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OPINION

The neural mechanisms of gustation: a distributed processing code

Sidney A. Simon, Ivan E. de Araujo, Ranier Gutierrez and Miguel A. L. Nicolelis

Abstract | Whenever food is placed in the mouth, taste receptors are stimulated. Simultaneously, different types of sensory fibre that monitor several food attributes such as texture, temperature and odour are activated. Here, we evaluate taste and oral somatosensory peripheral transduction mechanisms as well as the multi-sensory integrative functions of the central pathways that support the complex sensations that we usually associate with gustation. On the basis of recent experimental data, we argue that these brain circuits make use of distributed ensemble codes that represent the sensory and post-ingestive properties of tastants.

The gustatory system enables animals to detect and discriminate among foods, to select nutritious diets, and to initiate, sustain and terminate ingestion for the purpose of maintaining energy balance. For most mammals, the decision to ingest a particular food depends not only on its taste but also on its appearance, familiarity, odour, texture, temperature and, importantly, its post-ingestive effects (for example, the ability to reduce hunger). For humans, such factors also include cultural acceptance as well as the social, emotional and cognitive contexts[1] under which a given food is eaten.

Previous reviews on gustatory processing tended to focus on either the molecular bases of peripheral transduction events or on central taste representations in isolation from other modalities[2–7]. Here, we propose instead that the biological functions of gustation must be considered in combination with several sensory and physiological processes that occur simultaneously with taste receptor activation. According to this view, gustation is a distributed neural process by which information conveyed to the brain through specialized taste, orosensory and gastrointestinal fibres is integrated, so that the organism can engage in appropriate feeding behaviours. Such a view emerges from the analysis of recent experimental data[8–11] showing that the neural mechanisms of gustation rely on neural ensemble codes supported by populations of neurons that are capable of encoding the multisensory properties of intra-oral stimuli under particular physiological states. Revealing the logic of the neural mechanism of gustation is currently a major topic in neurobiology, given the efforts made so far towards the understanding of how

complex feeding behaviours can become dysfunctional (as in the case of obesity).

We cover three main topics. First, we describe the interactions between various oral taste and somatosensory receptors in the PNS. We then focus on the convergence of gustatory, somatosensory and visceral influences at the brainstem level. Finally, we describe current data on the behaviour of neural populations located in the forebrain relating to the multisensory and postingestive properties of intra-oral stimuli.

The peripheral gustatory system

Although the sense of taste is generally associated solely with the activation of taste buds, the act of placing food or drinks in the mouth automatically elicits responses from a different system that monitors the temperature and texture of the food. In this regard, gustation is inherently multisensory. It is generally accepted that there are five primary tastes: salt, sweet, bitter, umami (a savoury taste) and sour (acidic). However, every gourmet worth his/her salt is aware that this list should also include perceptual categories such as astringent, fatty, tartness, water, metallic, starchy, cooling, tingling and pungent. As we discuss, the subjective sensations associated with these non-primary tastes result from the co-activation of taste and specialized somatosensory neurons located in the oral cavity. These specialized neurons surround taste buds, and include different classes of mechano- and chemoreceptors that transmit information on the food's texture, weight and temperature to the brain mainly via the trigeminal system (FIG. 1).

