together in the human medial orbitofrontal cortex, the primate neurophysiology provides clear evidence for the exquisitely rich and separate representations of different types of sensory input, because each neuron in this region is tuned to one or to a unique combination of the range of food-related stimuli described here (Rolls, 2014, 2015a, 2016a). The information relevant to the control of food intake concerning the sensory properties of foods is thus made explicit in the firing-rate profiles of single neurons and groups of single neurons to the sensory stimuli. It is at the neuron level that brain computations are performed and that the information being transmitted between the computing elements of the brain, the neurons, can be measured by the spiking activity (Rolls, 2016b). By making models of the computations taking place in networks of neurons at the spiking neuron level, it is now possible, by integration over the energy required for the activated neurons, to predict signals at a much more global level of functional neuroimaging in humans. By combining information from the neuron and functional imaging level, we are beginning to understand the details of the neuronal operations that underlie the representation of food in the brain, and what makes food pleasant when we are hungry (Rolls, 2014, 2016b).

The outputs of the OFC reach brain regions such as the striatum, cingulate cortex, and dorsolateral prefrontal cortex, where behavioral responses to food may be elicited because these structures produce behavior that makes the OFC reward neurons fire, as they represent a goal for behavior (Rolls, 2014, 2016b). At the same time, outputs from the OFC and amygdala, in part via the hypothalamus, may provide for appropriate autonomic and endocrine responses to food to be produced, including the release of hormones such as insulin (Rolls, 2014, 2016b).

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