Reward Systems in the Brain and Nutrition

Edmund T. Rolls

Oxford Centre for Computational Neuroscience, Oxford, United Kingdom;
email: Edmund.Rolls@oxcns.org

Annu. Rev. Nutr. 2016. 36:435–70

First published online as a Review in Advance on May 4, 2016

The *Annual Review of Nutrition* is online at nutr.annualreviews.org

This article's doi:
10.1146/annurev-nutr-071715-050725

Keywords

taste, olfaction, food reward, obesity, fat texture, orbitofrontal cortex, hunger

Abstract

The taste cortex in the anterior insula provides separate and combined representations of the taste, temperature, and texture of food in the mouth independently of hunger and thus of reward value and pleasantness. One synapse on, in the orbitofrontal cortex, these sensory inputs are combined by associative learning with olfactory and visual inputs for some neurons, and these neurons encode food reward value in that they respond to food only when hunger is present and in that activations correlate linearly with subjective pleasantness. Cognitive factors, including word-level descriptions and selective attention to affective value, modulate the representation of the reward value of taste, olfactory, and flavor stimuli in the orbitofrontal cortex and a region to which it projects, the anterior cingulate cortex. These food reward representations are important in the control of appetite and food intake. Individual differences in reward representations may contribute to obesity, and there are age-related differences in these reward representations. Implications of how reward systems in the brain operate for understanding, preventing, and treating obesity are described.

Contents

INTRODUCTION

This article describes how taste, olfactory, food texture, and visual inputs are processed in the brain; how a representation of food reward value is produced and is related to subjective pleasure; how cognition and selective attention influence processing related to food reward value; how this reward value is affected by nutritional signals of hunger and satiety; how reward value acts as the signal for appetite for food and eating; and how sensory-related reward signals can override nutritional requirements to contribute to overeating and obesity and what the implications are for controlling overeating and obesity.

The concept here is that food reward is a goal that normally drives appetite and eating, and it is therefore important to understand the brain mechanisms involved in food reward in order to understand the control of appetite and food intake (114–116). It is normally the case that motivated behavior is performed for the reward or goal, and it is only when a habit or stimulus-response behavior becomes established that eating is no longer under the control of the reward (7); normally, goal-directed "liking" predicts motivation or "wanting" (114, 116).

Research in primates and humans is emphasized because evidence indicates that the rodent taste and food reward systems operate somewhat differently from those of primates and humans (114–116). In brief, the taste system is different in rodents in that there is a pontine taste area, which then projects subcortically, whereas in primates there is no pontine taste area, and cortical processing is performed first (**Figures 1** and **2*b***). Second, in rodents the taste and olfactory systems are modulated peripherally [in the nucleus of the solitary tract and the olfactory bulb (89, 90), respectively] by hunger so that reward is represented peripherally and is entangled with sensory processing, whereas in primates and humans food perception is separated from its reward value, as described below (**Figure 2*b***). A perceptual correlate of this is that when humans feed to satiety, the intensity of the flavor changes very little but the pleasantness of the flavor decreases to zero (139, 140), showing that in humans perceptual representations of taste and olfaction are kept separate from hedonic representations. This separation is adaptive in that we do not become insensitive to the sight, taste, and smell of food after eating it to satiety, and we can therefore still learn about where food is located in the environment even when we are not hungry (114). Third, the orbitofrontal cortex is very little developed in rodents (with only an agranular part) (183), yet it is one of the major brain areas involved in taste and olfactory processing, and emotion and motivation, in primates including humans (114). For these reasons, the rodent taste and olfactory system is a poor model of neural food reward processing in humans, and I therefore emphasize discoveries in primates and humans (114–116).

TASTE, OLFACTORY, AND ORAL TEXTURE PROCESSING IN THE PRIMATE, INCLUDING IN THE HUMAN BRAIN

Pathways

Diagrams of the taste and the related olfactory, somatosensory, and visual pathways in primates are shown in **Figures 1** and **2**. A multimodal convergence enables single neurons to respond to different combinations of taste, olfactory, texture, temperature, and visual inputs to represent different flavors produced by new combinations of sensory input and where reward is represented.

The Insular Primary Taste Cortex

Neuronal responses to taste. The primary taste cortex in the primate anterior (granular) insula and adjoining frontal operculum contains not only taste neurons tuned to sweet, salt, bitter, sour

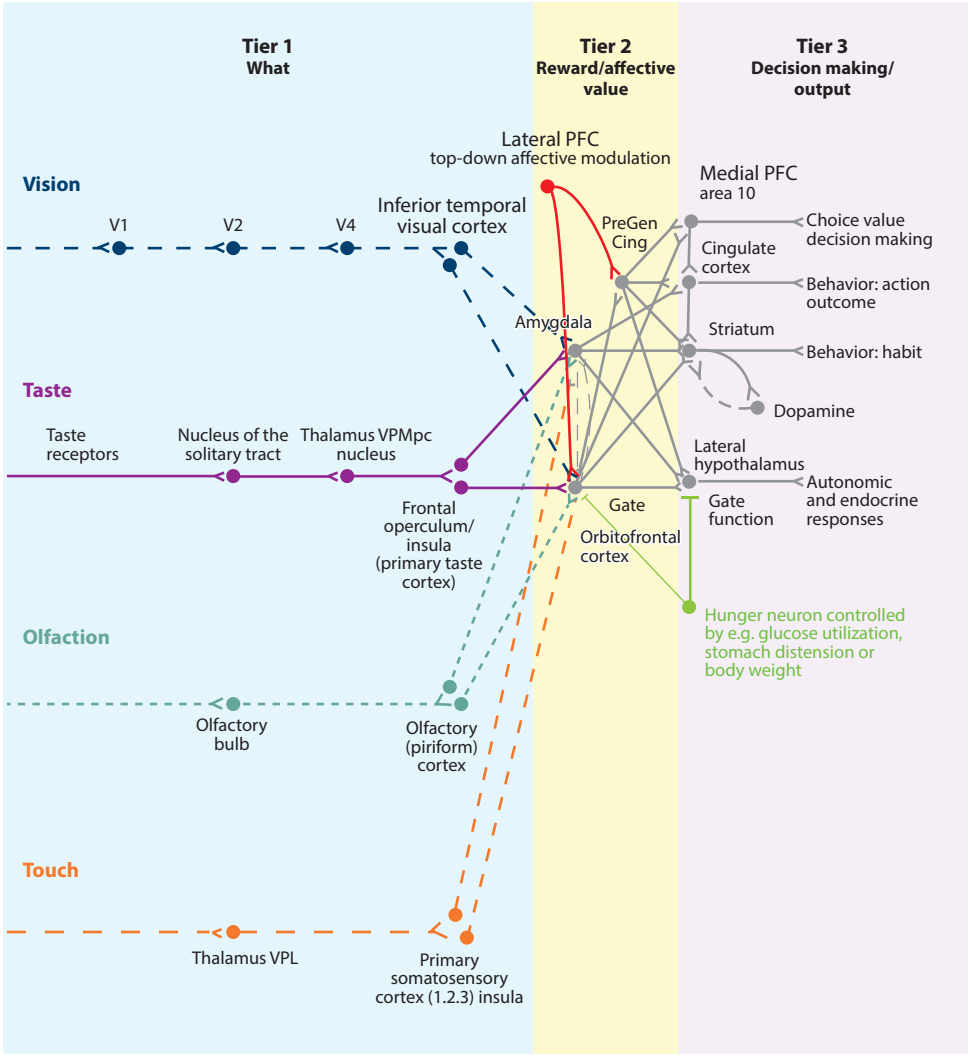


Figure 1

Schematic diagram showing some of the gustatory, olfactory, visual, and somatosensory pathways to the orbitofrontal cortex, and some of the outputs of the orbitofrontal cortex, in primates. The secondary taste cortex and the secondary olfactory cortex are within the orbitofrontal cortex. V1, V2, and V4 are visual cortical areas. Tier 1 is the column of brain regions, including and below the inferior temporal visual cortex, that represents regions in which "what" stimulus is present is made explicit in the neuronal representation. The reward or affective value of the stimulus is represented in Tier 2 brain regions, the orbitofrontal cortex and amygdala, and in the anterior cingulate cortex. In Tier 3 areas, such as medial prefrontal cortex area 10, choices or decisions about reward value are made (107, 114, 126). Top-down control of affective response systems by cognition and by selective attention from the dorsolateral prefrontal cortex is also indicated. Abbreviations: PFC, prefrontal cortex; PreGen Cing, pregenual cingulate cortex; VPL, ventral posterolateral thalamic nucleus, pars parvocellularis; VPMpc, ventral posteromedial thalamic nucleus (the thalamic nucleus for taste). "Gate" refers to the finding that inputs, such as the taste, smell, and sight of food, in some brain regions produce effects only when hunger is present (114).

(142, 157, 158, 188), and umami, as exemplified by monosodium glutamate (MSG) (2, 120), but also other neurons that encode oral somatosensory stimuli, including viscosity, fat texture, and temperature as well as capsaicin (found in hot peppers) (176). Some neurons in the primary taste cortex respond to particular combinations of taste and oral texture stimuli, but macaque insular taste cortex neurons do not respond to olfactory stimuli or to visual stimuli, such as the sight of food (176). Neurons in the insular and frontal opercular primary taste cortex do not represent the reward value of taste, that is, the appetite for a food, in that their firing is not decreased to zero by feeding the taste to satiety (143, 187). In macaques, neural processing peripheral to the primary taste cortex is consistent with this finding: Taste responses in the rostral part of the nucleus of the solitary tract (159) are not influenced by feeding to satiety (189).

Activations of the insular taste cortex in humans. Neuroimaging studies using functional magnetic resonance imaging (fMRI) in humans indicate that taste activates an area of the anterior insula/frontal operculum, which is probably the primary taste cortex (24, 43, 82, 163, 167). This area is generally found at coordinates between $Y = 10$ and $Y = 20$. **Figure 3** illustrates the primary taste cortex as well as activations to taste stimuli in the orbitofrontal cortex, which is the secondary taste cortex (24, 34, 82, 116), and the anterior cingulate cortex. We pioneered the use of a tasteless control with the same ionic constituents as saliva (24, 82), as water can activate some neurons in cortical taste areas (148) and can activate the taste cortex (24). The insular primary taste cortex is activated by oral temperature (51). In the insular taste cortex, there is a somatosensory representation of oral texture (25), which might be unpleasant, and this region can sometimes be activated by taste stimuli (**Figure 3**). If the insular taste cortex in humans is activated by odors, it may be because of taste recalled through back-projection pathways (117) from the more anterior agranular insular cortex, which is multimodal (26), or from the orbitofrontal cortex.

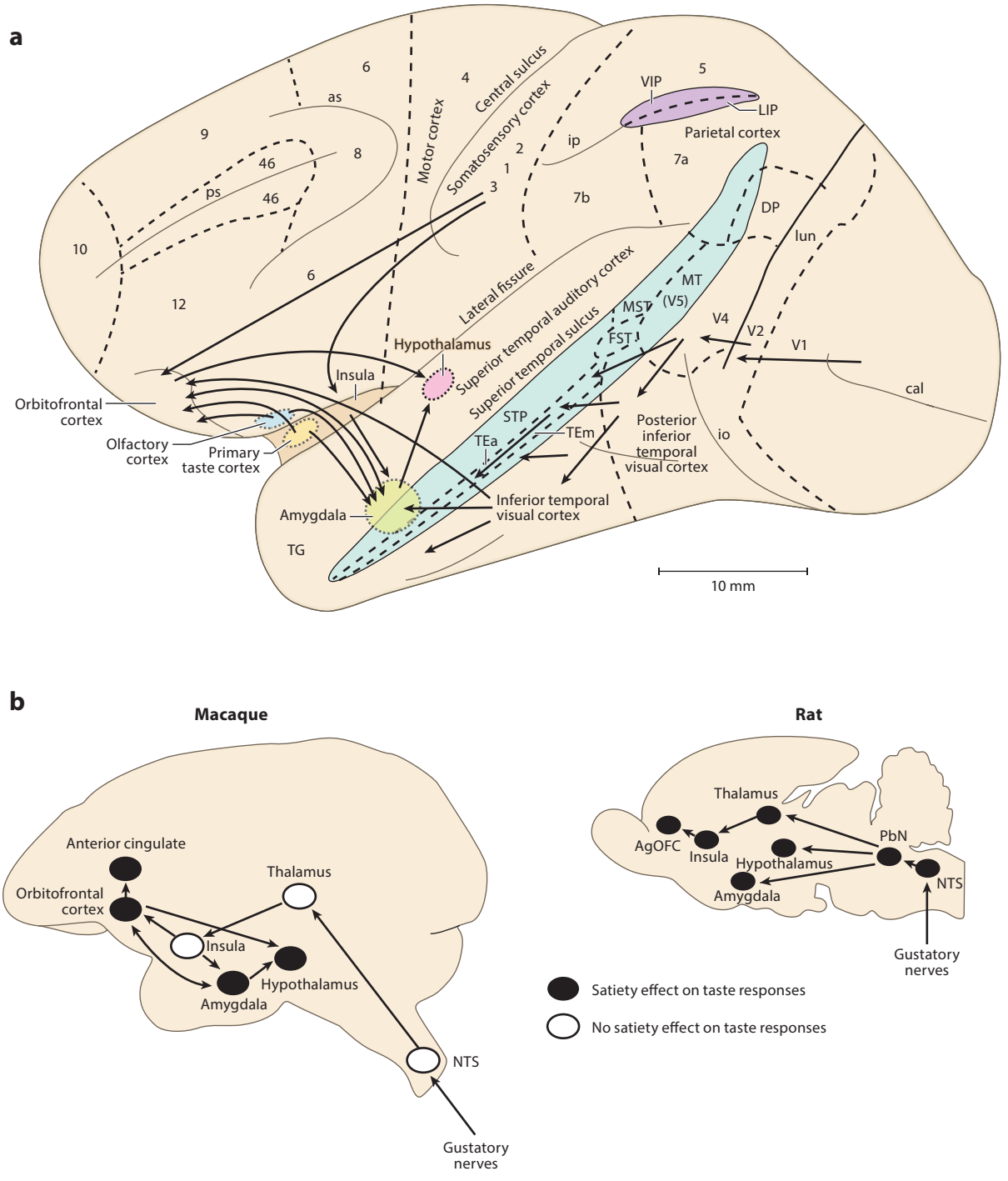
The primary taste cortex in the anterior (granular) insula of humans represents the identity and intensity of taste (115, 116) in that activations there correlate linearly with the subjective intensity of taste; the orbitofrontal and anterior cingulate cortices represent the reward value of taste in that activations there correlate with the subjective pleasantness of taste (43, 47) (**Figure 3**) and in that activations in the orbitofrontal cortex decrease when humans are fed to satiety but do not decrease in the insular taste cortex (68). The texture-related unpleasantness of some oral stimuli is represented in frontal opercular areas that are close to the insular taste cortex (134).

The Piriform Olfactory Cortex

In humans, the piriform (primary olfactory) cortex is activated by olfactory stimuli (39, 135, 169). Activations in the piriform cortex are correlated with the intensity of odors but not their pleasantness (135). In addition, feeding to satiety has not been shown to reduce the activations of the piriform cortex to odors, although satiety does reduce activations of the orbitofrontal cortex to food-related odors (83) and to flavors that include taste and olfactory components (68). These findings provide evidence that the human piriform cortex is involved in representing the intensity and identity of odors but not their reward value or pleasantness.