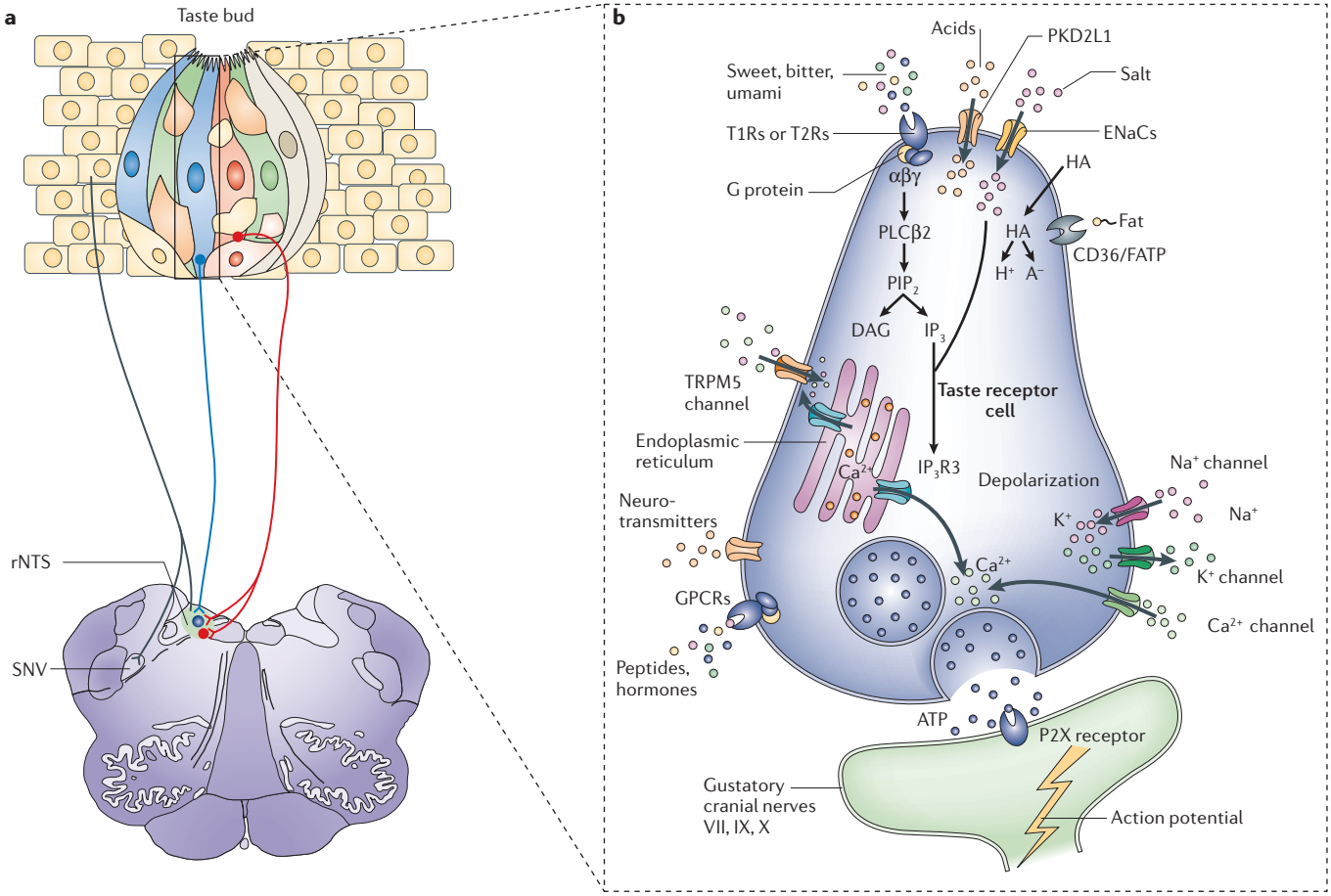

Figure 1 | **Schematic diagram of a taste bud, taste receptor cell and associated neurons. a** | Illustration of a taste bud that is embedded in an epithelium. The different types of taste receptor cell (TRC) are indicated by different colours as they can contain different types of receptor and intracellular modulator. The gustatory neurons with their associated colours that match the associated TRCs indicate that they might respond best to those stimuli that activate the particular TRCs. These primary gustatory neurons project ipsilaterally to the rostral nucleus tractus solitarius (rNTS). The black coloured axon that is embedded in the epithelia that surrounds the taste bud is likely to be a nociceptor. These neurons project ipsilaterally to the spinal nucleus of the trigeminal cranial nerve (SNV) and have collaterals that project to the rNTS. **b** | Diagram of a generic TRC with an associated neuron. The apical membrane of this TRC contains receptors for tastants that are not necessarily in the same TRC. These receptors include G-protein-coupled receptors (GPCRs) for amino acids (T1R1/T1R3), sweet tastants (T1R2/T1R3), bitter tastants (T2Rs) and for long chain fatty acids (CD36/FATP). The GPCRs and ion channels in the basolateral membrane have been shown to be responsive to peptides and hormones, and neurotransmitters, respectively. Ion channels that are likely to be involved in salt taste (epithelial sodium channels, ENaCs) and acid taste (PKD2L1) are also on the apical membrane. The undissociated form of the acid (HA) diffuses into the TRCs, and protons, sodium and calcium could permeate through PKD2L1 channels. The basolateral membranes of selected TRCs contain TRPM5 channels. Also shown are intracellular pathways that include α-gustducin and PLCβ2, which degrades phosphatidylinositol-4,5-bisphosphate (PIP_2) to produce diacylglycerol (DAG) and inositol-1,4,5-trisphosphate (IP_3). IP_3 could then bind to and activate IP_3R3 receptors on the endoplasmic reticulum that release calcium. The increase in calcium could activate TRPM5 receptors and cause transmitters such as ATP to be released from synaptic vesicles to bind to their receptors on primary neurons. In other TRCs, such as those activated by NaCl, their depolarization might evoke action potentials through the activation of voltage-dependent sodium, potassium and calcium channels. Note that all the transduction pathways and receptors are drawn in a single model TRC.

The taste bud and associated neural afferents. In the oral chemosensory epithelia, onion-shaped structures known as taste buds contain 50–100 taste receptor cells (TRCs) of various types[12]. These TRCs are embedded in stratified epithelia and are distributed throughout the tongue, palate, epiglottis and oesophagus[12–14]. On their apical end, taste cells make contact with the oral cavity through a small opening in the epithelium called the taste pore, which is filled with microvilli. The plasma membranes of these microvilli contain many of the receptors responsible for detecting the presence of various tastants (FIG. 1). Tight junctions, located just below the microvilli, protect the basolateral side of the TRCs from potentially cell-damaging compounds that are placed in the mouth[15]. Small clusters of TRCs are electrically and chemically coupled by gap junctions[16,17]. As TRCs have resistances in the giga-ohm range, it has been suggested that the activation of any TRC in a cluster will affect the responses of others via gap junctions[17–19].

On the palate and the anterior tongue, TRCs are innervated by the chorda tympani and greater superior petrosal branches of the facial nerve, respectively. These nerves transmit information about the identity and quantity of the chemical nature of the tastants. On the epiglottis, oesophagus and posterior tongue, TRCs are innervated by the lingual branch of the glossopharyngeal nerve and the superior laryngeal branch of the vagus nerve. These nerves are responsive to tastants[20,21] and participate primarily in the brainstem-based arch reflexes that mediate swallowing (ingestion) and gagging (rejection)[14,22,23]. TRCs transmit information to the peripheral nerves by releasing ATP[24] to $P2X_2$/$P2X_3$ purinergic receptors located on the postsynaptic membrane of primary afferents[5,25–27]. Other transmitters such as serotonin, glutamate and acetylcholine might also be released.

Transduction pathways for primary tastes. The key to understanding how TRCs transduce chemical stimuli lies in determining the identification and operation of different types of taste receptor and their downstream signalling pathways[4,6,28,29]. Proteins belonging to the G-protein-coupled receptor (GPCR) superfamily have been established as the receptors for sweet tastants (taste receptor, type 1, member 2 (T1R2)/T1R3), amino acids (T1R1/T1R3) and bitter (T2Rs) tastants[29–37]. Selected downstream pathways for these receptors are shown in FIG. 1. The sensations associated with the other two primary tastants, sour and salt (NaCl), are mediated by ion channels of the transient receptor potential (TRP)[38] and epithelial sodium channel (ENaC)[39] superfamilies, respectively.

The transduction of sweet tastants involves the presence of heterodimeric T1Rs — that is, T1Rs containing two different subunits, in this case T1R2/T1R3 (REFS 29,37,40). There seems to be only one type of broadly tuned receptor that subserves detection of both natural sugars and artificial sweeteners[40]. It is noteworthy, however, that saccharin can produce, in addition to sweetness, other interesting taste sensations. At high concentrations its sweet taste sensation is replaced by a bitter taste quality but, when the mouth is rinsed with water, a sweet 'water taste' is perceived[41].

Nearly all foods contain a variety of amino acids. The transduction of L-amino acids, including glutamate, is primarily accomplished through G-protein-coupled heterodimeric T1R1/T1R3 receptors[42]. In mice, the T1R1/T1R3 receptors are broadly tuned to respond to L-amino acids[37,42], whereas the human T1R1/T1R3 receptors are more narrowly tuned to glutamate. Some studies in rodents suggest that T1R1/T1R3 receptors might not exclusively transduce the response to glutamate[43–45].

Homodimeric T2Rs (that is, those that contain the same two subunits) have been found to be both necessary and sufficient for bitter taste transduction and perception[35]. T2Rs are co-expressed in TRCs with gustducin, suggesting that this protein is part of the signalling pathway for bitter taste transduction. Indeed, α-gustducin-knockout mice have a decreased sensitivity to bitter tastants[46]. The T2R family contains about 30 members[35,47]. Given the diversity of compounds that taste bitter, it is not surprising that the number of T2Rs is large[35,48]. This selectivity, as well as the fact that individuals might be missing one of the receptors or have less sensitive T2R variants[49] could explain why some people can eat certain foods with bitter tasting chemicals, such as brussels sprouts or broccoli, whereas others find them unpleasant. The latter group, however, retain their sensitivity to other bitter tastants[50,51].

In rodents, at least, an amiloride-sensitive sodium channel from the ENaC/Deg superfamily primarily accounts for the transduction of NaCl[52,53]. Amiloride reduces, but does not completely eliminate, the responses to NaCl in TRCs and chorda tympani neurons[54,55]. However, whether and the extent to which human responses to NaCl are inhibited by amiloride remain controversial[53,56].

In addition to the conventional salty taste of NaCl, salts with different cations and anions evoke different gustatory sensations[57,58]. The responses to these salts are not transduced by ENaCs and can be readily distinguished from NaCl[54,55]. Depending on the particular salt, they can be perceived as salty, bitter, metallic or astringent. Recent studies of TRCs in wild-type and TRPV1-null mice have indicated that this salt pathway might involve a capsaicin- and temperature-sensitive variant of a constitutively active TRPV1 channel[59,60]. The final evidence for the involvement of this variant in amiloride-insensitive salt taste must wait until this receptor is cloned and shown to be functional in TRCs.

The molecular mechanisms involved in sour taste transduction have recently been uncovered. Genetic and functional studies identified one member of the TRP superfamily, the polycystic kidney disease-like ion channel PKD2L1, as necessary for sour taste transduction[38,61,62]. In fact, peripheral neural recordings from animals lacking PKD2L1-expressing taste cells indicated that they were completely unresponsive to sour tasting stimuli[38]. Importantly, this channel was found to be expressed in a subset of taste receptor cells distinct from those responsible for sweet, bitter and umami taste transduction[38]. When co-expressed with the related protein PKD2L3 in heterologous cells, PKD2L1 was found to be a non-selective cation channel that is permeable to calcium and sodium[61]. Furthermore, it can be surmised from the nerve recording results[38] that it is also permeable to protons[63], at least in the absence of sodium. We note that this TRP channel has many characteristics associated with the amiloride-insensitive salt responses.

Finally, although the taste transduction processes described above were treated as if they operate independently, mixtures of tastants can interact in such a way that individual transduction processes could become altered. For example, in the case of acid–salt combinations, acidic compounds can reduce the salty taste of NaCl[3].

TRC modulation by non-sapid stimuli. Evidence for multisensory processing can already be found at the peripheral level of the gustatory system. One important example concerns the nerve responses to dietary fat. Many animals show a spontaneous attraction for lipids, and such behaviour raises the possibility that an orosensory system is responsible for the detection of

dietary lipids. Their intake is controlled by rapid orosensory stimuli and delayed postingestive signals[64]. Until recently, dietary fats and oils were believed to be sensed solely by their texture and/or viscosity[65,66]. However, recent studies in TRCs revealed that they express a fatty acid receptor/transporter, CD36, which binds long-chain fatty acids (LCFAs)[67] and facilitates their transfer into the cell[68]. When the *Cd36* gene is inactivated, preference for LCFA-enriched solutions, normally observed in wild-type mice, is abolished. Further studies are beginning to elucidate the transduction machinery for LCFAs[69,70].

TRCs also contain receptors for many circulating hormones and neuropeptides. Among these hormones are aldosterone and antidiuretic hormone (ADH), which enhance responses to NaCl by increasing the permeability of Na^+ through amiloride-sensitive sodium channels on the apical membrane of mammalian TRCs[71,72] (see below; FIG. 1). TRCs also contain appetite-modulating peptides, including leptin, neuropeptide Y (NPY)[19] and cholecystokinin (CCK)[73], as well as their receptors. The release of these peptides, and other compounds such as serotonin, into the taste bud has been suggested to modulate, in an autocrine or paracrine manner, the responses to tastants[5,19,74].

TRCs can also be modulated by other types of chemical compound. These include typical trigeminal stimulants such as capsaicin, tannic acid and menthol (see below). Physical variables, such as temperature, might also affect the ability of TRCs to transduce tastant information as evidenced by the fact that warming the anterior tongue produces a sweet sensation[75,76]. This phenomenon could arise as a consequence of the thermal sensitivity of TRPM5 channels in TRCs on the anterior tongue that have T1R2/T1R3 receptors[77]. A further degree of complexity arises when temperature interacts with other trigeminal stimulants, in such a way that their respective subjective perceptions are enhanced[78]. Together, these data indicate that, even at the level of taste buds, multiple non-sapid sensory and neurohormonal factors can affect how gustatory information is processed.

Intra-oral somatosensory responses. As noted, TRC activation by sapid stimuli is concurrent with the activation of the oral somatosensory system. More precisely, taste buds are intercalated and surrounded by general sensory nerve endings from the trigeminal, glossopharyngeal and vagal nerves[12]. Some of these nerve endings contain thermoreceptors[79,80], whereas others behave as rapidly or slowly adapting mechanoreceptors. These somatosensory receptors transduce information about the thermal, chemical and physical properties of foods[81,82]. For example, some general sensory nerve endings that contain thermosensitive TRPV1 receptors also respond to the presence of spices, such as capsaicin, found in chili peppers[83]. These capsaicin-sensitive neurons are nociceptors that when activated release vasodilators such as calcitonin gene-related peptide and substance P. This increases the tongue's temperature[84], which in turn could affect the responses of TRCs to sweet tastants[75]. Other thermoreceptors, such as TRPM8, are activated by menthol and produce a cooling sensation[85], whereas TRPV3 receptors are activated by oregano, savoury, clove and thyme[86].

Lowering intra-oral pH levels can also cause the activation of trigeminal neurons. This increase in acidity can produce an unpleasant burning sensation, or in the presence of CO_2 (or carbonic anhydrase, which produces HCO^-_3 and H^+) can cause a pleasant tingling sensation[87,88].

Interestingly, many of the general somatosensory nerve endings are also activated by the same chemicals that define some primary tastants, such as NaCl (FIG. 2), although this usually requires higher concentrations[87,89]. However, instead of encoding information about taste quality or concentration, these nerve endings signal the presence of compounds in foods that produce irritating, cooling or burning sensations, thereby providing inputs for the multisensory components of the gustatory system. Analogous processes occur when ethanol is placed in the mouth[90], resulting in the burning sensation that accompanies the ingestion of alcoholic drinks.

Some chemically induced taste sensations fall outside the usual categorization of tastes. For example, the astringent (or dry) taste sensation produced by polyphenols — such as tannic acid, a compound found in tea, wine and unripe fruits — arises not from the activation of TRCs, but primarily from the precipitation of proline-rich peptides in saliva[91,92].

In summary, the peripheral gustatory system extracts multisensory information from foods placed in the mouth, and conveys this information through multiple neural pathways to brainstem structures[93] (FIG. 2).

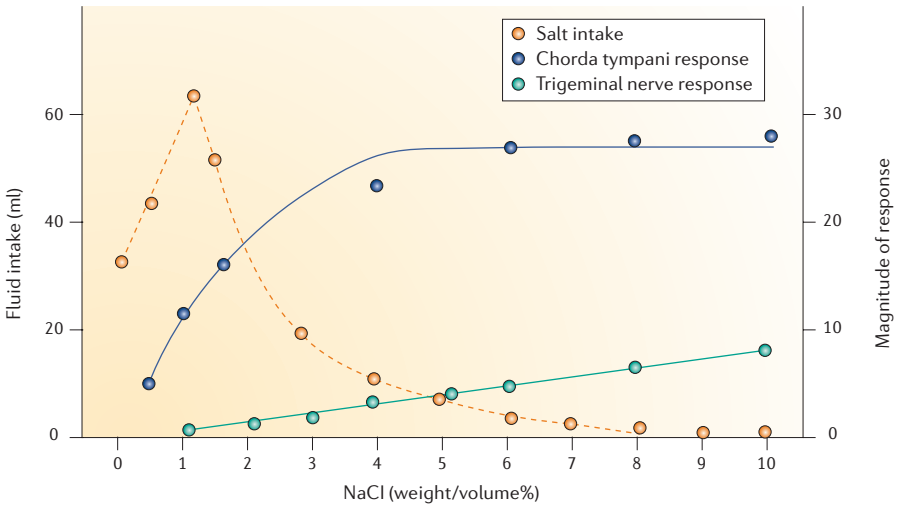

Figure 2 | **Salt intake is explained by input from both gustatory and trigeminal nerves.** Plots showing that as the NaCl concentration increases, the salt intake (orange circles) initially increases until it reaches a maximum of 1% (weight (gm)/volume (100 ml)) (0.17 M). The intake then monotonically decreases until the rats do not accept any NaCl after 7% (weight/volume). With increasing NaCl concentration the chorda tympani, which innervates taste receptor cells, thereby providing an indication of taste responses (blue circles), shows an increase in activity. With increasing NaCl the activity — most likely from nociceptors — obtained from the lingual branch of the trigeminal nerve increases linearly (green circles). Note that the maximum fluid intake occurs when the lingual nerve activity is essentially zero and the intake decreases as the lingual nerve activity increases. So, the hedonically positive aspects of NaCl are signalled by responses of the chorda tympani nerve, whereas the hedonically negative aspects of NaCl are signalled by the trigeminal nerve. Therefore, to explain the animals' behaviour, sensory information from both neuronal pathways needs to be taken into account. Modified, with permission, from REF. 93 © (1968) Elsevier Science.

Glossary

Amiloride
A potassium-sparing diuretic that inhibits epithelial sodium channels (ENaCs) in the kidney and in taste receptor cells.