The Secondary Taste and Olfactory Cortex in the Orbitofrontal Cortex and the Representation of Reward Value

Neuronal responses to taste. Rolls and colleagues (144, 148, 174) discovered a secondary cortical taste area in the orbitofrontal cortex in primates; it extends several millimeters in front of



the primary taste cortex. This area is defined as a secondary cortical taste area because it receives direct inputs from the primary taste cortex, as shown by an investigation that traced the neurophysiological and anatomical pathways (3). Different neurons in this region respond not only to each of the four classical prototypical tastes [sweet, salt, bitter, and sour (64, 147, 148, 177)] but also to umami tastants such as glutamate (which is present in many natural foods, such as tomatoes, mushrooms, and human milk) (2) and inosine monophosphate (which is present in meat and some fish, such as tuna) (120). This evidence, taken together with the identification of glutamate taste receptors (73, 193), indicates that five prototypical types of taste information channels exist, with umami contributing, often in combination with corresponding olfactory inputs (74, 109, 121), to the flavor of protein. In addition, other neurons respond to water (148), and still others to somatosensory stimuli, including astringency [as exemplified by tannic acid (20)] and capsaicin (63, 147).

Some of the coding principles are illustrated by the two neurons shown in **Figure 4**. Each neuron has its independent tuning to the set of stimuli. This independent tuning or coding with sparse distributed representations underlies the ability of the brain to represent the exact nature of a stimulus or event, and this tuning applies to taste in addition to other sensory modalities, including smell (116, 117, 124, 125, 146). This tuning also provides a foundation for the implementation of sensory-specific satiety (114, 116). Taste responses are found in a large mediolateral extent of the orbitofrontal cortex (20, 96, 106, 116, 127).

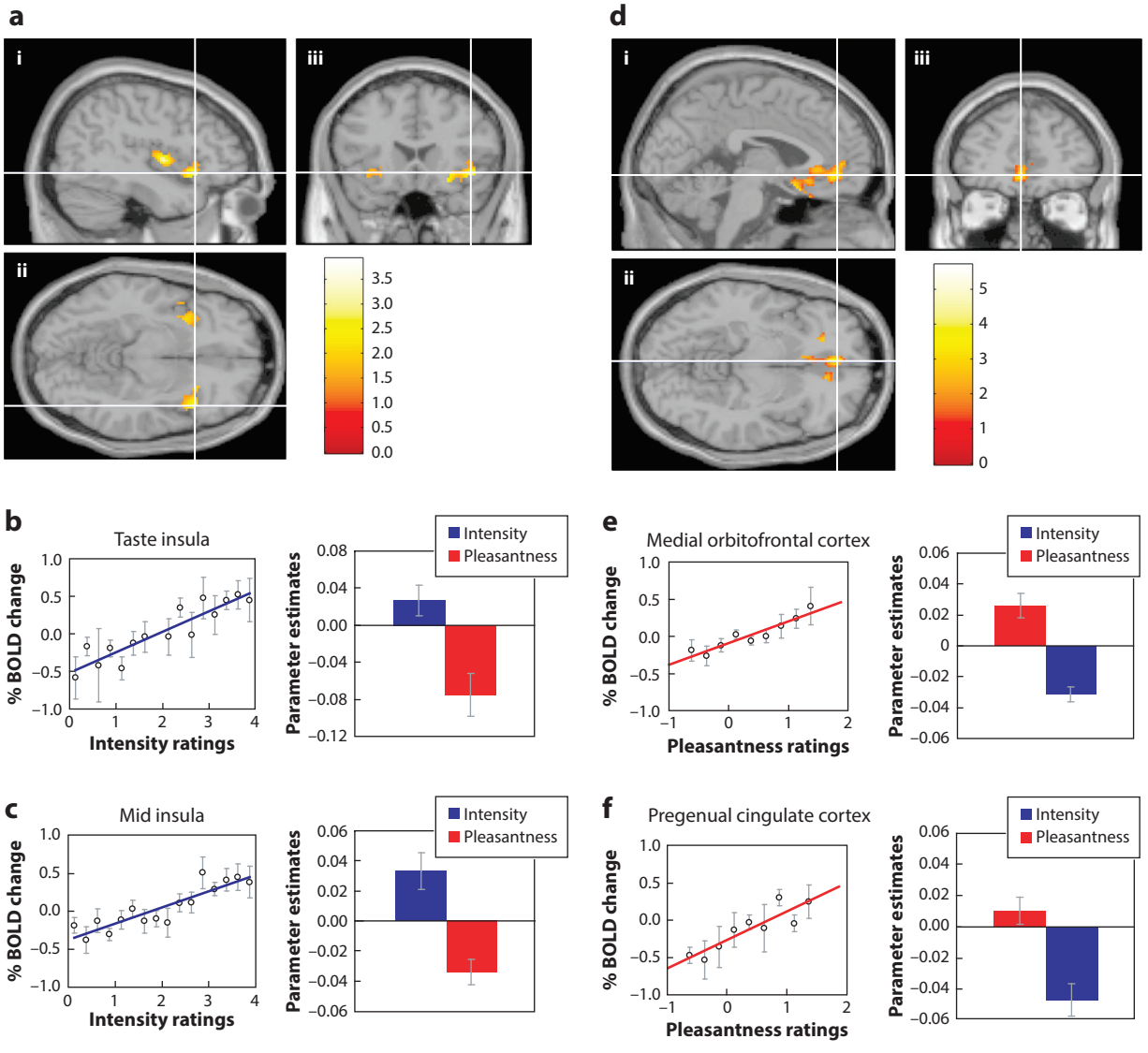
The majority of these orbitofrontal cortex neurons respond to taste and/or olfactory stimuli modulated by hunger (18), as illustrated in **Figure 5**. This response is described in more detail in the section titled Reward Value in the Orbitofrontal Cortex.

Figure 2

(*a*) Lateral view of some of the primate (macaque) brain pathways involved in processing food-related stimuli. Connections are shown from the primary taste and olfactory cortices to the orbitofrontal cortex and amygdala and from the ventral visual system (V1 to V2, to V4) to the inferior temporal visual cortex, etc., with some connections reaching the amygdala and orbitofrontal cortex (OFC). Also shown are connections from the somatosensory cortical areas 1, 2, and 3 that reach the orbitofrontal cortex directly and via the insular cortex and that reach the amygdala via the insular cortex. Numerals refer to architectonic areas and have the following approximate functional equivalence: 1, 2, and 3, somatosensory cortex (posterior to the central sulcus); 4, motor cortex; 5, superior parietal lobule; 6, lateral premotor cortex; 7a, inferior parietal lobule, visual part; 7b, inferior parietal lobule, somatosensory part; 8, frontal eye field; 12, part of orbitofrontal cortex; 46, dorsolateral prefrontal cortex. (*b*) Taste pathways in the macaque and rat. In the macaque, gustatory information reaches the 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. 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 in VPMpc). In rats, in contrast, the NTS projects to a pontine taste area, the PbN. The PbN then projects 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 there may be no equivalent to this in rats (92, 114, 116, 165, 183).] In the rat, satiety signals such as gastric distension and satiety-related hormones decrease neuronal responses in the NTS and by inference in the other brain areas with taste-related responses. Abbreviations: as, arcuate sulcus; cal, calcarine sulcus; DP, dorsal perilunate; FST, frontal superior temporal visual motion-processing area; io, inferior occipital sulcus; ip, intraparietal sulcus (which has been opened to reveal some of the areas it contains); LIP, lateral intraparietal area; lun, lunate sulcus; MST, medial superior temporal visual motion-processing area; MT, middle temporal visual motion-processing area (also called V5); NTS, nucleus of the solitary tract; PbN, parabrachial nucleus; ps, principal sulcus; STP, superior temporal plane; TE, architectonic area, including high-order visual association cortex, and some of its subareas (TEa and Tem); TG, architectonic area in the temporal pole; V1, V2, and V4, visual areas V1, V2, and V4; VIP, ventral intraparietal area; VPMpc, ventral posteromedial thalamic nucleus.

Activations of the orbitofrontal cortex in humans to taste stimuli. Different regions of the human orbitofrontal cortex can be activated by pleasant (e.g., sucrose or glucose) or aversive (e.g., quinine or sodium chloride) taste stimuli (82, 190, 191). Umami taste stimuli, of which an exemplar is MSG, capture what is described as the taste of protein. Umami stimuli activate the insular (primary), orbitofrontal (secondary), and anterior cingulate [tertiary (106)] taste cortical areas (23, 109).

Neuronal responses to odors in the primate orbitofrontal cortex. Some primate orbitofrontal cortex neurons respond well to olfactory stimuli (19, 123, 125). For many of these neurons, the response is related to tastes (19) and can be acquired by olfactory-to-taste association learning (123), providing evidence that the orbitofrontal cortex can remap odors from the olfactory gene-specified representation (12, 75) into a representation where the "meaning" in terms of the association of



the odor with other stimuli is paramount. Flavors are built by learning in the orbitofrontal cortex as combinations of taste and olfactory inputs, with oral texture also often being a component (123). The olfactory-to-taste association learning is slow, though, taking 30 to 60 trials to reverse, and thus flavor representations are somewhat stable (123). The representation of information by primate orbitofrontal cortex neurons (124) is approximately independent by different neurons, in that the information increases approximately linearly with the number of neurons (125).

Many primate olfactory orbitofrontal neurons encode the reward value of odor in that their activity is decreased in a sensory-specific satiety way by feeding a particular food to satiety (18) (see section titled Reward Value in the Orbitofrontal Cortex).

Olfactory representations in the human orbitofrontal cortex. In humans, the orbitofrontal cortex is strongly and consistently activated by olfactory stimuli (34, 135, 192). This region represents the reward value and pleasantness of odor, as demonstrated by a sensory-specific satiety experiment with banana versus vanilla odor (83). These reward-specific activations have been confirmed by Gottfried and colleagues (40, 57; personal communication), who also showed that odor devaluation by satiety did not decrease activations in the piriform (primary olfactory) cortex. In addition, pleasant odors tend to activate the medial orbitofrontal cortex, whereas unpleasant odors activate the more lateral orbitofrontal cortex (135), providing further evidence that a hedonic map is present in the orbitofrontal cortex as well as in the anterior cingulate cortex, which receives inputs from the orbitofrontal cortex (45, 114, 127). The primary olfactory (piriform) cortex represents the identity and intensity of odor, in that activations there correlate with the subjective intensity of the odor, whereas the orbitofrontal and anterior cingulate cortices represent the reward value of odor, in that activations there correlate with the subjective pleasantness (medially) or unpleasantness (laterally) of odor (45, 48, 114, 127, 130, 131, 135).

The texture of food, including fat texture.

Viscosity, particulate quality, and astringency. Some orbitofrontal cortex neurons have oral texture–related responses that parametrically encode the viscosity of food in the mouth (shown

Figure 3

Effect of paying attention to the pleasantness versus the intensity of the taste stimulus monosodium glutamate. (*a*) 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] $z = 3.03$, $p < 0.025$. (*b*) Taste insula. (*right*) The parameter estimates [mean ± standard error of mean (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 [% blood-oxygen-level-dependent (BOLD) change] at the specified coordinate ($r = 0.91$, $df = 14$, $p \ll 0.001$). (*c*) Mid insula. (*right*) The parameter estimates (mean ± 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. (*d*) 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). (*e*) Medial orbitofrontal cortex. (*right*) The parameter estimates (mean ± 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 ($r = 0.94$, $df = 8$, $p \ll 0.001$). (*f*) Pregenual cingulate cortex. Conventions are the same 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. (Figure adapted from Reference 43 with permission.)

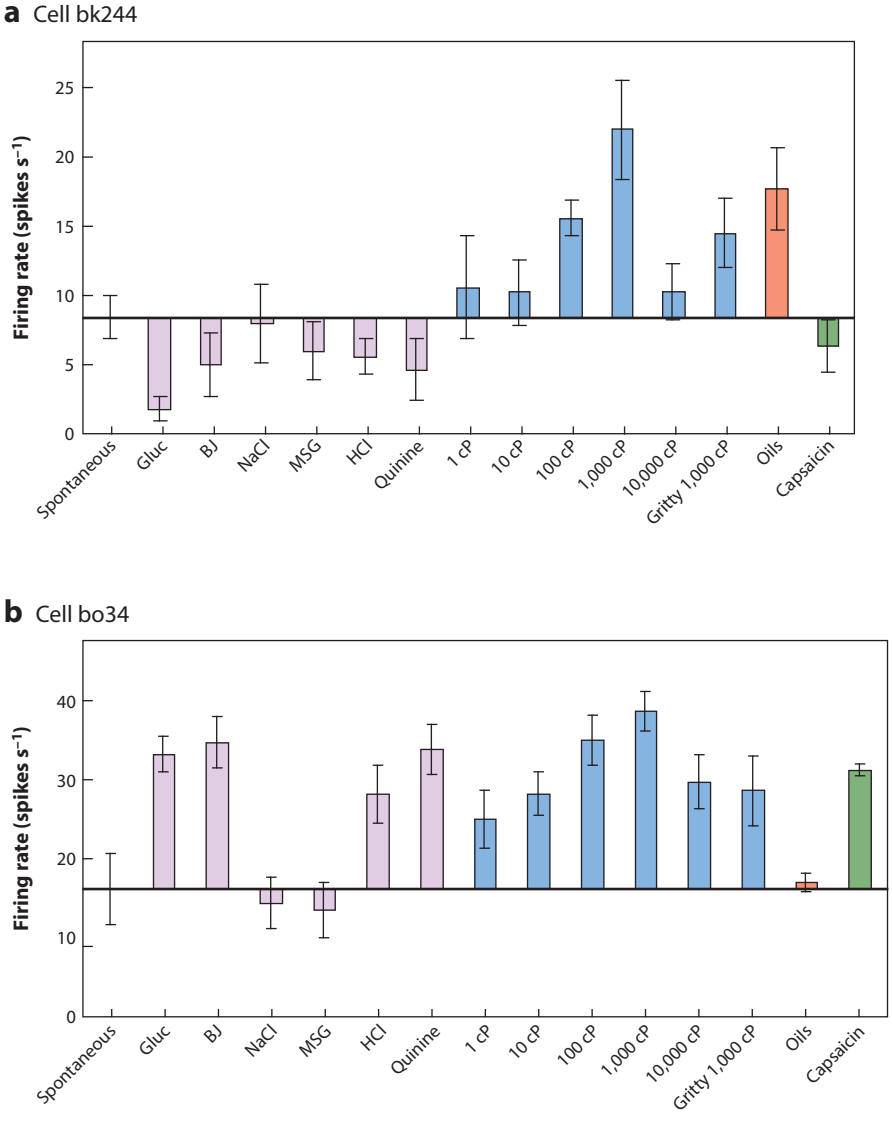


Figure 4

Independent coding of food-related stimuli shown by the responses of two orbitofrontal cortex neurons to taste and oral somatosensory inputs. (*a*) Firing rates [mean ± standard error of mean (SEM)] of viscosity-sensitive neuron bk244, which did not respond differentially to the different taste stimuli and thus did not have taste responses. The firing rates are shown to the viscosity series [carboxymethylcellulose 1–10,000 centipoise (cP)]; to the gritty stimulus (1,000 cP carboxymethylcellulose with Fillite microspheres); to the taste stimuli 1 M glucose (Gluc), 0.1 M sodium chloride (NaCl), 0.1 M monosodium glutamate (MSG), 0.01 M hydrochloric acid (HCl), and 0.001 M Quinine; and to black currant juice (BJ). (*b*) Firing rates (mean ± SEM) of viscosity-sensitive neuron bo34, which responded to some taste stimuli and did not respond to oils (mineral oil, vegetable oil, safflower oil, and coconut oil, which all have viscosities that are close to 50 cP). The neuron responded to the gritty stimulus as was expected given the viscosity of the stimulus; it was taste tuned and did respond to capsaicin. (Figure adapted from Reference 147 with permission.)