Carbonic anhydrase
Family of zinc-containing enzymes that catalyse the rapid interconversion of carbon dioxide and water into protons and bicarbonate ions.

Cholecystokinin
(CCK). A peptide hormone secreted from the mucosal epithelial cells in the small intestine (duodenum) that causes the release of digestive enzymes from the pancreas. Peripheral and central administration of CCK reduces appetite.

Chorda tympani nerve
Branch of cranial nerve VII that innervates the front two-thirds of the tongue and carries taste information to the brain.

Conditioned taste aversion
(CTA). This is a one-trial form of learning that occurs when a palatable tastant becomes aversive after pairing with gastric malaise.

ENaC/Deg
Epithelial sodium channel (ENaC)/degenerin (Deg) is a superfamily of ion channels involved in epithelial Na^+ transport, mechanotransduction and neurotransmission.

Forebrain
The anterior portion of the brain that includes the telencephalon and the diencephalon. It contains the cerebral cortex, the thalamus and the hypothalamus.

Gap junction
A junction between two cells consisting of pores that allow the passage of molecules (up to 1 kDa).

Glossopharyngeal nerve
Cranial nerve IX, receiving sensory fibres from the posterior one-third of the tongue, the tonsils and the pharynx.

Greater superior petrosal nerve
Branch of cranial nerve VII that innervates the back of the tongue and palate.

Gustducin
A G protein that is almost exclusively expressed in taste cells.

Neuropeptide Y
(NPY). A member of the pancreatic polypeptide hormone family, this peptide is produced and released by cell groups located in the hypothalamic arcuate nucleus. Central administration of NPY increases food intake and metabolism.

Purinergic receptors
These receptors are ion channels that are activated by ATP.

Sensory-specific satiety
Term referring to a specific reduction in the reward value of a particular food that has been eaten until satiety.

Superior laryngeal branch
Nerve that arises from the inferior vagal ganglion inferior to the pharyngeal branch of the vagus nerve.

Temporal coding models
These models propose that information on taste identity and quality is encoded in the temporal structure of spike trains.

TRPM5
A cation channel member of the transient receptor potential superfamily (subfamily M, member 5). Regulation of TRPM5 by Ca^{2+} could mediate transduction in taste receptor cells. It is required for the normal transduction of sweet, bitter and umami tastes.

Umami
A Japanese word used to describe the fifth primary taste. It corresponds to the savoury taste of food as produced, for example, by monosodium glutamate. Umami taste is found in vegetables, fish, meats and cheese.

Coding in the periphery. Historically, two schemes have been proposed in the taste literature to explain how taste processing is achieved through the interaction of TRCs with their associated afferent nerve fibres: the 'labelled line' model and the 'across-fibre pattern' (or 'distributed') model[94–96]. The assessment of experimental data supporting either of these hypotheses constitutes an important source of debate in the field of gustatory physiology. The labelled line model purports that sensory information is processed through segregated and feedforward circuitry that connects peripheral sensory receptors to higher-order structures in the CNS. By contrast, across-fibre pattern models propose that sensory fibres (or neurons) are broadly tuned, in such a way that stimulus identity and intensity are specified by a unique combinatorial pattern of activity distributed across populations of neurons. Here, we describe evidence from the PNS that supports both of these schemes.

Evidence in favour of the hypothesis that taste information transfer does not depend on labelled lines comes mainly from electrophysiological recordings performed in and around the oral cavity. These studies indicate that both TRCs and peripheral nerves are broadly tuned to gustatory stimuli[21,97–101]. For example, in a patch clamp study performed in polarized rat TRCs, Gilbertson and colleagues[98] found that a large percentage of individual TRCs responded to multiple gustatory stimuli. Similar results were found in a calcium imaging study[97].

However, data obtained in non-human primates indicate that peripheral nerve responses to tastants are segregated (but not completely) in a manner that would be more consistent with a labelled line model[102]. Recordings obtained from the chorda tympani and glossopharyngeal neurons in different non-human primate species identified specific taste fibres that responded almost exclusively to one primary tastant[20,103]. Behaviourally, compounds that activated only fibres best tuned to sweet tastants were always preferred over water. Conversely, compounds that activate fibres best tuned to bitter tastants were rejected by animals, and consumed less than water. Accordingly, a good correlation between the type of fibre activated and the animal's behaviour was obtained[20,102].

The elegant genetic and functional studies of Ryba, Zuker and colleagues provide much support for the existence of peripheral gustatory labelled lines[37]. As described above, this stems from the observation that receptors for tastants that have the sensations of sweet, sour (acid), bitter and umami are present in largely non-overlapping populations of TRCs[30,37,38,40]. Although these experiments clearly indicate that at the level of TRCs these tastant pathways are segregated, there has been no demonstration that salt (amiloride-sensitive), fat and water transduction machinery is not found in any of these TRCs.

To determine whether the activation of different TRCs is hard-wired to behavioural responses in mice, the same investigators engineered animals that express a modified opioid receptor (RASSL) in sweet-responsive TRCs. When these animals were presented with a tasteless opioid agonist, they promptly ingested it. Conversely, when the same opiate receptors were inserted in 'bitter cells' (T2R-expressing TRCs), the animals rejected the same tasteless opiate[37]. Moreover, by expressing T2R receptors in TRCs that normally respond to sweet tastants, the authors found that the mice became strongly attracted to bitter tastants[35]. These results seem to indicate that, regardless of the nature of the receptors present in TRCs, the activation of a given TRC and its associated nerve fibres triggers behaviours consistent with the notion that this complex (TRC plus afferent fibres) signals the presence of only one class of tastant stimuli (in this particular case, either hedonically positive or negative stimuli). However, these exciting results might not necessarily imply that tastant-specific labelled lines are present throughout the entire nervous system; rather, they might indicate that ingestive behaviour could rely on specific brainstem reflex pathways. This notion is supported by the finding that decerebrate rats can accept sweet and reject bitter tastants[104]. So, brainstem arch-reflex pathways could have contributed to the behavioural responses observed when exogenous receptors were

placed in bitter- or sweet-responsive TRCs. If this were the case, decerebration of the genetically manipulated mice would not abolish the acceptance and rejection behaviours observed in these studies.

In summary, at the peripheral level one can find experimental support for both labelled line and across-fibre pattern models, sometimes in the same species, although recent data from genetic studies strongly favour the existence of labelled lines. However, the validity of either model at the periphery should not necessarily be generalized to CNS circuits. In contrast to the periphery, the CNS possesses the anatomical structure required for multisensory integration and, in our view, this ability might determine a difference in coding strategies between the CNS and PNS. In fact, as discussed below, much of the current electroneurophysiological data describe gustatory processing as multisensory and distributed across several brain regions[105].

Taste coding at the level of the brainstem

The nucleus tractus solitarius. Information derived from taste-responsive cranial nerves converges on the rostral division of the nucleus tractus solitarius (rNTS) of the medulla[106]. However, besides taste, the NTS is also targeted by somatosensory inputs relayed through the trigeminal system (FIG. 1)[107,108]. In addition, a subdivision of the NTS, the caudal NTS (cNTS), is the main target of visceral (vagal) afferent inputs that convey information about the physiological status of the gastrointestinal system[109]. So, even at its first central stage, the gustatory system presents the anatomical requisites for the integration of taste information with somatosensory and gastrointestinal signals.

Neurophysiological evidence shows that subpopulations of neurons located in different NTS subnuclei are sensitive to mechanical stimulation of the gut, such as gastric and duodenal distension[110]. In addition, gastrointestinal processes such as small intestinal nutrient concentration and CCK release have been demonstrated to produce increases in NTS neuronal activity[111]. This arrangement allows for modulation of the firing rate activity of NTS taste neurons by afferent vagal activity, such as that produced by gastric distention[112].