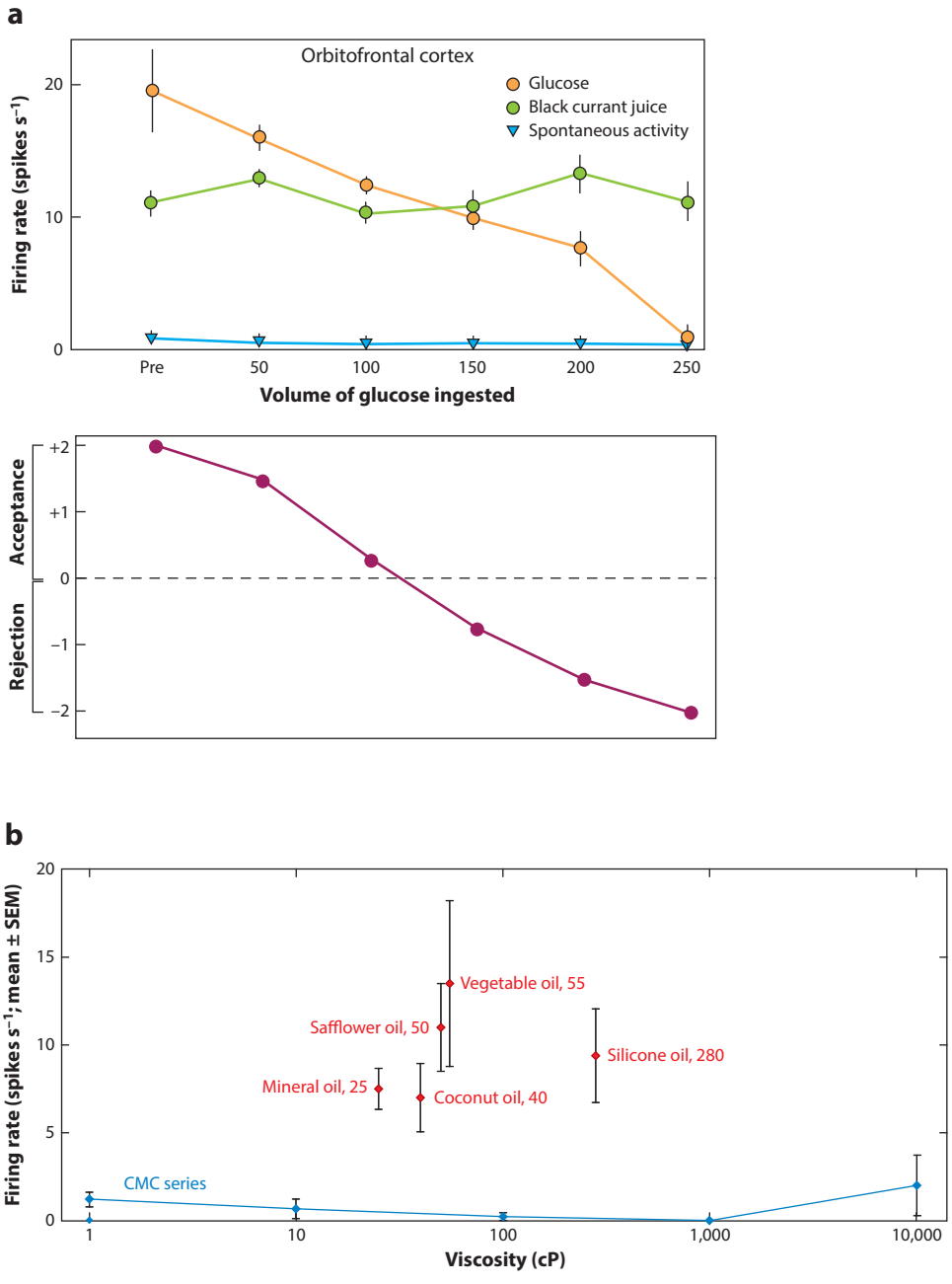
using a methylcellulose series in the range of 1 to 10,000 centipoise), and other neurons independently encode the particulate quality of food in the mouth (147). Somatosensory signals that transmit information about capsaicin and astringency are also reflected in neuronal activity in these cortical areas (20, 63, 64).

Oral fat texture. Texture in the mouth indicates whether fat is present in a food. Fat is important not only as a high-value energy source but also as a potential source of essential fatty acids. Rolls et al. (122) have found a population of neurons in the orbitofrontal cortex that responds when fat is in the mouth. The fat-related responses of these neurons are produced at least in part by the texture of the food rather than by receptors sensitive to certain chemicals, in that such neurons typically respond not only to foods such as cream and milk containing fat but also to paraffin oil (which is a pure hydrocarbon) and silicone oil [$(Si(CH_3)_2O)_n$]. Moreover, the responses of these neurons cannot be predicted by the viscosity of the oral stimuli, as illustrated in **Figure 5*b***, because the texture channels through which these fat-sensitive neurons are activated are separate from viscosity-sensitive channels (110, 177). The responses of these oral fat-encoding neurons are not related to free fatty acids such as linoleic or lauric acid (64, 110, 177), and the fat responsiveness of these primate orbitofrontal cortex neurons is therefore not related to fatty acid sensing (37, 38) but instead to oral texture sensing (110). [It is hypothesized that in rodents, with relatively high concentrations of lingual lipase, a fatty acid–responsive "taste" receptor might provide evidence about the presence of fat in the mouth (37, 38).] Primates have less lingual lipase, and the neuronal responses to fat placed in the mouth in macaques are fast (176, 177); thus, the intervention of digestion by a salivary enzyme is unlikely to be the main mechanism that detects fat in the mouth. Moreover, oils that have the same texture as fat but that contain no fat, such as silicone and paraffin oil, activate the neurons in macaques that respond to fat in the mouth. This finding has important implications for the development of foods with the mouth feel of fat but low energy content (110). A few neurons do respond to linoleic and/or lauric acid, but these neurons do not respond to fat in the mouth and may reflect the bad taste that rancid fats may have because of their free fatty acids (110, 177). In addition to taste inputs, some of these neurons respond to the odor associated with a fat, such as the odor of cream (122), which indicates that some of the fat-texture-related orbitofrontal cortex neurons have convergent inputs from the chemical senses. These fat-responsive neurons do not respond to a fat (e.g., cream) eaten to satiety, providing evidence that they encode the reward value of fat in the mouth, but if the neuron receives a taste input from, for example, glucose, that response is not decreased by feeding to satiety with cream (122).

Oral temperature. It has also been shown that some neurons in the insular cortex, orbitofrontal cortex, and amygdala reflect the temperature of substances in the mouth and that some neurons represent this temperature information independently of other sensory inputs, whereas other neurons represent the information in combination with taste or texture (63–65, 176). Neuronal activity in these brain areas also reflects somatosensory signals that transmit information about capsaicin (63, 64). Activations in the human orbitofrontal and insular taste cortices also reflect oral temperature (51).

Activations in humans. The viscosity of food in the mouth is represented in the human primary taste cortex (in the anterior insula) as well as in a mid-insular area that may not be primarily taste cortex but which represents oral somatosensory stimuli (25). Oral viscosity is also represented in the human orbitofrontal and perigenual cingulate cortices, and it is notable that the pregenual

cingulate cortex, an area in which many pleasant stimuli are represented, is strongly activated by the texture of fat in the mouth and also by oral sucrose (25). We have shown that the pleasantness and reward value of fat texture is represented in the mid-orbitofrontal and anterior cingulate cortices, where activations are correlated with the subjective pleasantness of oral fat texture (50, 109). This finding provides a foundation for future studies of whether activations in the fat reward system are heightened in people who tend to become obese (112). Interestingly, high-fat stimuli



with a pleasant flavor increase the coupling of activations between the orbitofrontal cortex and somatosensory cortex, which suggests that the somatosensory cortex plays a role in processing the sensory properties of food in the mouth (46).

Convergence of olfactory, taste, and visual inputs in the orbitofrontal cortex.

Neuronal activity. Taste and olfactory pathways are brought together in the orbitofrontal cortex, where flavor is formed by learned associations at the neuronal level between these inputs (see **Figure 1**) (19, 118, 124). Visual inputs also become associated by learning in the orbitofrontal cortex with the taste of food to represent the sight of food and contribute to flavor (123, 174). Olfactory-to-taste association learning by these orbitofrontal cortex neurons may take 30 to 40 trials to reverse in an olfactory-to-taste discrimination task, and this slow learning may help to make a flavor stable (123). Olfactory neurons are found in a considerable anterior-posterior extent of the primate orbitofrontal cortex, extending far into areas 11 and 14 (18, 19, 118, 123, 124), and are not restricted to a posterior region, as some have thought (41).

Visual-to-taste association learning and its reversal by neurons in the orbitofrontal cortex can take place in as little as one trial (28, 123, 174). This fast learning has clear adaptive value in enabling particular foods with a good or bad taste to be learned and recognized quickly, which is important in foraging and in food selection for ingestion. The visual inputs reach the orbitofrontal cortex from the inferior temporal visual cortex, where neurons respond to visual objects independently of their reward value (e.g., taste), as shown by satiety and reversal learning tests (107, 111, 133). The visual-to-taste associations are thus learned in the orbitofrontal cortex (114). These visual-taste neurons thus respond to expected value (114).

Different neurons in the orbitofrontal cortex respond when a visually signaled expected taste reward is not obtained, that is, the neurons respond to negative reward prediction error (114, 127, 174). Dopamine neurons in the ventral tegmentum respond to positive reward prediction error (152), and as such, they do not respond to taste reward (114). The inputs to the dopamine neurons may originate from structures such as the orbitofrontal cortex, where expected value, reward outcome (e.g., taste), and negative reward prediction error are represented (114).

Activations in humans demonstrate taste-olfactory convergence. Taste and olfactory conjunction analyses, and the measurement of supra-additive effects that provide evidence for convergence

Figure 5

(*a*, *top*) The effect of feeding to satiety with glucose solution on the responses [firing rate ± standard error of mean (SEM)] of a neuron in the primate orbitofrontal (secondary taste) cortex to the taste of glucose and black currant juice. The spontaneous firing rate is also indicated (spontaneous activity). Pre is the firing rate of the neuron before the satiety experiment started. (*a*, *bottom*) Behavioral measure of the monkey's acceptance or rejection of the solution on a scale from +2 (strong acceptance) to −2 (strong rejection). 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. (**Panel *a*** adapted from Reference 144 with permission.) (*b*) A neuron (bk265) in the primate orbitofrontal cortex responding to the texture of fat in the mouth independently of viscosity. The cell increased its firing rate to a range of fats and oils [the viscosity of which is shown in centipoise (cP)]. The information that reaches this type of neuron is independent of a viscosity-sensing channel in that the neuron did not respond to the carboxymethylcellulose (CMC) viscosity series. Evidence indicates that the neuron responded to the texture rather than the chemical structure because it also responded to silicone oil [$(Si(CH_3)_2O)_n$] and paraffin (mineral) oil (hydrocarbon). Some of these neurons have taste inputs. **Panel *b*** adapted from Reference 177 with permission.)

and interactions in fMRI investigations, showed convergence for taste (sucrose) and odor (strawberry) in the orbitofrontal and anterior cingulate cortices, and activations in these regions were correlated with the pleasantness ratings given by the participants (26, 164, 166). These results provide evidence on the neural substrate for the convergence of taste and olfactory stimuli to produce flavor in humans as well as evidence on where the pleasantness of flavor is represented in the human brain (114, 116). The effects of this olfactory-taste convergence are first found in an agranular part of what cytoarchitecturally is the insula, which is topologically found in the posterior orbitofrontal cortex, though it is anterior to the insular taste cortex and posterior to the granular orbitofrontal cortex (26, 115, 116).

McCabe & Rolls (74) have shown that the convergence of taste and olfactory information in the orbitofrontal cortex appears to be important for the delicious flavor of umami. They showed that when glutamate was given in combination with a consonant, savory odor (vegetable), the resulting flavor could be much more pleasant than the glutamate taste or vegetable odor alone, which 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; these combinations are formed in the brain far beyond the taste or olfactory receptors (109).

O'Doherty et al. (84) showed that visual stimuli associated with the taste of glucose activate the orbitofrontal cortex and some connected areas, consistent with the primate neurophysiology. Simmons et al. (162) found that showing pictures of foods, compared to pictures of places, can also activate the orbitofrontal cortex. Similarly, presenting food stimuli to food-deprived subjects activated the orbitofrontal cortex and connected areas (179).

Reward value in the orbitofrontal cortex. The visual and olfactory as well as the taste inputs represent the reward value of the food, as shown by sensory-specific satiety effects (18) (see **Figure 5*a***). The modulation of the reward value of a sensory stimulus such as the taste of food by motivational state, for example, hunger, is one important way in which motivational behavior is controlled (114, 116). The subjective correlate of this modulation is that food tastes pleasant when hunger is present and tastes hedonically neutral when it has been eaten to satiety. Following Edmund Rolls's discovery of sensory-specific satiety revealed by the selective reduction in the responses of lateral hypothalamic neurons to a food eaten to satiety (105, 137), it has been shown that sensory-specific satiety is implemented by neurons in a region that projects to the hypothalamus, the orbitofrontal (secondary taste) cortex, for the taste, odor, and sight of food (18, 116, 144). Consistent changes are found in humans (68), and this study provided evidence that the subjective pleasantness of the flavor of food, and sensory-specific satiety, are represented in the human orbitofrontal cortex.

This evidence shows that the reduced acceptance and reward value of food that occurs when food is eaten to satiety, the reduction in the pleasantness of its taste and flavor, and the effects of variety on increasing food intake (55, 99–104, 138, 140) are produced in the primate orbitofrontal cortex but not at earlier stages of processing, including in the insular-opercular primary taste cortex (143, 187) and the nucleus of the solitary tract (189), where the responses reflect factors such as the intensity of the taste, which is little affected by satiety (127, 139). In addition to providing an implementation of sensory-specific satiety (probably by adaptation of the synaptic afferents to orbitofrontal cortex neurons with a time course on the order of the length of one course of a meal), it is likely that visceral and other satiety-related signals reach the orbitofrontal cortex (as indicated in **Figure 1**) (from the nucleus of the solitary tract via thalamic nuclei, insular visceral cortex, and possibly hypothalamic nuclei) and there modulate the representation of food, resulting in an output that reflects the reward (or appetitive) value of each food (114, 116).

The Neuroeconomics of food reward value in the orbitofrontal cortex. The reward value representations in the primate orbitofrontal cortex of taste, olfactory, and flavor stimuli are appropriate for economic decision making in a number of ways (114, 116). First, the responses of orbitofrontal cortex neurons reflect the quality of the commodity or "good" (e.g., the sight or taste of food) multiplied by the amount available (86, 87). In humans, activations in the orbitofrontal cortex reflect the "subjective value" of foods (where "subjective value" in economics strictly refers to what is chosen by a subject rather than to conscious subjective pleasantness) (114, 116), measured in a task in which the value is assessed by choices between different foods and different amounts of money (94). Moreover, these neurons reflect the value of reward stimuli and not actions made to obtain them (87, 114, 148, 174, 177).

Representations in the orbitofrontal cortex of reward value on a common scale but not in a common currency. For decision making, it is important that representations of reward value are on a common scale (so that they can be compared) but are not in a common currency of general reward value, for the specific reward must be represented to guide actions (114, 116). To investigate whether specific reward representations are on a common scale of reward value, we performed an fMRI study in which we were able to show that even fundamentally different primary rewards—taste in the mouth and warmth on the hand—produced activations in the human orbitofrontal cortex that were scaled to the same range (42). Further fMRI studies are consistent with this finding (69). These reward value representations in the orbitofrontal cortex are thus in a form suitable for making decisions about, for example, whether to choose and eat a particular food, and the decision-making mechanisms are now starting to be understood (45, 114, 116, 126, 128, 129, 132).

The Amygdala

The amygdala is a structure in the temporal lobe with connections somewhat similar to those of the orbitofrontal cortex (see **Figure 1**). The amygdala has been present in evolution for much longer than the primate orbitofrontal cortex and appears to differ from the orbitofrontal cortex in that it cannot implement one-trial, rule-based, visual discrimination reversal when the taste or flavor associated with the visual stimulus is reversed (114). The primate amygdala contains neurons that respond to taste and oral texture (64, 65, 150, 156). Some neurons respond to visual stimuli associated with reinforcers such as taste but do not reflect the reinforcing properties very specifically, do not rapidly learn and reverse visual-to-taste associations, and are much less affected by reward devaluation by feeding to satiety than are orbitofrontal cortex neurons (64, 65, 114, 150, 182, 186). The primate orbitofrontal cortex appears to be much more closely involved in flexible (rapidly learned, and affected by reward devaluation) reward representations than is the primate amygdala (114).

Fat texture, oral viscosity, and temperature, for some neurons in combination with taste, as well as the sight and smell of food are represented in the macaque amygdala (64, 65, 142). Interestingly, the responses of these amygdala neurons do not correlate well with the preferences of the macaques for the oral stimuli (64), and feeding to satiety does not produce the large reduction in the responses of amygdala neurons to food (142, 186) that is typical of orbitofrontal cortex neurons.

We (34) found activation of the human amygdala by the taste of glucose. Extending this study, O'Doherty et al. (82) showed that the human amygdala was as much activated by the affectively pleasant taste of glucose as by the affectively negative taste of sodium chloride and thus provided evidence that the human amygdala is not especially involved in processing aversive as compared to rewarding stimuli. Zald et al. (190, 191) also showed that the human amygdala responds to

aversive (e.g., quinine) and to sucrose taste stimuli. Rolls (114) compared and contrasted the roles of the orbitofrontal cortex and the amygdala.

The Anterior Cingulate Cortex: A Tertiary Taste Cortical Area

The orbitofrontal cortex, including the extensive areas where the taste neurons noted above are found, projects to the pregenual cingulate cortex area 32 (16) (see **Figures 1** and **2**). In human imaging studies it has been shown that reward-related stimuli, such as the taste of sucrose and the texture of oral fat, activate the pregenual cingulate cortex (25, 45, 108, 127). In recordings made in the primate pregenual cingulate cortex, Rolls (106) showed that neurons can respond to taste and related food texture stimuli such as glucose, fruit juice, and cream, to MSG and to quinine, and that such neurons show a sensory-specific decrease in the response to the taste of glucose after feeding to satiety with glucose. These investigators hypothesized that the outcomes, the rewards and punishers, are represented in the anterior cingulate cortex because it is involved in action-outcome learning (45, 106, 108, 114, 149).

Hypothalamus

The orbitofrontal cortex and amygdala project to the hypothalamus, which is implicated in the control of food intake (114). The primate lateral hypothalamus contains taste-responsive neurons, which only respond to food when hunger is present and indeed reflect sensory-specific satiety (105, 137). The lateral hypothalamus also contains neurons that respond to the sight of food, and they also respond to food only when hunger is present, that is, when the food is rewarding (14, 76, 105, 114, 119, 137, 141). The traditional view of the hypothalamus is that it integrates many of the hormonal and nutritional signals that control appetite (77, 172, 184) (see section titled Hormonal Signals Related to Hunger and Satiety and Their Effects on the Hypothalamus), but this neurophysiological evidence shows that the hypothalamus is also involved in the reward signals from taste, olfaction, and vision that need to be interfaced to hunger and satiety signals (114).

Striatum

The primate ventral striatum and adjoining part of the head of the caudate nucleus receive connections from the orbitofrontal cortex and amygdala (52, 114). Consistent with these connections, some neurons in these striatal regions respond to the taste, flavor, and/or sight of food (114, 145, 171, 181).

These taste and related inputs to the basal ganglia may be involved in stimulus-response habit formation, with the taste and other reinforcers helping to stamp in the connections between environmental stimuli and behavioral responses that co-occur just prior to receiving a reinforcer such as the taste, flavor, or sight of food (114). Perhaps as part of this functionality, incentive stimuli such as the food can have effects on behavior that are mediated through the striatum (31, 168). Investigators (17) have questioned the hypothesis that there is less D2 receptor binding in the dorsal striatum of the obese and that this system contributes to human obesity (178). Blood-oxygen-level-dependent (BOLD) responses in the dorsal striatum to palatable food are smaller with increasing body mass index, with the reduced striatal response being interpreted as a consequence of the reduced incentive value of food in the overweight. In contrast, the relation of D2/D3 receptor binding to body mass index is positive, and this is not associated with the change in the BOLD response (17).

The striatum receives a dopaminergic input that has been suggested to be a positive reward prediction error signal (153), although there may be too much diversity in the activity of dopamine neurons for this to apply in a simple way (11, 114). Moreover, there is no evidence that the dopamine neurons encode a specific reward signal (e.g., for the taste of food versus the texture of fat) in the way that is required to account for the control of goal-directed rewarded behavior and that is present in the primate orbitofrontal cortex (114). Furthermore, the activity of ventral striatal neurons appears to be more influenced by orbitofrontal cortex types of signal rather than by positive reward prediction error signals (171). The role of the striatum and of dopamine in the control of behavior is considered in more detail elsewhere (114).

FURTHER IMAGING STUDIES ON REWARD VALUE REPRESENTATIONS IN HUMANS

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

To what extent does cognition influence the hedonics of food-related stimuli, and how far down into the sensory system does the cognitive influence reach? We measured the activation to a standard test odor (isovaleric acid combined with cheddar cheese odor, presented orthonasally using an olfactometer) that was paired with a descriptor word on a screen, which on different trials was "cheddar cheese" or "body odor." Participants rated the affective value of the standard test odor, isovaleric acid, as significantly more pleasant when labeled "cheddar cheese" than when labeled "body odor," and these effects reflected activations in the medial orbitofrontal cortex and pregenual cingulate cortex (27). The implication is that cognitive factors can have profound effects on our responses to the hedonic and sensory properties of food, in that these effects are manifest quite far down into sensory and hedonic processing (in the orbitofrontal cortex; see **Figure 1**) and affect hedonic representations of odors (27).

Similar cognitive effects and mechanisms have now been found for the taste and flavor of food in a study where the cognitive word-level descriptor was, for example, "rich delicious flavor," and activations to flavor were increased in the orbitofrontal cortex and regions to which it projects, including the pregenual cingulate cortex and ventral striatum, but were not influenced in the insular primary taste cortex, where activations reflected the intensity (concentration) of the stimuli (47) (see **Figure 6**). Cognitive factors can also influence the release of the hunger-related hormone ghrelin (21). If self-control of reward-related processing is required, the dorsolateral prefrontal cortex may be involved in the attentional and related aspects of the processing (53, 114).

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

With taste, flavor, and olfactory food-related stimuli, selective attention to pleasantness modulates representations in the orbitofrontal cortex, whereas selective attention to intensity modulates activations in areas such as the primary taste cortex (see **Figure 3**) (35, 43, 44, 71, 113, 131).

This differential biasing of brain regions engaged in processing a sensory stimulus depending on whether the cognitive demand is for affect-related versus more sensory-related processing may be an important aspect of cognition and attention that has implications for how strongly the reward system is driven by food and thus for eating and the control of appetite (43, 45, 112, 114, 131). The top-down modulations of processing have many implications for investigations of taste and olfactory and other sensory processing, and for the development of new food products.

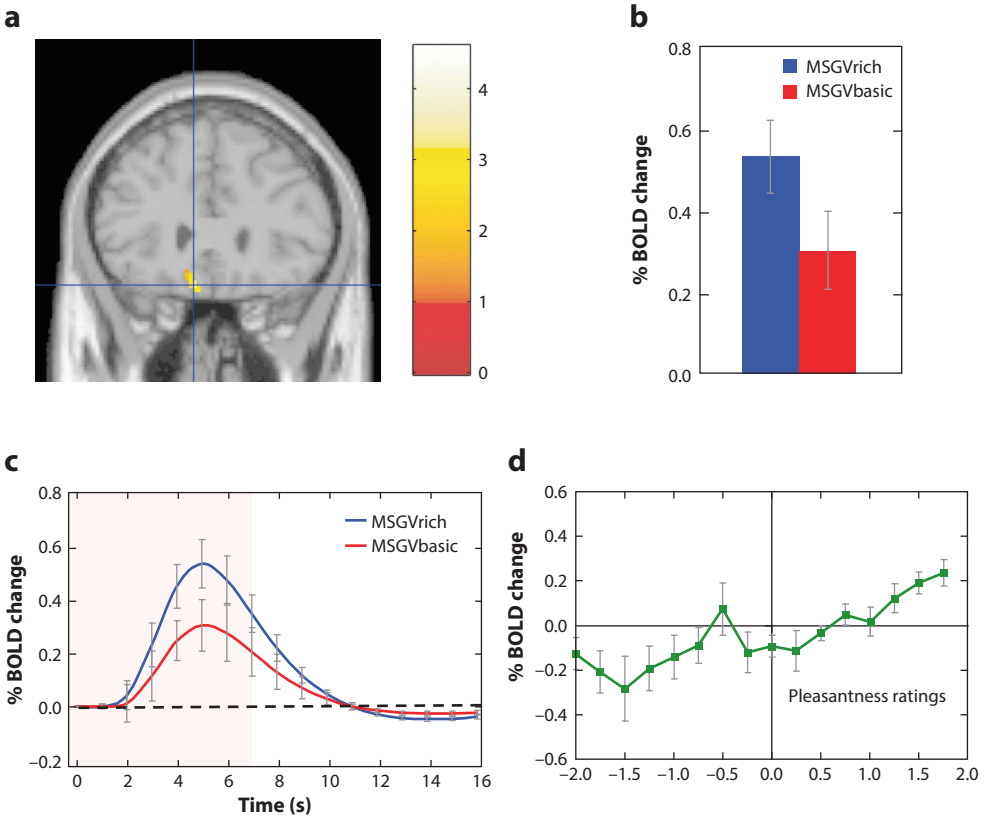


Figure 6

Cognitive modulation of flavor reward processing in the brain. (*a*) The medial orbitofrontal cortex was more strongly activated when a flavor stimulus was labeled "rich and delicious flavor" (MSGVrich) than when it was labeled "boiled vegetable water" (MSGVbasic) (−8 28 −20). The flavor stimulus, MSGV, was the taste 0.1 M monosodium glutamate + 0.005 M inosine 5′monophosphate combined with a consonant 0.4% vegetable odor. (*b*) The peak values of the BOLD signal (mean across subjects ± SEM) were significantly different ($t = 3.06$, $df = 11$, $p = 0.01$). (*c*) The time course of the blood-oxygen-level-dependent (BOLD) signals for the two conditions. (*d*) The BOLD signal in the medial orbitofrontal cortex was correlated with the subjective pleasantness ratings of taste and flavor, as shown by the Statistical Parametric Mapping (SPM) analysis and as illustrated (mean across subjects ± SEM, $r = 0.86$, $p < 0.001$). (Figure adapted from Reference 47 with permission.)

Individual Differences in the Reward System

An important hypothesis is that in humans, reward systems may differ in how strongly they are activated, and differences in these activations are driven by the sensory and cognitive factors that make taste, olfactory, and flavor stimuli attractive. In a test of this hypothesis, Rolls et al. (136) showed that activations to the sight and flavor of chocolate in the orbitofrontal and pregenual cingulate cortex were much higher in chocolate cravers than noncravers, although there were no differences at the level of the insular taste cortex. This finding provides evidence that differences in specific reward systems, and not necessarily in earlier sensory processing, can lead to individual differences in behavior to taste, olfactory, and flavor stimuli. This evidence is consistent with the hypothesis that evolution results in effective specific reward systems in part through utilization of natural variation in these reward systems and selection for reward systems that lead to reproductive success (114). The concept that individual differences in responsiveness to food reward are reflected

in brain activations in regions related to the control of food intake (4, 136) may provide a way to understand and help control food intake and obesity (112, 114).

Age-Related Differences in Food Reward Representations

Age-related differences exist in the acceptability of different foods. For example, children may not take readily to a wide range of vegetables yet find sweet foods palatable (9, 56). Adults may find a wide range of foods pleasant. As people age, smell and even taste may become less sensitive, and this may contribute to the changes in eating that can occur in aging (60). In an examination of the neural mechanisms underlying these age-related differences in the acceptability of different flavors and foods with three age groups (21, 41, and 61 years), Rolls et al. (134) found that orange flavor was liked by all age groups, whereas vegetable juice was disliked by the young and liked by the elderly. In the insular primary taste cortex, the activations to these stimuli were similar in the three age groups, indicating that the differences in liking for these stimuli between the three groups were not represented in this first stage of cortical taste processing. In the supracallosal anterior cingulate cortex, where unpleasant stimuli are represented, a greater activation to the vegetable than to the orange stimuli was identified in the young but not in the elderly. In the amygdala (and orbitofrontal cortex), where the activations were correlated with the pleasantness of the stimuli, there was a smaller activation to the vegetable than to the orange stimuli in the young but not in the elderly. These findings indicate that in some brain areas where olfactory, taste, and flavor stimuli are represented in terms of their hedonic value, age differences in the activations to different flavors can be related to, and probably cause, the age-related differences in pleasantness of foods (134).

BEYOND REWARD VALUE TO DECISION MAKING

Representations of the reward value of food, and their subjective correlate, the pleasantness of food, are fundamental in determining appetite and processes such as food-related economic decision making (86, 88, 114). But after the reward evaluation, a decision has to be made about whether to search for and consume the reward. We are now starting to understand how the brain makes decisions [as described in *The Noisy Brain: Stochastic Dynamics as a Principle of Brain Function* (126) and *Emotion and Decision-Making Explained* (114)], and this decision-making process has implications for whether a reward of a particular value will be selected (29, 45, 107, 114, 126, 127).

A tier of processing beyond the orbitofrontal cortex, in the medial prefrontal cortex area 10, becomes engaged when choices are made between odor stimuli based on their pleasantness (49, 128, 129, 132) (Tier 3 in **Figure 1**). For example, activations in this area are larger when humans make a decision about which of two odors they prefer compared to when they only rate the odors on a continuous scale of reward value (49).

HORMONAL SIGNALS RELATED TO HUNGER AND SATIETY AND THEIR EFFECTS ON THE HYPOTHALAMUS

Many peripheral signals, including hormonal signals, are produced when food is eaten, and some of these influence hunger and satiety by their direct or indirect effects on hypothalamic nuclei (5, 77, 185). These hunger/satiety signals modulate the reward value of food, that is, when hunger is present the reward value of food is high, and when satiety is present the reward value of food is low or zero. To modulate reward value, it is likely that these hypothalamic hunger/satiety signals reach the primate, including human, orbitofrontal cortex, where they affect neuronal responsiveness to

taste, olfactory, flavor, and visual stimuli to produce the food reward signal present in orbitofrontal cortex neurons. Some of the effects of these hunger/satiety signals on the hypothalamus are summarized in **Figure 7**.