These integrative properties also hold for the case of taste–somatosensory interactions. The firing activity of taste-related rNTS neurons can be modulated by trigeminal stimulation, as when lingual stimulation by tastants is preceded by capsaicin treatment[107,108]. This effect is also obtained in the presence of other trigeminal-activating (irritating) compounds such as nicotine[113]. Interestingly, the rNTS also exerts controls over the production of orosensory behaviours, such as swallowing[114,115], licking, chewing and mastication[116]. The existence of a topographical overlap between taste and orosensory maps has also been proposed to exist in the rNTS[117].

Given their ability to integrate gustatory information with signals from several sources, what do the electrophysiological data from tastant-sensitive NTS neurons tell us about their tuning properties? Despite the molecular marker evidence for the segregation of taste modalities in transduction pathways[118], electrophysiological recordings in both rodents and monkeys have demonstrated that NTS taste neurons are preferentially broadly tuned[119]. Nevertheless, there is evidence for some degree of topographical segregation between neural responses to different taste qualities, such as the rostral versus caudal pattern reflecting responses in the rNTS to bitter and sweet tastants[120]. However, this same study shows that rNTS neurons that responded best to bitter tastants still exhibit a high sensitivity to sodium salts and acids. So, although there is evidence for some degree of segregation between taste

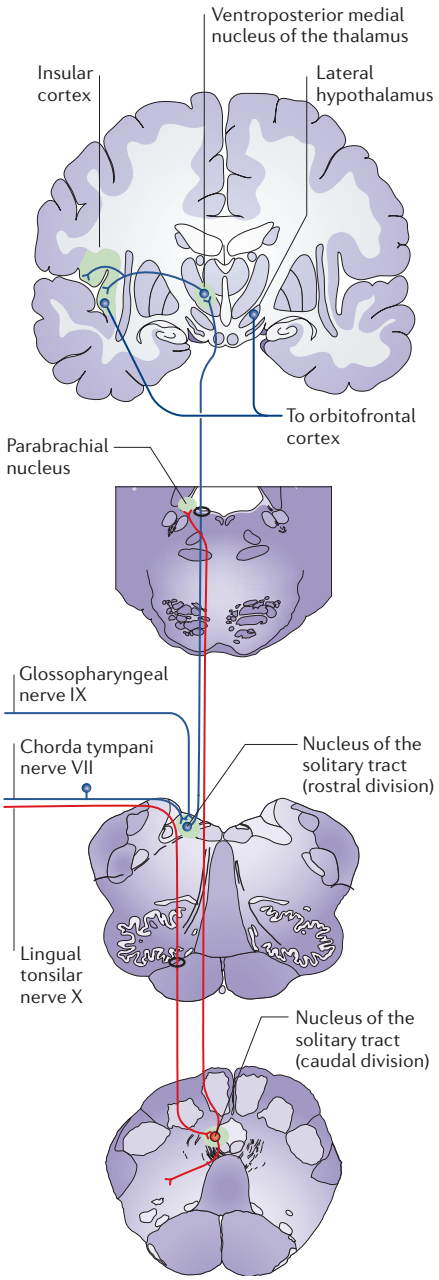

Figure 3 | **Anatomical overview of the central taste pathways.** Electrical signals from cranial nerves VII, IX and X that contain information on the chemical properties of tastants are conveyed to the rostral division of the nucleus tractus solitarius (rNTS) of the medulla, the principal visceral-sensory nucleus of the brainstem. In the rat, second-order fibres (that is, rNTS efferents) project ipsilaterally to gustatory centres in parabrachial nuclei (PBN) of the pons, from where a first (dorsal) pathway projects to the parvicellular part of the ventroposterior medial nucleus of the thalamus (VPMpc), the taste thalamic nucleus. The second (ventral) pathway includes direct projections from PBN to the central nucleus of the amygdala and lateral hypothalamus. In primates, however, the NTS projection fibres bypass the PBN only to join the central tegmental tract and synapse directly into the VPMpc, whereas the PBN seems to be dedicated to convey general visceral information (mainly through vagal afferents) to specialized thalamic nuclei. In either case, thalamic afferents then project to the primary gustatory cortex, which is defined as the VPMpc cortical target. The VPMpc also sends projections to regions neighbouring the primary somatosensory cortex, adjacent to the precentral gyrus, and that overlap with cortical somatotopic sites for the face and oral cavity. The primary taste cortex projects to the central nucleus of the amygdala, from where gustatory information reaches the lateral hypothalamus and midbrain dopaminergic regions. The primary taste cortex also projects anteriorly to the caudolateral orbitofrontal region, called the secondary taste cortex. Taste neurons in the caudolateral orbitofrontal cortex converge with cells receiving projections from the primary olfactory cortex, which might have implications for flavour perception. The orbitofrontal cortex is also targeted by projections from the lateral hypothalamus, allowing taste responses to be modulated by satiety states. Finally, cortical taste areas send afferents to the rNTS/PBN, allowing for top-down modulation of gustatory processing at the level of the brainstem. Blue, projections to rNTS; green, primary taste areas; red, projections to caudal NTS. Modified, with permission, from REF. 164 © (2004) Macmillan Publishers Ltd.

qualities in terms of neuronal responses at the level of the brainstem, it should be noted that broad tuning seems to be a property held by most taste-responsive cells in the NTS. In another example, a recent study[51] found that although a subpopulation of NTS neurons responded exclusively to some bitter tastants, most of the other taste responses were broadly tuned[51]. This broad tuning of taste-sensitive neurons indicates that populations of NTS neurons might encrypt individual taste qualities via distributed codes[121] (although it should be noted that it is not certain whether these broadly tuned neurons are direct targets of TRCs).

It has been argued that labelled lines and population codes are not the only mechanism by which taste-specific information is represented in the rNTS. In an innovative study, DiLorenzo and colleagues showed that electrical stimulation of the NTS — under a specific temporal pattern, while rats lick water — might simulate the perception of bitter or sweet qualities[122]. When stimulation with a temporal pattern representing sucrose was followed by malaise induction (systemic administration of LiCl), these authors observed that rats frequently generalized their aversion to real sucrose stimuli. Replaying the 'sucrose' neuronal firing template in the absence of malaise extinguished the aversion.

Do these results provide unequivocal evidence for a temporally structured, single-cell code for taste quality in the rNTS? Not necessarily. Although the 'sucrose-best' templates were based on individual NTS cells, the current applied in these experiments activated a sphere of tissue of up to ~500 μm in diameter, suggesting the recruitment of a population and not of single cells; this might explain why a template from one rat was successfully applied to other rats.

Forebrain modulation of brainstem responses. The distributed properties of the neural functions associated with gustation can be illustrated by the ability of individual forebrain regions to modulate taste activity in the brainstem. In fact, many descending afferent fibres from forebrain structures converge in the rNTS. These include dense projections from the central nucleus of the amygdala, the lateral hypothalamus and the gustatory cortex[123,124] (GC; the cortical region that specifically receives direct projections from the taste thalamic nucleus: see FIG. 3 for details on the anatomy of central taste pathways). Electrical stimulation of each of these areas was shown to modulate neuronal responses to tastants in the rNTS[125,126]. Similarly, taste-responsive neurons in the parabrachial nucleus (PBN), the main target of NTS projections in rodents, are also modulated by forebrain electrical stimulation[127,128]. Indeed, the same PBN neuron can be modulated by stimulation at all three of the sites mentioned above, indicating that single PBN cells integrate multiple descending forebrain inputs[129]. In addition, temporary inactivation of the GC, which gives off dense descending projections to both the NTS and PBN, induces a profound and selective effect in the across-unit pattern of neuronal response to sweet stimuli in both these brainstem nuclei[125,130].