Many investigators (15, 77, 175) have examined the hormone leptin, with some of the findings as follows. Leptin or OB protein is the hormone encoded by the mouse *ob* gene (here ob stands for obesity). Genetically obese mice that are double recessive for the *ob* gene (i.e., *ob/ob* mice) produce no leptin. Leptin reduces food intake in wild-type (lean) mice (which have genes that are *OB/OB* or *OB/ob*; thus, these mice produce leptin) and in *ob/ob* mice (showing that *ob/ob* mice have receptors that are sensitive to leptin). Leptin does not produce satiety (and thus reduce food intake) in another type of genetically obese mouse designated *db/db*. These mice may be obese because they lack the leptin receptor or mechanisms associated with it. Leptin has a long time course: It fluctuates over 24 hours but not in relation to individual meals. Leptin concentration may correlate with body weight/adiposity, consistent with the evidence that it is produced by fat cells, and can signal the total amount of body fat.

A hypothesis consistent with these findings is that leptin is produced in proportion to the amount of body fat and that this is a signal that influences how much food is eaten. Although leptin production is an interesting mechanism implicated in the long-term control of body weight, it

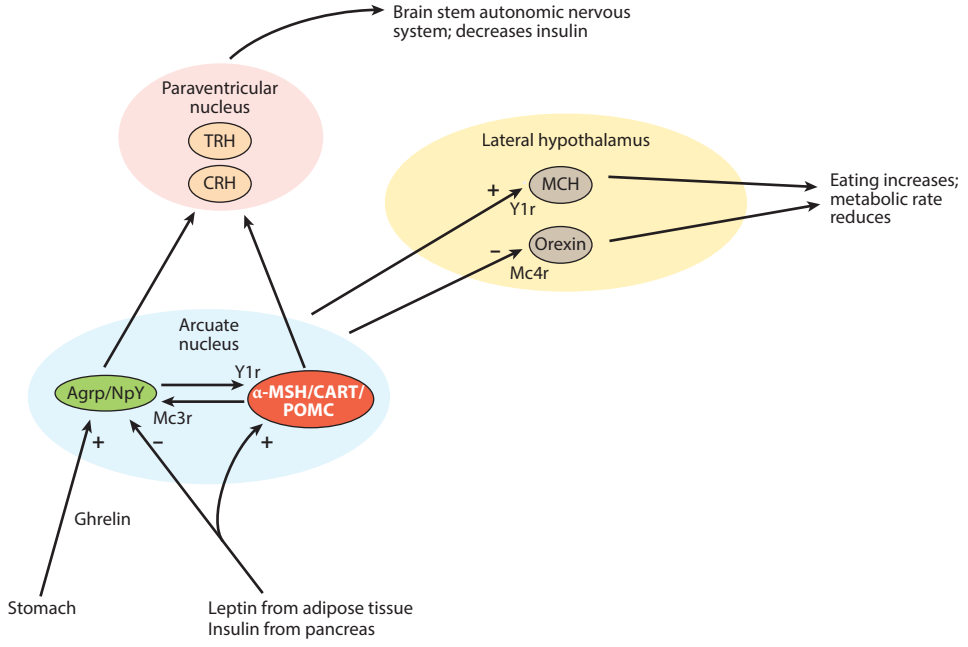


Figure 7

Effects of peripheral hunger and satiety-related signals on some of the neurochemically identified feeding-related neurons of the hypothalamus, including neurons in the arcuate, lateral hypothalamic, and paraventricular nuclei. The agouti-related peptide/neuropeptide Y (Agrp/NpY) neurons have hunger-related activity and effects (*green oval*). The α-MSH/CART/POMC neurons contain alpha-melanocyte-stimulating hormone, cocaine- and amphetamine-regulated transcript, and pro-opiomelanocortin and have satiety-related activity and effects (*red oval*). Abbreviations: CRH, corticotropin-releasing hormone; Mc3r, melanocortin-3 receptor; Mc4r, melanocortin-4 receptor; MCH, melanin-concentrating hormone; TRH, thyrotropin-releasing hormone; Y1r, NpY receptor type 1. Excitatory is indicated by +; inhibitory is indicated by −.

appears that most obesity in humans cannot be accounted for by malfunction of the leptin system because even though genetic malfunctions of this system can produce obesity in humans, such genetic malfunctions are very rare (32, 33, 175).

The brain mechanisms involved in sensing leptin and other hormones that influence feeding (77) are summarized in **Figure 7**. The lateral hypothalamus contains melanin-concentrating hormone and orexin-producing neurons, and an increase in their activity increases food intake and decreases metabolic rate (**Figure 7**). These neurons are activated by neuropeptide Y (NpY), itself a potent stimulator of food intake, which is produced by neurons in the arcuate nucleus, a hypothalamic nucleus in the ventromedial hypothalamic region. The arcuate NpY neurons also release agouti-related peptide (Agrp), itself a potent stimulator of food intake. One of the signals that activates NpY/Agrp neurons is ghrelin, a hunger hormone produced by the stomach (77, 78) (**Figure 7**). NpY/Agrp neurons increase their firing rates during fasting and are inhibited by leptin (77), so these neurons may be thought of as signaling hunger.

Leptin also inhibits the lateral hypothalamic orexin-producing neurons that are linked to eating, which may decrease feeding (77). The alpha-melanocyte-stimulating hormone/cocaine- and amphetamine-regulated transcript/pro-opiomelanocortin (α-MSH/CART/POMC) "satiety" neurons in the arcuate nucleus produce CART, which reduces hunger (i.e., is anorexigenic or increases satiety). α-MSH, which is produced by the same neurons, also reduces hunger, and these satiety neurons are also activated by leptin, providing more ways in which leptin may act to reduce feeding (77) (**Figure 7**). Consistent with these activities, the very rare humans with clear genetic dysfunctions of the leptin receptor systems may show overeating and obesity that is treatable by leptin, and approximately 4% of obese people have deficient melanocortin-4 receptors for MSH (175). Also consistently, a very rare mutation in the gene encoding POMC in humans results in low MSH levels and obesity (175).

The paraventricular nucleus contains the anorectic thyrotropin-releasing hormone and corticotropin-releasing hormone. Destruction of the paraventricular nucleus causes hyperphagia and obesity. A number of hormones released when food enters the gut also influence food intake and act via effects on the hypothalamus and on brain stem areas such as the nucleus of the solitary tract, which contains a brain stem relay of afferents from the gut. These hormones include glucagon-like peptide-1, cholecystokinin, pancreatic polypeptide, peptide YY, and oxyntomodulin (59, 95). The afferents from the gut convey the effects of gastric distension, which is essential for satiety (36, 114), and of taste and other receptors in the gut, which probably contribute to satiety.

These findings show that many hormones and other signals that influence hunger, satiety, and body weight act on the hypothalamus, but they do not address how these effects in the hypothalamus impact the reward value of the sensory stimuli produced by food to influence appetite and food intake. That impact is likely to occur in primates as a result of these hunger and satiety signals influencing taste and flavor neurons, including those in the human orbitofrontal cortex; the resulting food reward value signal is then relayed to the lateral hypothalamus, where neurons respond to food reward, in particular to the sight and taste of food when hunger is present (14, 114, 141).

POSTINGESTIVE EFFECTS OF NUTRIENTS, INCLUDING CONDITIONED APPETITE AND SATIETY

Oral signals of taste, texture, and temperature as well as retronasally sensed olfactory effects implement the hedonic reward value of food, with subjective pleasantness correlated with activations in the orbitofrontal cortex and anterior cingulate cortex. Animals including humans work to

obtain small quantities of these oral signals. Small quantities of food placed directly into the gut or provided intravenously do not produce immediate unconditioned reward (81, 155). That is, a reduction in hunger produced by directly placing food into the gut and bypassing taste and smell is not very rewarding. Consistent with this finding, turning off hunger-related Agrp neurons in the arcuate nucleus of the hypothalamus is not a good reward for instrumental behavior, although it can produce some conditioned preferences for foods or places with which the hunger reduction is associated (170).

Food sensed in the gut after ingestion can produce conditioned (learned) appetite or preference for a food and can also produce conditioned satiety, as was demonstrated by David Booth (10), who fed participants either high-energy sandwiches with flavor 1 or low-energy sandwiches with flavor 2. After subjects were fed one of these pairings for several days, when medium-energy sandwiches were provided, subjects ate more of those with flavor 2, as it had previously been paired with low-energy nutrition that was sensed after ingestion. This demonstrates how postingestive signals can influence humans' flavor preferences through conditioning. It is important to bear in mind these conditioned appetite and satiety effects in the design of low-energy foods because postingestive conditioning is likely to produce some compensation through an increase in the amount eaten of such foods.

There is considerable interest in how signals sensed in the gut contribute to the postingestive effects of nutrients. When ingested food reaches the gastrointestinal tract, it produces satiety through gastric distension and stimulation of intestinal hormone release [as shown by the absence of satiety in sham feeding in primates, when food is drained from a gastric or duodenal cannula (36)], and gastric distension occurs only if food enters the duodenum, where it activates gut receptors and causes closing of the pyloric sphincter. The closing is probably an unconditioned satiety effect produced by gastric distension and intestinal hormonal release (160). If the distension is reduced at the end of a meal, then feeding resumes very quickly, typically within one minute in primates (36, 114). In addition to the unconditioned effects of food in the gut, conditioned effects occur whereby the metabolic and other nutritive consequences of the ingestion of a flavor can influence the reward value of the flavor later [for example, in conditioned appetite (10)], which sometimes is referred to as appetition (154).

When food enters the gastrointestinal tract, it activates a wide range of gut receptors, including gut taste receptors, which locally stimulate the release of peptides, such as cholecystokinin, peptide YY, ghrelin, and glucagon-like peptide-1, from endocrine cells (30, 66, 67, 72). These gut endocrine cells play a crucial role in the regulation of food intake (59, 91, 95). The gut sensing mechanisms and their role in conditioned appetite are reviewed elsewhere (1, 62, 154). Many of the studies conducted have focused on conditioned preferences produced by food in the gastrointestinal tract, and it will be of interest in future research to analyze how visceral signals can produce conditioned satiety for the flavor with which they are paired. It also would be of interest to develop our understanding of conditioned satiety, which may be relevant to food intake control and the treatment of food intake disorders.

RELEVANCE TO THE CONTROL OF FOOD INTAKE

The investigations described in the previous sections have established that a principle of brain function is that representations of the reward/hedonic value and pleasantness of sensory stimuli, including food-related stimuli, are formed separately from representations of the stimuli and their intensity. The pleasantness/reward value is represented in areas such as the orbitofrontal cortex and pregenual cingulate cortex, and it is in those areas that hunger/satiety signals modulate the representations of food to lead to a representation of reward value. The satiety signals that help in this

modulation may reach the orbitofrontal cortex from the hypothalamus; in turn, the orbitofrontal cortex projects to the lateral hypothalamus, where neurons respond to the sight, smell, and taste of food if hunger is present (14, 105, 114, 119, 127). The principal factors that help to make a food pleasant, including particular combinations of taste, olfactory, texture, visual, and cognitive inputs, have been described in detail above and play a significant role in controlling food intake.

IMPLICATIONS FOR UNDERSTANDING, PREVENTING, AND TREATING OBESITY

Understanding the mechanisms that control appetite is becoming an increasingly important issue, given the increasing incidence of obesity: Using the World Health Organization's definition of a body mass index (weight in kg/height in meters^2) of more than 30 kg/m^2 to define obesity (**http://www.who.int/features/factfiles/obesity/facts/en/**), 30% of Americans and 10% to 20% of Europeans are classified as obese, with the prevalence rising in many developing countries. As body mass index increases, so does the relative risk of type 2 diabetes, hypertension, and cardiovascular disease (8).

Many factors can cause or contribute to obesity in humans (77, 175). Rapid progress is being made in understanding these factors at present, with the aim of improving ways to minimize and treat obesity. These factors are discussed below.

Genetic Factors

The obesity "epidemic" that has occurred since 1990 cannot be attributed to genetic changes because the time scale has been far too short for such changes to take place. Instead, the increased palatability, variety, and availability of food in our modern environment are some of the crucial drivers of the type and amount of food that is eaten (54, 112, 114). However, evidence for genetic contributions to body weight comes from family, twin, and adoption studies, which demonstrate that the heritability (fraction of the total phenotypic variance of a quantitative trait attributable to genes in a specified environment) of body mass index is between 0.71 and 0.86 (161). In a small fraction of cases, obesity can be related to particular genes, as described in the next section.

Endocrine Factors and Their Interaction with Brain Systems

A small proportion of cases of obesity can be related to gene-related dysfunctions of the peptide systems in the hypothalamus; for example, 2% to 5% of obese people have deficient melanocortin-4 receptors for melanocyte-stimulating hormone (175). Cases of obesity that can be related to changes in the leptin hormone satiety system are also rare (1–5%) (85, 175). Furthermore, obese people generally have high levels of leptin, so leptin production is not the problem, and instead leptin resistance (i.e., insensitivity) may be somewhat related to obesity, with the resistance perhaps related in part to smaller effects of leptin on arcuate nucleus NpY/Agrp neurons (79). Oxytocin can reduce hunger and may act on hypothalamic hunger-regulating neurons, and central oxytocin signaling provides a potential target in the treatment of obesity (77, 175).

Brain Processing of the Sensory Properties and Pleasantness/Reward Value of Food

The way in which the sensory factors produced by the taste, smell, texture, and sight of food interact in the brain with satiety signals (such as gastric distension and satiety-related hormones)

to determine the pleasantness and palatability of food, and therefore whether and how much food will be eaten, is described above and shown in **Figures 1** and **8**. The convergence of sensory inputs produced by the taste, smell, texture, and sight of food occurs in the orbitofrontal cortex to build a representation of food flavor. The orbitofrontal cortex is where the pleasantness and palatability of food are represented, as shown by the discoveries that these representations of food are activated only if hunger is present, and they correlate with the subjective pleasantness of the food flavor (114–116). The orbitofrontal cortex representation of whether food is pleasant (given any satiety signals present) then drives activity in brain areas, such as the striatum and cingulate cortex, that then leads to eating behavior (114).

The fundamental concept this leads to about some of the major causes of obesity is that, over the past 30 years, sensory stimulation produced by the taste, smell, texture, and appearance of food has increased dramatically, as has the availability of food, yet the satiety signals produced by stomach distension, satiety hormones, and so forth (22, 59, 95) have remained essentially unchanged, so that the effect on the brain's control system for appetite (shown in **Figures 1** and **8**) is to lead to a net average increase in the reward value and palatability of food that overrides the satiety signals and contributes to the tendency to be overstimulated by food and to overeat.

In this scenario, the prevention and treatment of obesity will be enhanced by an improved understanding of the system the brain uses to produce the representation of the pleasantness of food, how this system is modulated by eating and satiety, and how sensory factors can be designed

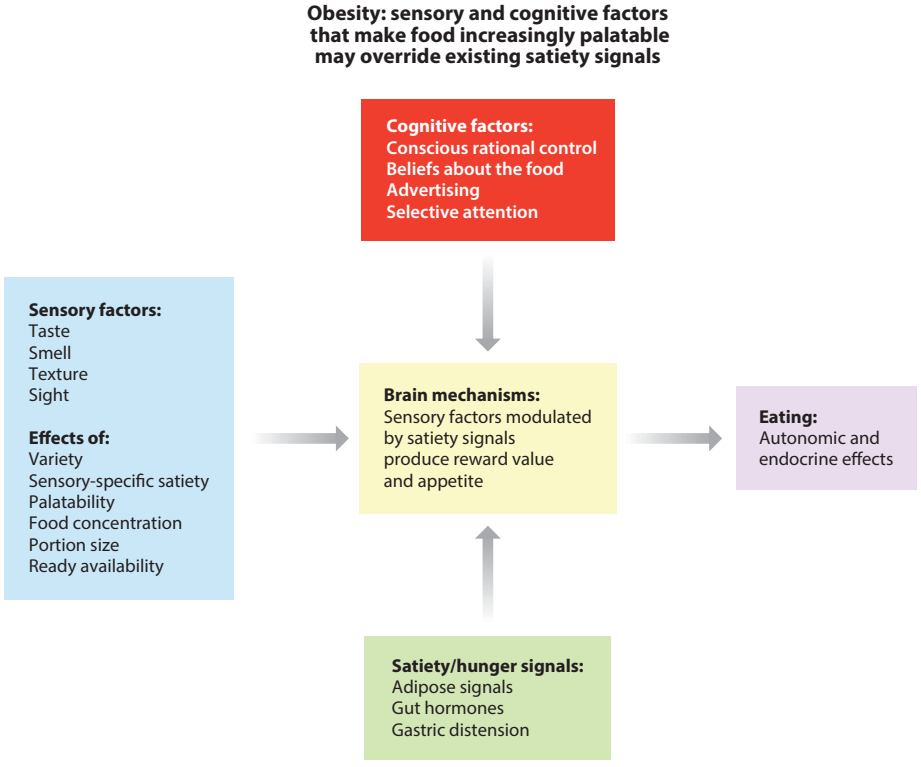


Figure 8

Sensory factors interact in the orbitofrontal cortex with satiety signals to produce the hedonic, rewarding value of food, which leads to appetite and eating. Cognitive and attentional factors directly modulate the reward system in the brain.

and controlled so as not to override satiety signals. Advances in understanding the receptors that encode the taste and olfactory properties of food (13, 193) and the processing in the brain of these and texture properties (110, 116) are also needed to provide the potential to produce food that is highly palatable as well as nutritious and healthy.

An important aspect of this hypothesis is that some humans may have reward systems that are especially strongly driven by the sensory and cognitive factors that make food highly palatable. In a test of this theory, Rolls & McCabe (136) showed that activation to the sight and flavor of chocolate in the orbitofrontal and pregenual cingulate cortex was much higher in chocolate cravers than in noncravers (136). Furthermore, the brain systems that process the sometimes aversive bitter and texture properties of food vary with age, and these properties affect people in their 40s and 60s less than those in their 20s (134). The concept that brain activations in regions related to the control of food intake reflect individual differences in responsiveness to food reward (4, 136) may provide a way to understand and help control food intake.

Food Palatability

With modern methods of food production, food palatability can now be greater than it would have been during the evolution of our feeding control systems. Brain systems evolved so that internal signals from, for example, gastric distension and glucose utilization could act to decrease the pleasantness of the sensations produced by feeding sufficiently by the end of a meal to stop further eating (114). However, the greater palatability of modern food may have altered this balancing ability, contributing to the excess consumption of food (see **Figure 8**).

Sensory-Specific Satiety and the Effects of Variety on Food Intake

Sensory-specific satiety is the decrease in the appetite for a particular food as it is eaten in a meal, without a decrease in the appetite for different foods (114, 116, 137, 140). It is an important factor influencing how much of each food is eaten in a meal, and its evolutionary significance may have been to encourage eating of a range of different foods to obtain a range of nutrients. As a result of sensory-specific satiety, if a wide variety of foods is available, overeating in a meal can occur. It is now possible to make food readily available in a very wide range of flavors, textures, and appearances, and this variety effect may be a factor that promotes excess food intake (55).

Fixed Meal Times and the Availability of Food

Another factor that could contribute to obesity is fixed meal times, in that the normal control of food intake by alterations in intermeal interval is not readily available in humans, and food may be eaten at a mealtime even if hunger is not present (114). Additionally, because of the high and easy availability of food (in the home and workplace) and stimulation by advertising, a tendency exists to start eating again when satiety signals after a previous meal have decreased only a little, and as a consequence the feeding control system becomes overloaded.

Food Saliency and Portion Size

Making food salient, for example by placing it on display, may increase food selection, particularly in the obese (151). Portion size is also a factor, with more being eaten if a large portion of food is presented (98). The driving effects of visual and other stimuli, including advertising, on the brain systems that food reward activates may differ among individuals and may contribute to obesity.

Energy Density of Food

Although gastric emptying rate is slower for high-energy-density foods, this slower rate does not fully compensate for the energy density of the food (58). It has been suggested that eating energy-dense foods (e.g., high-fat foods) may not allow gastric distension to contribute sufficiently to satiety, and thus the energy density of foods may be an important factor that influences how much energy is consumed in a meal (97). Indeed, it is notable that obese people tend to eat high-energy-density foods and to visit restaurants with high-energy-density (e.g., high-fat) foods. In addition, gastric emptying is faster in obese than in thin individuals, which indicates that gastric distension may play a less effective role in contributing to satiety in the obese. It is also important to remember that the flavor of a food can be conditioned to its energy density, which over a few days can lead to eating more low-energy-dense than high-energy-dense foods, a phenomenon known as conditioned satiety (10) (discussed in section titled Postingestive Effects of Nutrients, Including Conditioned Appetite and Satiety).

Eating Rate

A factor related to the energy density of food is the eating rate, which is typically fast in the obese and may provide insufficient time for the full effect of satiety signals to operate as food reaches the intestine.

Stress

Another factor that potentially contributes to obesity is stress, which can induce eating (93). Results of a study in a rat model indicated that mild stress experienced in the presence of food could lead to overeating and obesity. In this study, antianxiety drugs reduced overeating.

Food Craving

Binge eating has some parallels to addiction (80). In one rodent model of binge eating, access to sucrose for several hours each day can lead to binge-like consumption of sucrose over a period of days (6). Binge eating is associated with the release of dopamine. Binge eating is close to an addictive process, at least in this rodent model, in that after binge eating has become a habit, sucrose withdrawal decreases dopamine release in the ventral striatum (a part of the brain involved in addiction to drugs such as amphetamine), altered binding of dopamine to its receptors in the ventral striatum is produced, and signs of withdrawal from an addiction occur, including teeth chattering. In withdrawal, the animals are also hypersensitive to the effects of amphetamine (80). Another rat model is being used to investigate binge eating of fat and whether the associated reinforcing cues can be reduced by the $GABA_B$ receptor agonist baclofen (6).

Energy Output

If energy intake is greater than energy output, body weight increases; thus, energy output is an important factor. However, studies in humans show that although exercise has cardiovascular and brain health benefits, it does not have very significant effects on body weight gain and adiposity in the obese or in those who become obese (61, 173, 180). These findings emphasize the importance of understanding the factors that lead to overeating, including increased responsiveness of the reward system for food in some individuals as well as the effects that contribute to reward signals

produced in modern society being greater than satiety signals, which have not changed from those in our evolutionary history (54).

Cognitive Factors and Attention

As shown above, cognitive factors, such as preconceptions about the nature of a particular food or odor, can reach down into the olfactory and taste system in the orbitofrontal cortex, which controls the palatability of food, to influence how pleasant an olfactory, taste, or flavor stimulus is (27, 47). This finding has implications for further ways in which food intake can be controlled by cognitive factors, and it needs further investigation. For example, the cognitive factors that have been investigated in these studies are descriptors of the reward value of the food, such as "rich and delicious." But it could be that cognitive descriptions of the consequences of eating a particular food, such as "This food tends to increase body weight," "This food tends to alter your body shape toward fatness," "This food tends to make you less attractive," and "This food will reduce the risk of a particular disease," could also modulate the reward value of the food as it is represented in the orbitofrontal cortex. If so, these further types of cognitive modulation could be emphasized in the prevention and treatment of obesity.

Furthermore, attention to the affective properties of food modulates processing of the reward value of food in the orbitofrontal cortex (43, 131), and this again suggests that how attention is directed may be important in the extent to which food overstimulates food intake. Not drawing attention to the reward properties of food, or drawing attention to other properties such as its nutritional value and energy content, could reduce the activation of the brain's reward system by the food and could be another useful way to help prevent and treat obesity.

Summary

Overall, I suggest that new avenues in the control of overeating and body weight may be provided through a more complete understanding of all the above processes and their effects in combination rather than purely individually. I have outlined a number of factors that may tend to promote overeating and obesity in our modern society, including increasing the impact of reward signals on the brain's appetite control system and making it difficult for individuals to resist the increased hedonic value of food. Any one of these factors, or a few in combination, could produce overeating and obesity, and the conclusion I therefore reach is that in the prevention and treatment of obesity, a focus on, or the testing of, just one or a few of these factors is unlikely to be sufficient. It may be important to address all of the above factors together. The science I have described suggests that taking this overall approach and minimizing the impact of all these factors could be an important aim for future research and strategy.

CONCLUSION AND FUTURE ISSUES

In this review, some of the rules of the cortical processing of taste, olfactory, and flavor stimuli in primates including humans have been described. The discoveries provide an important foundation for understanding the brain mechanisms underlying the control of food intake.

Important future research issues and questions include:

1. Can our increasing understanding of the taste, olfactory, and food texture, including fat texture systems (110, 116), help in the development of new highly palatable and rewarding but nutritionally healthy foods?

2. What is the mechanism of transduction and peripheral encoding of oral texture (for viscosity, fat texture, etc.), and how is it relevant to the development of new foods?
3. How do hypothalamic neurons that signal hunger and satiety modulate the activity of food reward neurons in the orbitofrontal cortex and related areas?
4. Do these hypothalamic areas project their hunger- and satiety-related signals to the orbitofrontal cortex?
5. Given that hunger and satiety signals in rodents modulate taste and olfactory processing in early neural processing stages—such as in the nucleus of the solitary tract for taste and the olfactory bulb for olfaction—but do not modulate processing in primates including humans, future studies of the operation of the food reward system in primates including humans will be especially relevant to appetite control in humans.
6. To what extent does the food reward system operate differently in different individuals and predict food intake and obesity? Individual differences in these reward processes, and how they change in aging, are important and may be more significant than individual differences in hunger and satiety signals.
7. Individual differences in impulsivity may impact overeating and may reflect weaker inhibition of behavior by reward error/correction systems in the lateral orbitofrontal cortex that restrain behavior (114). The influence of this system on eating behavior is of interest, as is the question of how alcohol consumption that affects this system by increasing impulsivity (70) may also lead to an increase in eating.
8. To what extent does the explicit, reasoning system (114) provide top-down cognitive and attentional modulation of food reward information processing in the human brain, and to what extent can this influence feeding behavior and obesity?
9. In what ways are decisions about actions (such as whether to eat) made by decision-making systems in the brain based on reward value (114, 116)?
10. Many different factors acting separately may contribute to overeating and obesity. To what extent can taking into account *all* of the factors help in the control of the amount of food eaten and the prevention and control of obesity?

DISCLOSURE STATEMENT

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

ACKNOWLEDGMENTS

The Medical Research Council supported this research. The author sincerely acknowledges the participation of many colleagues in the studies cited, including Ivan de Araujo, Gordon Baylis, Leslie Baylis, Hugo Critchley, Paul Gabbott, Fabian Grabenhorst, Mikiko Kadohisa, Morten Kringelbach, Christian Margot, Ciara McCabe, Francis McGlone, John O'Doherty, Barbara Rolls, Juliet Rolls, Thomas Scott, Zenon Sienkiewicz, Simon Thorpe, Maria Ines Velazco, Justus Verhagen, and Simon Yaxley. The author warmly thanks Professor Anthony Sclafani for comments on a previous version of the Postingestive Effects of Nutrients section, which later had to be reduced in length.

LITERATURE CITED

1. Ackroff K, Sclafani A. 2014. Rapid post-oral stimulation of intake and flavor conditioning in rats by glucose but not a non-metabolizable glucose analog. *Physiol. Behav.* 133:92–98

2. Baylis LL, Rolls ET. 1991. Responses of neurons in the primate taste cortex to glutamate. *Physiol. Behav.* 49:973–79
3. Baylis LL, Rolls ET, Baylis GC. 1995. Afferent connections of the orbitofrontal cortex taste area of the primate. *Neuroscience* 64:801–12
4. Beaver JD, Lawrence AD, Ditzhuijzen JV, Davis MH, Woods A, Calder AJ. 2006. Individual differences in reward drive predict neural responses to images of food. *J. Neurosci.* 26:5160–66
5. Begg DP, Woods SC. 2013. The endocrinology of food intake. *Nat. Rev. Endocrinol.* 9:584–97
6. Berner LA, Bocarsly ME, Hoebel BG, Avena NM. 2011. Pharmacological interventions for binge eating: lessons from animal models, current treatments, and future directions. *Curr. Pharm. Des.* 17:1180–87
7. Berridge KC, Robinson TE, Aldridge JW. 2009. Dissecting components of reward: "liking," "wanting," and learning. *Curr. Opin. Pharmacol.* 9:65–73
8. Berrington de Gonzalez A, Hartge P, Cerhan JR, Flint AJ, Hannan L, et al. 2010. Body-mass index and mortality among 1.46 million white adults. *N. Engl. J. Med.* 363:2211–19
9. Birch LL. 1999. Development of food preferences. *Annu. Rev. Nutr.* 19:41–62
10. Booth DA. 1985. Food-conditioned eating preferences and aversions with interoceptive elements: learned appetites and satieties. *Ann. N. Y. Acad. Sci.* 443:22–37
11. Bromberg-Martin ES, Matsumoto M, Hikosaka O. 2010. Dopamine in motivational control: rewarding, aversive, and alerting. *Neuron* 68:815–34
12. Buck L, Axel R. 1991. A novel multigene family may encode odorant receptors: a molecular basis for odor recognition. *Cell* 65:175–87
13. Buck L, Bargmann CI. 2013. Smell and taste: the chemical senses. In *Principles of Neural Science*, ed. ER Kandel, JH Schwartz, TH Jessell, SA Siegelbaum, AJ Hudspeth, pp. 712–42. New York: McGraw-Hill
14. Burton MJ, Rolls ET, Mora F. 1976. Effects of hunger on the responses of neurones in the lateral hypothalamus to the sight and taste of food. *Exp. Neurol.* 51:668–77
15. Campfield LA, Smith FJ, Guisez Y, Devos R, Burn P. 1995. Recombinant mouse OB protein: evidence for a peripheral signal linking adiposity and central neural networks. *Science* 269:546–49
16. Carmichael ST, Price JL. 1996. Connectional networks within the orbital and medial prefrontal cortex of macaque monkeys. *J. Comp. Neurol.* 371:179–207
17. Cosgrove KP, Veldhuizen MG, Sandiego CM, Morris ED, Small DM. 2015. Opposing relationships of BMI with BOLD and dopamine D2/3 receptor binding potential in the dorsal striatum. *Synapse* 69:195–202
18. Critchley HD, Rolls ET. 1996. Hunger and satiety modify the responses of olfactory and visual neurons in the primate orbitofrontal cortex. *J. Neurophysiol.* 75:1673–86
19. Critchley HD, Rolls ET. 1996. Olfactory neuronal responses in the primate orbitofrontal cortex: analysis in an olfactory discrimination task. *J. Neurophysiol.* 75:1659–72
20. Critchley HD, Rolls ET. 1996. Responses of primate taste cortex neurons to the astringent tastant tannic acid. *Chem. Senses* 21:135–45
21. Crum AJ, Corbin WR, Brownell KD, Salovey P. 2011. Mind over milkshakes: mindsets, not just nutrients, determine ghrelin response. *Health Psychol.* 30:424–29; discussion 430–31
22. Cummings DE, Overduin J. 2007. Gastrointestinal regulation of food intake. *J. Clin. Investig.* 117:13–23
23. de Araujo IET, Kringelbach ML, Rolls ET, Hobden P. 2003. The representation of umami taste in the human brain. *J. Neurophysiol.* 90:313–19
24. de Araujo IET, Kringelbach ML, Rolls ET, McGlone F. 2003. Human cortical responses to water in the mouth, and the effects of thirst. *J. Neurophysiol.* 90:1865–76
25. de Araujo IET, Rolls ET. 2004. The representation in the human brain of food texture and oral fat. *J. Neurosci.* 24:3086–93
26. de Araujo IET, Rolls ET, Kringelbach ML, McGlone F, Phillips N. 2003. Taste-olfactory convergence, and the representation of the pleasantness of flavour, in the human brain. *Eur. J. Neurosci.* 18:2059–68
27. de Araujo IET, Rolls ET, Velazco MI, Margot C, Cayeux I. 2005. Cognitive modulation of olfactory processing. *Neuron* 46:671–79
28. Deco G, Rolls ET. 2005. Synaptic and spiking dynamics underlying reward reversal in orbitofrontal cortex. *Cereb. Cortex* 15:15–30