In summary, several independent findings indicate that descending forebrain axons from various areas can selectively modulate brainstem taste-evoked responses. These data clearly show, at the very least, that taste processing does not involve simple feed-forward pathways. Rather, in real world situations where information has to be continually updated, gustatory responses that originate from the periphery are modulated by forebrain circuits and their projections to brainstem nuclei.

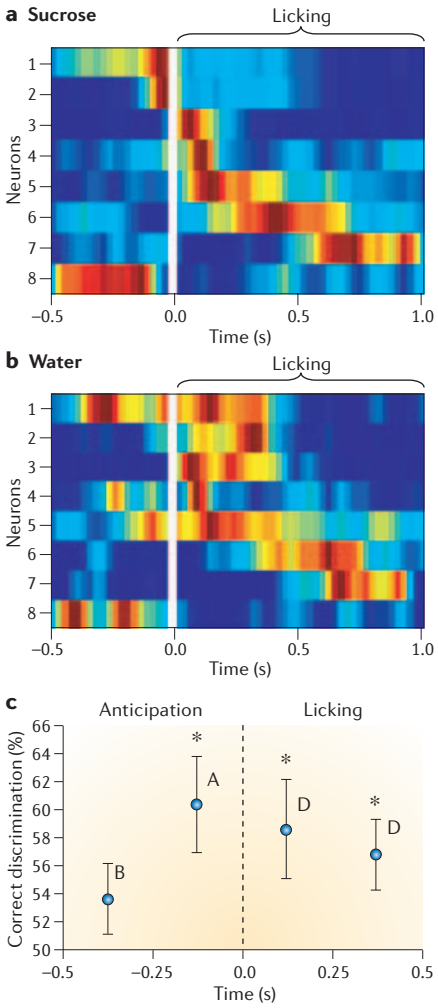

Figure 4 | **Ensemble activity of OFC neurons discriminates and anticipates natural rewards.** Panels **a** and **b** are colour-coded post-stimulus time histograms of eight simultaneously recorded orbitofrontal cortex (OFC) neuronal responses to sucrose and water, respectively. The times around licking initiation (at 0 s) are shown. Red colours represent maximal activity and blue the minimum activity of each single unit. Although some similarities can be observed in the activation pattern of this neuronal ensemble during the rat's intake of water or sucrose, many differences were also evident, indicating that OFC neuronal ensembles might be used to discriminate between gustatory stimuli both when they anticipate what tastant is coming and also after it is tasted (see below). **c** | A graph showing the ability of the ensembles to discriminate between water and sucrose (mean±SE of 16 ensembles) during four time epochs: baseline (B), approach (A) and drinking (D). Note that on a single trial basis, the temporal dynamics of neuronal ensemble activity could rapidly identify the natural rewards in some ensembles, even before a licking cluster started (A). Asterisks indicate statistical differences with respect to chance (50%). Presumably, this anticipatory effect was due to presenting the tastants in separate blocks and thereby allowing the animals to anticipate the tastants prior to drinking. These results suggest that ensembles of OFC neurons can monitor the intake of natural rewards by tracking the onset of a licking cluster as well as anticipating and rapidly identifying natural rewards (sucrose and water). Modified, with permission, from REF. 10 © (2006) American Physiological Society.

Taste coding in cortical circuits

Multisensory integration in the gustatory cortices. The next question to ask is whether the integrative and distributed properties of taste processing observed in specialized brainstem nuclei are also supported by gustatory-related cortical circuits. As we will see, this indeed seems to be the case for the GC.

Sparse and distributed representations, as well as temporal coding models, have been proposed to explain how cortical networks encode gustatory information[14,131,132]. Sparse representations were proposed in view of electrophysiological data obtained in awake monkeys which showed that single-neuron responses to various taste qualities and other sensory properties (for example, viscosity or temperature) can be highly specific[133]. However, a review of the literature revealed that the vast majority of the studies measuring gustatory responses from GC neurons

have found them to be broadly tuned[134,135]. The broad tuning of single neurons suggests, once again, the need to rely on populations of such cells (FIGS 4,5) to define taste quality. Evidence for distributed gustatory processing in the GC is provided by the fact that taste identity, concentration and palatability are more efficiently decoded from neuronal patterns when the activity of populations of simultaneously recorded neurons are taken into account[105,136].

Another fundamental property of cortical taste processing is that it is fast. Most researchers who study gustatory coding at the cortical level have relied on average neuronal evoked activity, over several seconds after stimulus delivery, to measure potential correlations between taste quality and neural firing activity. As trained animals can detect and discriminate tastant stimuli in a single lick (~200 ms)[137], such long averages of neuronal firing modulation (in the order of seconds) will probably represent many other parameters, such as hedonics, mouth movements and so on[132]. Recently, electrophysiological data collected in freely behaving animals have shed new light on this issue. In accordance with the timing of licking, we have shown that chemosensory-specific information is conveyed by taste-responsive GC neurons within 150 ms of stimulus delivery[11] (FIG. 5). Moreover, individual GC neurons were shown to be broadly tuned, even to the extent that they can be responsive to both sucrose and quinine[11,138], corroborating the need for population codes in the GC.

GC neurons were also shown to respond to various sensory stimuli[11,132,139,140], suggesting an ability for multisensory integration. Indeed, the multimodality of cortical gustatory processing has been indicated anatomically, electrophysiologically[84,107] and perceptually[141,142]. However, the detailed neural mechanisms underlying such multimodal integration remain elusive. Electrophysiological studies have demonstrated that the same GC neurons can respond to taste, somatosensory and olfactory inputs[11,143] (although the exact function of these neurons in the formation of flavour percepts has not yet been elucidated). Indeed, several groups have shown that rat GC neurons are sensitive to both orosensory (for example, mouth/jaw movements, temperature) and gustatory inputs[11,138–140]. Recordings in the macaque GC showed that they preferentially respond to oral somatosensory or oromotor stimulation[144]. In fact, the taste-responsive areas of the anterior insular (the putative human primary taste cortex) largely overlap with areas that represent somatosensory inputs from the oral cavity, which might account for the ability to sense the temperature and viscosity of food[145,146]. These findings highlight the fact that somatosensory–gustatory integration is likely to be widespread in the mammalian GC.