29. Deco G, Rolls ET, Albantakis L, Romo R. 2013. Brain mechanisms for perceptual and reward-related decision-making. *Prog. Neurobiol.* 103:194–213
30. Depoortere I. 2014. Taste receptors of the gut: emerging roles in health and disease. *Gut* 63:179–90
31. Everitt BJ, Robbins TW. 2013. From the ventral to the dorsal striatum: devolving views of their roles in drug addiction. *Neurosci. Biobehav. Rev.* 37:1946–54
32. Farooqi IS, O'Rahilly S. 2014. 20 years of leptin: human disorders of leptin action. *J. Endocrinol.* 223:T63–70
33. Farr OM, Gavrieli A, Mantzoros CS. 2015. Leptin applications in 2015: What have we learned about leptin and obesity? *Curr. Opin. Endocrinol. Diabetes Obes.* 22:353–59
34. Francis S, Rolls ET, Bowtell R, McGlone F, O'Doherty J, et al. 1999. The representation of pleasant touch in the brain and its relationship with taste and olfactory areas. *Neuroreport* 10:453–59
35. Ge T, Feng J, Grabenhorst F, Rolls ET. 2012. Componential Granger causality, and its application to identifying the source and mechanisms of the top-down biased activation that controls attention to affective versus sensory processing. *NeuroImage* 59:1846–58
36. Gibbs J, Maddison SP, Rolls ET. 1981. Satiety role of the small intestine examined in sham-feeding rhesus monkeys. *J. Comp. Physiol. Psychol.* 95:1003–15
37. Gilbertson TA. 1998. Gustatory mechanisms for the detection of fat. *Curr. Opin. Neurobiol.* 8:447–52
38. Gilbertson TA, Fontenot DT, Liu L, Zhang H, Monroe WT. 1997. Fatty acid modulation of K+ channels in taste receptor cells: gustatory cues for dietary fat. *Am. J. Physiol.* 272:C1203–10
39. Gottfried JA. 2010. Central mechanisms of odour object perception. *Nat. Rev. Neurosci.* 11:628–41
40. Gottfried JA. 2015. Structural and functional imaging of the human olfactory system. In *Handbook of Olfaction and Gustation*, ed. RL Doty, pp. 279–303. New York: Wiley Liss
41. Gottfried JA, Zald DH. 2005. On the scent of human olfactory orbitofrontal cortex: meta-analysis and comparison to non-human primates. *Brain Res.* 50:287–304
42. Grabenhorst F, D'Souza A, Parris BA, Rolls ET, Passingham RE. 2010. A common neural scale for the subjective pleasantness of different primary rewards. *NeuroImage* 51:1265–74
43. Grabenhorst F, Rolls ET. 2008. Selective attention to affective value alters how the brain processes taste stimuli. *Eur. J. Neurosci.* 27:723–29
44. Grabenhorst F, Rolls ET. 2010. Attentional modulation of affective versus sensory processing: functional connectivity and a top-down biased activation theory of selective attention. *J. Neurophysiol.* 104:1649–60
45. Grabenhorst F, Rolls ET. 2011. Value, pleasure, and choice in the ventral prefrontal cortex. *Trends Cogn. Sci.* 15:56–67
46. Grabenhorst F, Rolls ET. 2014. The representation of oral fat texture in the human somatosensory cortex. *Hum. Brain Mapp.* 35:2521–30
47. Grabenhorst F, Rolls ET, Bilderbeck A. 2008. How cognition modulates affective responses to taste and flavor: top-down influences on the orbitofrontal and pregenual cingulate cortices. *Cereb. Cortex* 18:1549–59
48. Grabenhorst F, Rolls ET, Margot C, da Silva MAAP, Velazco MI. 2007. How pleasant and unpleasant stimuli combine in different brain regions: odor mixtures. *J. Neurosci.* 27:13532–40
49. Grabenhorst F, Rolls ET, Parris BA. 2008. From affective value to decision-making in the prefrontal cortex. *Eur. J. Neurosci.* 28:1930–39
50. Grabenhorst F, Rolls ET, Parris BA, D'Souza A. 2010. How the brain represents the reward value of fat in the mouth. *Cereb. Cortex* 20:1082–91
51. Guest S, Grabenhorst F, Essick G, Chen Y, Young M, et al. 2007. Human cortical representation of oral temperature. *Physiol. Behav.* 92:975–84
52. Haber SN, Knutson B. 2010. The reward circuit: linking primate anatomy and human imaging. *Neuropsychopharmacology* 35:4–26
53. Hare TA, Camerer CF, Rangel A. 2009. Self-control in decision-making involves modulation of the vmPFC valuation system. *Science* 324:646–48
54. Heitmann BL, Westerterp KR, Loos RJ, Sorensen TI, O'Dea K, et al. 2012. Obesity: lessons from evolution and the environment. *Obes. Rev.* 13:910–22
55. Hetherington MM. 2007. Cues to overeat: psychological factors influencing overconsumption. *Proc. Nutr. Soc.* 66:113–23

56. Hetherington MM, Cecil JE, Jackson DM, Schwartz C. 2011. Feeding infants and young children. From guidelines to practice. *Appetite* 57:791–95
57. Howard JD, Gottfried JA, Tobler PN, Kahnt T. 2015. Identity-specific coding of future rewards in the human orbitofrontal cortex. *PNAS* 112:5195–200
58. Hunt JN. 1980. A possible relation between the regulation of gastric emptying and food intake. *Am. J. Physiol.* 239:G1–4
59. Hussain SS, Bloom SR. 2013. The regulation of food intake by the gut-brain axis: implications for obesity. *Int. J. Obes. (Lond.)* 37:625–33
60. Jacobson A, Green E, Murphy C. 2010. Age-related functional changes in gustatory and reward processing regions: an fMRI study. *NeuroImage* 53:602–10
61. Johns DJ, Hartmann-Boyce J, Jebb SA, Aveyard P, Behav. Weight Manag. Rev. Group. 2014. Diet or exercise interventions versus combined behavioral weight management programs: a systematic review and meta-analysis of direct comparisons. *J. Acad. Nutr. Diet.* 114:1557–68
62. Kadohisa M. 2015. Beyond flavour to the gut and back. *Flavour* 4:1–11
63. Kadohisa M, Rolls ET, Verhagen JV. 2004. Orbitofrontal cortex neuronal representation of temperature and capsaicin in the mouth. *Neuroscience* 127:207–21
64. Kadohisa M, Rolls ET, Verhagen JV. 2005. Neuronal representations of stimuli in the mouth: the primate insular taste cortex, orbitofrontal cortex, and amygdala. *Chem. Senses* 30:401–19
65. Kadohisa M, Rolls ET, Verhagen JV. 2005. The primate amygdala: neuronal representations of the viscosity, fat texture, temperature, grittiness and taste of foods. *Neuroscience* 132:33–48
66. Kokrashvili Z, Mosinger B, Margolskee RF. 2009. T1r3 and α-gustducin in gut regulate secretion of glucagon-like peptide-1. *Ann. N. Y. Acad. Sci.* 1170:91–94
67. Kokrashvili Z, Mosinger B, Margolskee RF. 2009. Taste signaling elements expressed in gut enteroendocrine cells regulate nutrient-responsive secretion of gut hormones. *Am. J. Clin. Nutr.* 90:822–25S
68. Kringelbach ML, O'Doherty J, Rolls ET, Andrews C. 2003. Activation of the human orbitofrontal cortex to a liquid food stimulus is correlated with its subjective pleasantness. *Cereb. Cortex* 13:1064–71
69. Levy DJ, Glimcher PW. 2012. The root of all value: a neural common currency for choice. *Curr. Opin. Neurobiol.* 22:1027–38
70. López-Caneda E, Rodríguez Holguín S, Cadaveira F, Corral M, Doallo S. 2014. Impact of alcohol use on inhibitory control (and vice versa) during adolescence and young adulthood: a review. *Alcohol Alcohol.* 49:173–81
71. Luo Q, Ge T, Grabenhorst F, Feng J, Rolls ET. 2013. Attention-dependent modulation of cortical taste circuits revealed by Granger causality with signal-dependent noise. *PLOS Comput. Biol.* 9:e1003265
72. Margolskee RF, Dyer J, Kokrashvili Z, Salmon KS, Ilegems E, et al. 2007. T1R3 and gustducin in gut sense sugars to regulate expression of Na^+-glucose cotransporter 1. *PNAS* 104:15075–80
73. Maruyama Y, Pereira E, Margolskee RF, Chaudhari N, Roper SD. 2006. Umami responses in mouse taste cells indicate more than one receptor. *J. Neurosci.* 26:2227–34
74. McCabe C, Rolls ET. 2007. Umami: a delicious flavor formed by convergence of taste and olfactory pathways in the human brain. *Eur. J. Neurosci.* 25:1855–64
75. Mombaerts P. 2006. Axonal wiring in the mouse olfactory system. *Annu. Rev. Cell Dev. Biol.* 22:713–37
76. Mora F, Rolls ET, Burton MJ. 1976. Modulation during learning of the responses of neurones in the lateral hypothalamus to the sight of food. *Exp. Neurol.* 53:508–19
77. Morton GJ, Meek TH, Schwartz MW. 2014. Neurobiology of food intake in health and disease. *Nat. Rev. Neurosci.* 15:367–78
78. Muller TD, Nogueiras R, Andermann ML, Andrews ZB, Anker SD, et al. 2015. Ghrelin. *Mol. Metab.* 4:437–60
79. Munzberg H, Myers MG. 2005. Molecular and anatomical determinants of central leptin resistance. *Nat. Neurosci.* 8:566–70
80. Murray S, Tulloch A, Gold MS, Avena NM. 2014. Hormonal and neural mechanisms of food reward, eating behaviour and obesity. *Nat. Rev. Endocrinol.* 10:540–52
81. Nicolaidis S, Rowland N. 1977. Intravenous self-feeding: long-term regulation of energy balance in rats. *Science* 195:589–91

82. O'Doherty J, Rolls ET, Francis S, Bowtell R, McGlone F. 2001. The representation of pleasant and aversive taste in the human brain. *J. Neurophysiol.* 85:1315–21
83. O'Doherty J, Rolls ET, Francis S, Bowtell R, McGlone F, et al. 2000. Sensory-specific satiety related olfactory activation of the human orbitofrontal cortex. *Neuroreport* 11:893–97
84. O'Doherty JP, Deichmann R, Critchley HD, Dolan RJ. 2002. Neural responses during anticipation of a primary taste reward. *Neuron* 33:815–26
85. O'Rahilly S. 2009. Human genetics illuminates the paths to metabolic disease. *Nature* 462:307–14
86. Padoa-Schioppa C. 2011. Neurobiology of economic choice: a good-based model. *Annu. Rev. Neurosci.* 34:333–59
87. Padoa-Schioppa C, Assad JA. 2006. Neurons in the orbitofrontal cortex encode economic value. *Nature* 441:223–26
88. Padoa-Schioppa C, Cai X. 2011. The orbitofrontal cortex and the computation of subjective value: consolidated concepts and new perspectives. *Ann. N. Y. Acad. Sci.* 1239:130–37
89. Pager J, Giachetti I, Holley A, Le Magnen J. 1972. A selective control of olfactory bulb electrical activity in relation to food deprivation and satiety in rats. *Physiol. Behav.* 9:573–79
90. Palouzier-Paulignan B, Lacroix MC, Aime P, Baly C, Caillol M, et al. 2012. Olfaction under metabolic influences. *Chem. Senses* 37:769–97
91. Parker HE, Gribble FM, Reimann F. 2014. The role of gut endocrine cells in control of metabolism and appetite. *Exp. Physiol.* 99:1116–20
92. Passingham REP, Wise SP. 2012. *The Neurobiology of the Prefrontal Cortex*. Oxford, UK: Oxford Univ. Press
93. Peters A, McEwen BS. 2015. Stress habituation, body shape and cardiovascular mortality. *Neurosci. Biobehav. Rev.* 56:139–50
94. Plassmann H, O'Doherty J, Rangel A. 2007. Orbitofrontal cortex encodes willingness to pay in everyday economic transactions. *J. Neurosci.* 27:9984–88
95. Price SL, Bloom SR. 2014. Protein PYY and its role in metabolism. *Front. Horm. Res.* 42:147–54
96. Pritchard TC, Edwards EM, Smith CA, Hilgert KG, Gavlick AM, et al. 2005. Gustatory neural responses in the medial orbitofrontal cortex of the Old World monkey. *J. Neurosci.* 25:6047–56
97. Rolls BJ. 2010. Dietary strategies for the prevention and treatment of obesity. *Proc. Nutr. Soc.* 69:70–79
98. Rolls BJ. 2014. What is the role of portion control in weight management? *Int. J. Obes. (Lond.)* 38(Suppl. 1):S1–8
99. Rolls BJ, Rolls ET, Rowe EA. 1983. Body fat control and obesity. *Behav. Brain Sci.* 4:744–45
100. Rolls BJ, Rolls ET, Rowe EA, Sweeney K. 1981. Sensory specific satiety in man. *Physiol. Behav.* 27:137–42
101. Rolls BJ, Rowe EA, Rolls ET. 1982. How sensory properties of foods affect human feeding behavior. *Physiol. Behav.* 29:409–17
102. Rolls BJ, Rowe EA, Rolls ET, Kingston B, Megson A, Gunary R. 1981. Variety in a meal enhances food intake in man. *Physiol. Behav.* 26:215–21
103. Rolls BJ, Van Duijvenvoorde PM, Rolls ET. 1984. Pleasantness changes and food intake in a varied four-course meal. *Appetite* 5:337–48
104. Rolls BJ, Van Duijenvoorde PM, Rowe EA. 1983. Variety in the diet enhances intake in a meal and contributes to the development of obesity in the rat. *Physiol. Behav.* 31:21–27
105. Rolls ET. 1981. Central nervous mechanisms related to feeding and appetite. *Br. Med. Bull.* 37:131–34
106. Rolls ET. 2008. Functions of the orbitofrontal and pregenual cingulate cortex in taste, olfaction, appetite and emotion. *Acta Physiol. Hung.* 95:131–64
107. Rolls ET. 2008. *Memory, Attention, and Decision-Making: A Unifying Computational Neuroscience Approach*. Oxford, UK: Oxford Univ. Press
108. Rolls ET. 2009. The anterior and midcingulate cortices and reward. In *Cingulate Neurobiology and Disease*, ed. BA Vogt, pp. 191–206. Oxford, UK: Oxford Univ. Press
109. Rolls ET. 2009. Functional neuroimaging of umami taste: what makes umami pleasant. *Am. J. Clin. Nutr.* 90:803–14S
110. Rolls ET. 2011. The neural representation of oral texture including fat texture. *J. Texture Stud.* 42:137–56
111. Rolls ET. 2012. Invariant visual object and face recognition: neural and computational bases, and a model, VisNet. *Front. Comput. Neurosci.* 6(35):1–70