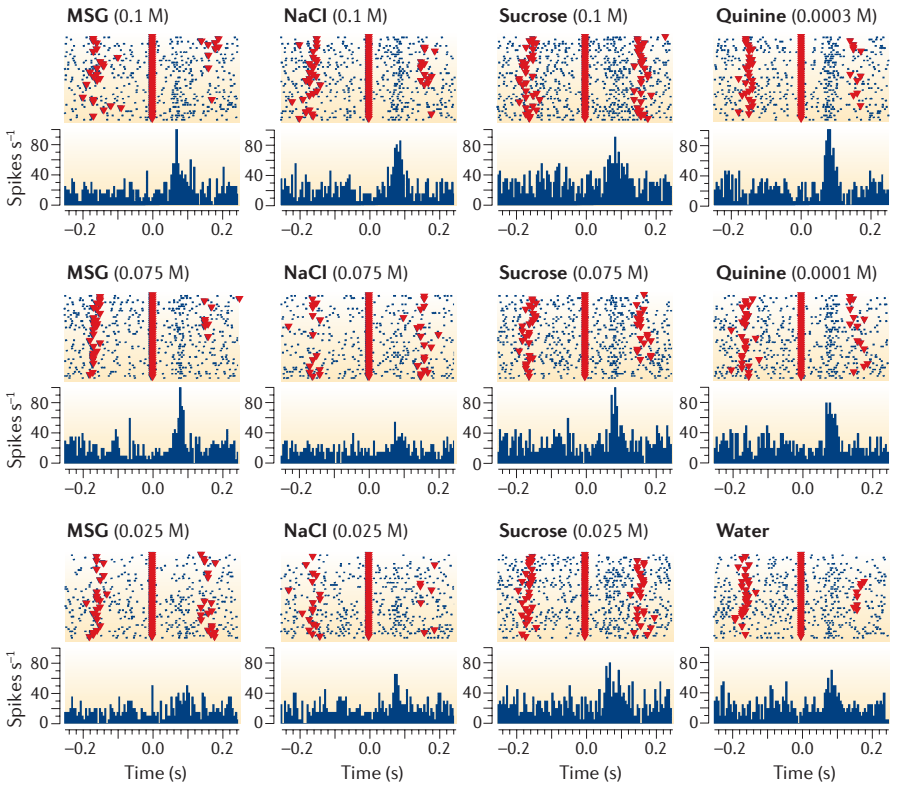

Figure 5 | **Taste processing in the gustatory cortex is fast.** Rats were trained to receive tastants on a fixed ratio schedule (FR5) while gustatory cortex responses were recorded from implanted microelectrode bundles. In the FR5 protocol, rats licked a dry sipper spout four times and received a tastant only on the fifth lick (at 0 s). This figure presents the raster plots and post-stimulus time histograms of a neuron to four tastants at multiple concentrations. The neuron is broadly tuned, even to the extent that responses were evoked by sucrose and quinine. In addition, it is seen that gustatory cortical neurons exhibit rapid (< 150ms) and reproducible responses to different tastants (for example, see 0.0003 M quinine). The concentration profile might or might not be monotonic. Whereas the response to quinine is greater at the higher concentration, for sucrose the intermediate concentration elicits the largest response. Modified, with permission, from REF. 11 © (2006) Society for Neuroscience.

As in the GC, the orbitofrontal cortex (OFC) — which contains the secondary taste cortex, defined as a direct target of the GC — neurons also show multisensory responses. For example, we recently reported that rat OFC neuronal populations are able to encode simultaneously the identity of a tastant as well as the temporal structure of rhythmic licking patterns performed to ingest that tastant[10] (FIG. 4). More generally, data obtained in primates show that the OFC receives convergent somatosensory, olfactory and taste afferents. Indeed, taste-responsive OFC neurons have also been shown to respond to the temperature and/or texture of foods[147]. Analogous multisensory responses have been found in the primate insula[148] and amygdala[133].

These findings further emphasize the relevance of multisensory processing as one of the keys to achieving a real understanding of the basic neural mechanisms underlying flavour perception. Clearly, flavour perception also depends on the convergence of gustatory and olfactory information, which occurs at multiple cortical and subcortical neural structures. Rapid taste and olfactory neuronal processing have been described recently[11,149], and some of their analogous properties might underlie the ability of the cortex to form multimodal taste–odour combinations[150]. In humans, detection of sub-threshold tastants is facilitated by combined presentations with odours[141]. Moreover, a region located in the anterior insular cortex has been suggested to perform integration of taste and olfactory inputs[151–153] (FIG. 6).

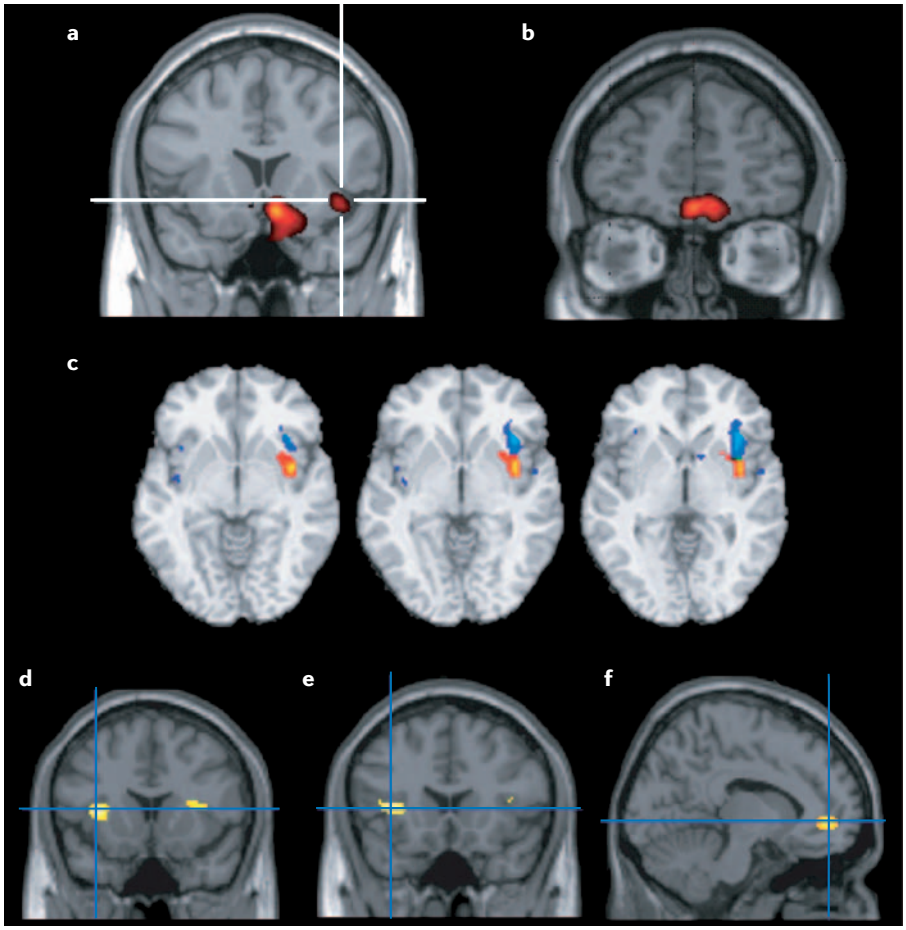

Figure 6 | **Functional MRI shows multimodal integration in the human taste cortex. a** | Coronal section illustrating taste–olfactory integration in the human anterior insula and caudal orbitofrontal cortex (OFC)[152]. **b** | A horizontal section through the medial OFC where the subjective pleasantness for taste–odour mixtures is represented[152]. **c** | Axial sections showing the human insula at different heights (the most dorsal cut is shown on the left). The mid-posterior part of the insula responds to water in the mouth only when subjects are thirsty (red areas indicate a rewarding aspect of water), whereas a more anterior part is responsive independently of thirst (blue areas)[163]. Responses to water were subtracted from responses to artificial saliva. **d** | Region of the human primary taste cortex, in the anterior insula, responding for both a prototypical taste (sucrose) and highly viscous tasteless stimuli, showing integration of taste and somatosensory information in the taste cortex[145]. **e** | Region of the human taste cortex in the anterior insula responding to fatty oils in the mouth, subtracted from artificial saliva, showing responses to fat in the taste cortex[145]. **f** | Region of the medial OFC, adjoining the rostral anterior cingulate cortex, responding to both sucrose and fat in the mouth (subtracted from artificial saliva)[145].

Modulation of taste responses by post-ingestive factors. Efficient feeding behaviour does not depend solely on multisensory integration at gustatory central regions. The post-ingestive, metabolic consequences of ingesting nutritious compounds must also be computed in conjunction with taste identity. Taste perception is heavily influenced by previous experience and by the memory of the gastric consequences that followed the past intake of different types of food[154]. Animals can quickly develop aversion to a particular tastant if it is associated with the administration of a compound such as LiCl that produces gastric malaise. This phenomenon is known as conditioned taste aversion (CTA)[155]. Accumulating evidence indicates that there are also post-ingestive positive controls of ingestion. For example, rats trained to consume a flavoured solution paired with intragastric carbohydrate infusions significantly increased their solution intake[156]. This indicates that brain regions sensitive to sapid stimulation integrate this information with the nutritive value of what is being ingested.

Gustatory responses in higher brain centres are indeed modulated by the animal's physiological state, showing that taste-related neurons could alter their preferred responsive category as a function of metabolism. Evidence showing modulation of taste responses by satiety in the lateral hypothalamus and in the OFC comes mainly from primate (including human) studies. Rolls *et al.*[157] have shown that feeding to satiety decreases the responses of lateral hypothalamic neurons to the taste of a food that a monkey has been fed. However, the responses of the same neurons to other foods remain unchanged. This phenomenon, which is the neural representation of a behavioural pattern known as sensory-specific satiety, was also observed in taste-sensitive OFC neurons[158]. These findings indicate that the pleasantness generated by the taste of a particular food, as well as its acceptability, decreases as animals become satiated, and that taste-sensitive neural circuits can represent these dynamic changes in reward value. However, this is specific to the particular food, as the animal might still be motivated to ingest other types of food, indicating the existence of neural mechanisms involved in diversifying the components of a diet. Functional neuroimaging studies in humans provide further evidence that the reward value of a tastant is represented in the OFC[159]. In particular, specific sub-regions of the OFC in humans represent the changing reward value of a food eaten to satiety[160]. Studies using sensory-specific designs also confirm the role of the OFC in modulating taste responses according to physiological state[161,162].

We have recently shown that simultaneously recorded populations of neurons located in several taste-sensitive forebrain regions can encode the current motivation of the animal to drink a sucrose solution[8] (FIG. 7). This encoding was shown to be distributed because only when combined in populations could gustatory neurons convey information on the motivation to ingest sucrose at different phases of a feeding cycle (that is, hunger–satiety–hunger phases). This corroborates further the view proposed here that gustation is a multimodal process, the complexity of which can only be captured at the neural level by distributed codes.

Conclusions

We have described evidence indicating that the central gustatory pathways make use of distributed, ensemble codes to achieve integration of taste, olfactory and somatosensory inputs reaching the brain from the oral cavity through highly specialized peripheral nerve fibres. In contrast to the highly specialized information transfers performed by TRCs and peripheral fibres, central gustatory processing seems to be distributed, probably

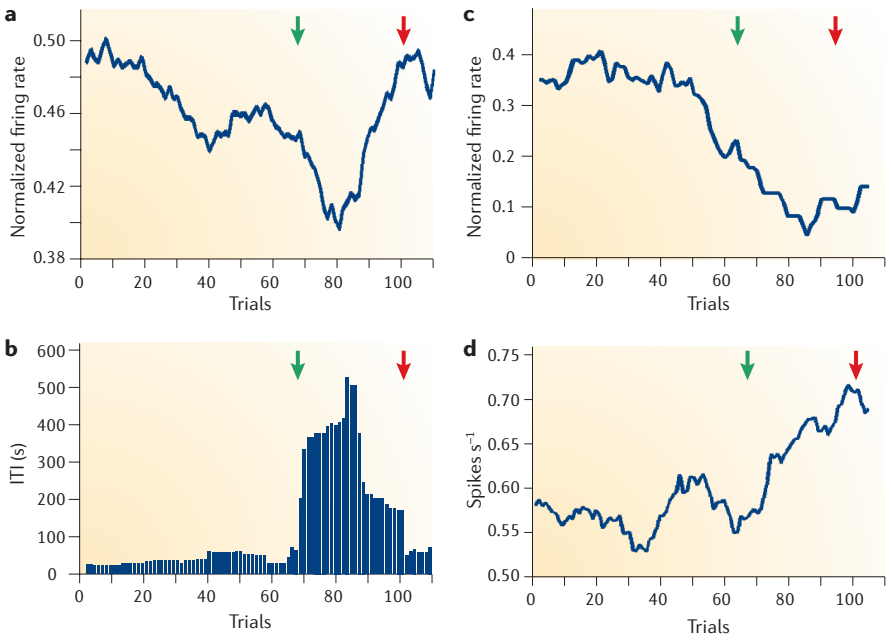

Figure 7 | **Coding of satiety states by neuronal ensembles in the rat forebrain.** The firing activity of ensembles of simultaneously recorded neural units in different areas of the rat forebrain can represent the current motivation of the animal to ingest a nutritive sucrose solution more efficiently than its constituent single units. In a typical experimental session, an initially hungry rat will reduce the frequency with which it approaches and licks a sipping tube containing sucrose. The time interval measured between two consecutive licking bouts is called an inter-trial interval (ITI). These intervals can be used as behavioural indexes for the motivation of the animal to ingest sucrose, such that at 'hunger' periods they tend to be short (high sucrose consumption per unit of time) whereas at 'satiation' phases they tend to be longer. We found[8] that when combined in a population mean, ensembles of simultaneously recorded neural units reflect more efficiently the hunger/satiation state of the animal compared to their constituent single units, with relatively higher population firing rates during hunger phases. **a** | Example of an experimental session in which the population mean firing rate correlated significantly with ITIs. Green and red arrows indicate start and end points respectively of a satiety phase. **b** | Corresponding ITIs for this session. Note the significant satiety phase (large ITI values) starting around trial number 65. However, in general, single units did not reflect as precisely the time course of the ITIs. **c** | Example of a cell from the original population monotonically decreasing its firing rate during the experiment. **d** | The same as in **c**, but depicting a monotonical increase in activity. The combination of these individual cell types in a population mean increases the accuracy of this distributed code to reflect feeding behaviour. Modified, with permission, from REF. 8 © (2005) Elsevier Science.

as a result of its capacity for multimodal integration. Approaching the encoding of a gustatory stimulus in this manner will provide new insights into how information is encoded, beyond the theories that have been historically proposed to model the mechanisms by which taste quality is coded in the periphery. Indeed, how these sensory modalities are synthesized into a single percept, which allows animals to rapidly decide whether to ingest or reject a particular food, is one of the great challenges in gustatory physiology.

However, the main conclusion to be drawn from this article is that many fundamental problems in this emerging field are still to be resolved. For example, what is the coding logic for multisensory integration? Would an ideal observer (that is, a hypothetical experimenter who has optimal performance on a discrimination task given the source noise) be able to identify, in a single trial, the components of a taste–olfactory–somatosensory multimodal intra-oral input from the simultaneous activity of the corresponding primary sensory cortices? Or is such information preferentially conveyed by a population of highly integrative, multimodal single neural units? Note that this is a particular instance of the more general controversy related to the sensory specificity of neural responses to gustatory stimuli.

Another fundamental aspect concerns the influences of the metabolic state of the body on central taste representations. How does morbid obesity, or its malnutrition counterpart, affect the cortical representation of different tastants? How do abnormal circulating levels of glucose and insulin, such as those found in diabetes mellitus patients, modulate responses to sweet-tasting and other highly caloric compounds? Which neural mechanisms regulate flavour preferences that are independent of orosensory stimulation (post-ingestive effects)? Answers to these basic questions might help us to understand why we are so easily prone to over-consume highly caloric 'tasty' foods.

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DATABASES

The following terms in this article are linked online to:

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