112. Rolls ET. 2012. Taste, olfactory, and food texture reward processing in the brain and the control of appetite. *Proc. Nutr. Soc.* 71:488–501
113. Rolls ET. 2013. A biased activation theory of the cognitive and attentional modulation of emotion. *Front. Hum. Neurosci.* 7:74
114. Rolls ET. 2014. *Emotion and Decision-Making Explained*. Oxford, UK: Oxford Univ. Press
115. Rolls ET. 2015. Functions of the anterior insula in taste, autonomic, and related functions. *Brain Cogn.* doi: 10.1016/j.bandc.2015.07.002
116. Rolls ET. 2015. Taste, olfactory, and food reward value processing in the brain. *Prog. Neurobiol.* 127–128:64–90
117. Rolls ET. 2016. *Cerebral Cortex: Principles of Operation.* Oxford, UK: Oxford Univ. Press
118. Rolls ET, Baylis LL. 1994. Gustatory, olfactory, and visual convergence within the primate orbitofrontal cortex. *J. Neurosci.* 14:5437–52
119. Rolls ET, Burton MJ, Mora F. 1976. Hypothalamic neuronal responses associated with the sight of food. *Brain Res.* 111:53–66
120. Rolls ET, Critchley H, Wakeman EA, Mason R. 1996. Responses of neurons in the primate taste cortex to the glutamate ion and to inosine 5'-monophosphate. *Physiol. Behav.* 59:991–1000
121. Rolls ET, Critchley HD, Browning A, Hernadi I. 1998. The neurophysiology of taste and olfaction in primates, and umami flavor. *Ann. N. Y. Acad. Sci.* 855:426–37
122. Rolls ET, Critchley HD, Browning AS, Hernadi A, Lenard L. 1999. Responses to the sensory properties of fat of neurons in the primate orbitofrontal cortex. *J. Neurosci.* 19:1532–40
123. Rolls ET, Critchley HD, Mason R, Wakeman EA. 1996. Orbitofrontal cortex neurons: role in olfactory and visual association learning. *J. Neurophysiol.* 75:1970–81
124. Rolls ET, Critchley HD, Treves A. 1996. The representation of olfactory information in the primate orbitofrontal cortex. *J. Neurophysiol.* 75:1982–96
125. Rolls ET, Critchley HD, Verhagen JV, Kadohisa M. 2010. The representation of information about taste and odor in the orbitofrontal cortex. *Chemosens. Percept.* 3:16–33
126. Rolls ET, Deco G. 2010. *The Noisy Brain: Stochastic Dynamics as a Principle of Brain Function*. Oxford, UK: Oxford Univ. Press
127. Rolls ET, Grabenhorst F. 2008. The orbitofrontal cortex and beyond: from affect to decision-making. *Prog. Neurobiol.* 86:216–44
128. Rolls ET, Grabenhorst F, Deco G. 2010. Choice, difficulty, and confidence in the brain. *NeuroImage* 53:694–706
129. Rolls ET, Grabenhorst F, Deco G. 2010. Decision-making, errors, and confidence in the brain. *J. Neurophysiol.* 104:2359–74
130. Rolls ET, Grabenhorst F, Franco L. 2009. Prediction of subjective affective state from brain activations. *J. Neurophysiol.* 101:1294–308
131. Rolls ET, Grabenhorst F, Margot C, da Silva MAAP, Velazco MI. 2008. Selective attention to affective value alters how the brain processes olfactory stimuli. *J. Cogn. Neurosci.* 20:1815–26
132. Rolls ET, Grabenhorst F, Parris BA. 2010. Neural systems underlying decisions about affective odors. *J. Cogn. Neurosci.* 22:1069–82
133. Rolls ET, Judge SJ, Sanghera M. 1977. Activity of neurones in the inferotemporal cortex of the alert monkey. *Brain Res.* 130:229–38
134. Rolls ET, Kellerhals MB, Nichols TE. 2015. Age differences in the brain mechanisms of good taste. *NeuroImage* 113:298–309
135. Rolls ET, Kringelbach ML, de Araujo IET. 2003. Different representations of pleasant and unpleasant odors in the human brain. *Eur. J. Neurosci.* 18:695–703
136. Rolls ET, McCabe C. 2007. Enhanced affective brain representations of chocolate in cravers versus non-cravers. *Eur. J. Neurosci.* 26:1067–76
137. Rolls ET, Murzi E, Yaxley S, Thorpe SJ, Simpson SJ. 1986. Sensory-specific satiety: food-specific reduction in responsiveness of ventral forebrain neurons after feeding in the monkey. *Brain Res.* 368:79–86

138. Rolls ET, Rolls BJ. 1977. Activity of neurones in sensory, hypothalamic and motor areas during feeding in the monkey. In *Food Intake and Chemical Senses*, ed. Y Katsuki, M Sato, S Takagi, Y Oomura, pp. 525–49. Tokyo: Univ. Tokyo Press
139. Rolls ET, Rolls BJ, Rowe EA. 1983. Sensory-specific and motivation-specific satiety for the sight and taste of food and water in man. *Physiol. Behav.* 30:185–92
140. Rolls ET, Rolls JH. 1997. Olfactory sensory-specific satiety in humans. *Physiol. Behav.* 61:461–73
141. Rolls ET, Sanghera MK, Roper-Hall A. 1979. The latency of activation of neurons in the lateral hypothalamus and substantia innominata during feeding in the monkey. *Brain Res.* 164:121–35
142. Rolls ET, Scott TR. 2003. Central taste anatomy and neurophysiology. In *Handbook of Olfaction and Gustation*, ed. RL Doty, pp. 679–705. New York: Dekker
143. Rolls ET, Scott TR, Sienkiewicz ZJ, Yaxley S. 1988. The responsiveness of neurones in the frontal opercular gustatory cortex of the macaque monkey is independent of hunger. *J. Physiol.* 397:1–12
144. Rolls ET, Sienkiewicz ZJ, Yaxley S. 1989. Hunger modulates the responses to gustatory stimuli of single neurons in the caudolateral orbitofrontal cortex of the macaque monkey. *Eur. J. Neurosci.* 1:53–60
145. Rolls ET, Thorpe SJ, Maddison SP. 1983. Responses of striatal neurons in the behaving monkey. 1: Head of the caudate nucleus. *Behav. Brain Res.* 7:179–210
146. Rolls ET, Treves A. 2011. The neuronal encoding of information in the brain. *Prog. Neurobiol.* 95:448–90
147. Rolls ET, Verhagen JV, Kadohisa M. 2003. Representations of the texture of food in the primate orbitofrontal cortex: neurons responding to viscosity, grittiness and capsaicin. *J. Neurophysiol.* 90:3711–24
148. Rolls ET, Yaxley S, Sienkiewicz ZJ. 1990. Gustatory responses of single neurons in the caudolateral orbitofrontal cortex of the macaque monkey. *J. Neurophysiol.* 64:1055–66
149. Rushworth MF, Noonan MP, Boorman ED, Walton ME, Behrens TE. 2011. Frontal cortex and reward-guided learning and decision-making. *Neuron* 70:1054–69
150. Sanghera MK, Rolls ET, Roper-Hall A. 1979. Visual responses of neurons in the dorsolateral amygdala of the alert monkey. *Exp. Neurol.* 63:610–26
151. Schachter S. 1971. Importance of cognitive control in obesity. *Am. Psychol.* 26:129–44
152. Schultz W. 2007. Multiple dopamine functions at different time courses. *Annu. Rev. Neurosci.* 30:259–88
153. Schultz W. 2013. Updating dopamine reward signals. *Curr. Opin. Neurobiol.* 23:229–38
154. Sclafani A. 2013. Gut-brain nutrient signaling. Appetition versus satiation. *Appetite* 71:454–58
155. Sclafani A, Ackroff K, Schwartz GJ. 2003. Selective effects of vagal deafferentation and celiac-superior mesenteric ganglionectomy on the reinforcing and satiating action of intestinal nutrients. *Physiol. Behav.* 78:285–94
156. Scott TR, Karadi Z, Oomura Y, Nishino H, Plata-Salaman CR, et al. 1993. Gustatory neural coding in the amygdala of the alert macaque monkey. *J. Neurophysiol.* 69:1810–20
157. Scott TR, Plata-Salaman CR. 1999. Taste in the monkey cortex. *Physiol. Behav.* 67:489–511
158. Scott TR, Yaxley S, Sienkiewicz ZJ, Rolls ET. 1986. Gustatory responses in the frontal opercular cortex of the alert cynomolgus monkey. *J. Neurophysiol.* 56:876–90
159. Scott TR, Yaxley S, Sienkiewicz ZJ, Rolls ET. 1986. Taste responses in the nucleus tractus solitarius of the behaving monkey. *J. Neurophysiol.* 55:182–200
160. Seeley RJ, Kaplan JM, Grill HJ. 1995. Effect of occluding the pylorus on intraoral intake: a test of the gastric hypothesis of meal termination. *Physiol. Behav.* 58:245–49
161. Silventoinen K, Magnusson PK, Tynelius P, Kaprio J, Rasmussen F. 2008. Heritability of body size and muscle strength in young adulthood: a study of one million Swedish men. *Genet. Epidemiol.* 32:341–49
162. Simmons WK, Martin A, Barsalou LW. 2005. Pictures of appetizing foods activate gustatory cortices for taste and reward. *Cereb. Cortex* 15:1602–8
163. Small DM. 2010. Taste representation in the human insula. *Brain Struct. Funct.* 214:551–61
164. Small DM, Prescott J. 2005. Odor/taste integration and the perception of flavor. *Exp. Brain Res.* 166:345–57
165. Small DM, Scott TR. 2009. Symposium overview: What happens to the pontine processing? Repercussions of interspecies differences in pontine taste representation for tasting and feeding. *Ann. N. Y. Acad. Sci.* 1170:343–46

166. Small DM, Voss J, Mak YE, Simmons KB, Parrish T, Gitelman D. 2004. Experience-dependent neural integration of taste and smell in the human brain. *J. Neurophysiol.* 92:1892–903
167. Small DM, Zald DH, Jones-Gotman M, Zatorre RJ, Pardo JV, et al. 1999. Human cortical gustatory areas: a review of functional neuroimaging data. *Neuroreport* 10:7–14
168. Smith DG, Robbins TW. 2013. The neurobiological underpinnings of obesity and binge eating: a rationale for adopting the food addiction model. *Biol. Psychiatry* 73:804–10
169. Sobel N, Prabkakaran V, Zhao Z, Desmond JE, Glover GH, et al. 2000. Time course of odorant-induced activation in the human primary olfactory cortex. *J. Neurophysiol.* 83:537–51
170. Sternson SM. 2013. Hypothalamic survival circuits: blueprints for purposive behaviors. *Neuron* 77:810–24
171. Strait CE, Sleezer BJ, Hayden BY. 2015. Signatures of value comparison in ventral striatum neurons. *PLOS Biol.* 13:e1002173
172. Suzuki K, Simpson KA, Minnion JS, Shillito JC, Bloom SR. 2010. The role of gut hormones and the hypothalamus in appetite regulation. *Endocr. J.* 57:359–72
173. Thomas DM, Bouchard C, Church T, Slentz C, Kraus WE, et al. 2012. Why do individuals not lose more weight from an exercise intervention at a defined dose? An energy balance analysis. *Obes. Rev.* 13:835–47
174. Thorpe SJ, Rolls ET, Maddison S. 1983. Neuronal activity in the orbitofrontal cortex of the behaving monkey. *Exp. Brain Res.* 49:93–115
175. van der Klaauw AA, Farooqi IS. 2015. The hunger genes: pathways to obesity. *Cell* 161:119–32
176. Verhagen JV, Kadohisa M, Rolls ET. 2004. The primate insular/opercular taste cortex: neuronal representations of the viscosity, fat texture, grittiness, temperature and taste of foods. *J. Neurophysiol.* 92:1685–99
177. Verhagen JV, Rolls ET, Kadohisa M. 2003. Neurons in the primate orbitofrontal cortex respond to fat texture independently of viscosity. *J. Neurophysiol.* 90:1514–25
178. Volkow ND, Wang GJ, Tomasi D, Baler RD. 2013. Obesity and addiction: neurobiological overlaps. *Obes. Rev.* 14:2–18
179. Wang GJ, Volkow ND, Telang F, Jayne M, Ma J, et al. 2004. Exposure to appetitive food stimuli markedly activates the human brain. *NeuroImage* 21:1790–97
180. Wilks DC, Besson H, Lindroos AK, Ekelund U. 2011. Objectively measured physical activity and obesity prevention in children, adolescents and adults: a systematic review of prospective studies. *Obes. Rev.* 12:e119–29
181. Williams GV, Rolls ET, Leonard CM, Stern C. 1993. Neuronal responses in the ventral striatum of the behaving macaque. *Behav. Brain Res.* 55:243–52
182. Wilson FAW, Rolls ET. 2005. The primate amygdala and reinforcement: a dissociation between rule-based and associatively-mediated memory revealed in amygdala neuronal activity. *Neuroscience* 133:1061–72
183. Wise SP. 2008. Forward frontal fields: phylogeny and fundamental function. *Trends Neurosci.* 31:599–608
184. Woods SC. 2013. Metabolic signals and food intake. Forty years of progress. *Appetite* 71:440–44
185. Woods SC, Begg DP. 2016. Regulation of the motivation to eat. *Curr. Topics Behav. Neurosci.* In press
186. Yan J, Scott TR. 1996. The effect of satiety on responses of gustatory neurons in the amygdala of alert cynomolgus macaques. *Brain Res.* 740:193–200
187. Yaxley S, Rolls ET, Sienkiewicz ZJ. 1988. The responsiveness of neurons in the insular gustatory cortex of the macaque monkey is independent of hunger. *Physiol. Behav.* 42:223–29
188. Yaxley S, Rolls ET, Sienkiewicz ZJ. 1990. Gustatory responses of single neurons in the insula of the macaque monkey. *J. Neurophysiol.* 63:689–700
189. Yaxley S, Rolls ET, Sienkiewicz ZJ, Scott TR. 1985. Satiety does not affect gustatory activity in the nucleus of the solitary tract of the alert monkey. *Brain Res.* 347:85–93

190. Zald DH, Hagen MC, Pardo JV. 2002. Neural correlates of tasting concentrated quinine and sugar solutions. *J. Neurophysiol.* 87:1068–75
191. Zald DH, Lee JT, Fluegel KW, Pardo JV. 1998. Aversive gustatory stimulation activates limbic circuits in humans. *Brain* 121:1143–54
192. Zatorre RJ, Jones-Gotman M, Evans AC, Meyer E. 1992. Functional localization of human olfactory cortex. *Nature* 360:339–40
193. Zhao GQ, Zhang Y, Hoon MA, Chandrashekar J, Erlenbach I, et al. 2003. The receptors for mammalian sweet and umami taste. *Cell* 115:255–66

Annual Review of Nutrition

Volume 36, 2016

Contents

Indexes

Errata

An online log of corrections to *Annual Review of Nutrition* articles may be found at http://www.annualreviews.org/errata/nutr