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Recognizing taste: coding patterns along the neural axis in mammals

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Abstract

The gustatory system encodes information about chemical identity, nutritional value, and concentration of sensory stimuli before transmitting the signal from taste buds to central neurons that process and transform the signal. Deciphering the coding logic for taste quality requires examining responses at each level along the neural axis - from peripheral sensory organs to gustatory cortex. From the earliest single fiber recordings, it was clear that some afferent neurons respond uniquely, others to stimuli of multiple qualities. There is frequently a "best stimulus" for a given neuron, leading to the suggestion that taste exhibits "labeled line coding". In the extreme, a strict "labeled line" requires neurons and pathways dedicated to single qualities (e.g. sweet, bitter, etc.). At the other end of the spectrum, "across-fiber", "combinatorial", or "ensemble" coding requires minimal specific information to be imparted by a single neuron. Instead, taste quality information is encoded by simultaneous activity in ensembles of afferent fibers. Further, "temporal coding" models have proposed that certain features of taste quality may be embedded in the cadence of impulse activity. Taste receptor proteins are often expressed in non-overlapping sets of cells in taste buds apparently supporting "labeled lines". Yet, taste buds include both narrowly- and broadly-tuned cells. As gustatory signals proceed to the hindbrain and on to higher centers, coding become more distributed, and temporal patterns of activity become important. Here, we present the conundrum of taste coding in the light of current electrophysiological and imaging techniques at several levels of the gustatory processing pathway.

Keywords: gustatory coding, taste quality, taste bud, geniculate ganglion, nucleus of solitary tract, gustatory cortex

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Introduction

All sensory systems must address the problem of conveying information about the quality, intensity, and location of sensory stimulation from peripheral receptors to the brain. For both olfaction and taste, stimuli can be chemically diverse. The olfactory system is known to encode this chemical diversity, in part, through the use of hundreds of molecular receptors with overlapping receptive ranges. Olfactory signals from peripheral neurons are carried on circuits that exhibit convergence and distributed patterns at different stages along the neural axis to encode odor recognition and discrimination (Laurent 2002; Nara *et al.* 2011; Nunez-Parra *et al.* 2014; Srinivasan and Stevens 2018). The gustatory system, which serves to detect nutrients, minerals, and toxins, also identifies diverse chemical structures across broad concentration ranges. The logic of how the mammalian gustatory system encodes information on chemical identity, i.e. quality coding, is the subject of active investigation using a variety of experimental approaches and resulting in competing models of taste coding. The present review examines some of the evidence, interpretations and controversies regarding gustatory quality coding.

Most research on taste quality coding focuses on discriminating “sweet” (for example sugars), “salty” (Na+ salts), “sour” (acids) and so forth. Labeled line coding posits that quality-specific taste receptor cells (TRCs) (for example “sweet”-specific) synapse only with primary sensory afferent(s) that are dedicated to that same quality. This, then, establishes a dedicated transmission line from the taste bud cell to the brain that is “labeled” for a single quality. According to this coding, the different transmission lines (“sweet”, “salty”, “sour”, etc.) are separate, distinct, and parallel. The sensory afferent neurons are all highly tuned to transmit one given quality. They are all “specialists” for a given quality.

In contrast, combinatorial coding allows more flexibility in the responses of primary afferent fibers. Thus, a given taste compound can elicit impulses in in an ensemble of several primary afferent fibers, each of which varies in their response profiles. That is, some fibers might be “sweet-best”, others might be “salt-best”; they respond robustly to sugars or Na+ salts, respectively, while retaining weaker responses to other tastes (“specialists”). Other fibers in the ensemble may respond quite broadly to many different taste compounds with no strong preference (“generalists”). However, when activated by a specific taste compound, the entire ensemble of afferent fibers generates a particular combinatorial signal that identifies that stimulus. Collectively, the combination of specialists and generalists, not any individual sensory afferent axon on its own, transmits the information about taste quality. Temporal coding conveys information in the pattern of impulses in individual primary sensory afferents. Different taste stimuli may elicit different patterns of action potentials in afferent fibers, which might lead to differential excitation/inhibition of neurons in the CNS.

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For theorists, both models present a dilemma: how do multi-sensitive cells convey an unambiguous message that identifies taste quality? The labeled line and across-neuron pattern theories share the notion that spikes are integrated over time, and ignore the dynamics of firing rate changes that occur during a taste response. These dynamic aspects of the response may also carry taste information, a form of signaling called "temporal coding".

The origins of labeled line coding in the sensory nervous system might be said to come from René Descartes, who, in his classical drawing of the innocent cherub toasting his toes (Descartes 1664, p. 27), clearly outlined a labeled line (here, for painful heat) from peripheral sensory organ to the brain (Roper 2014). However, the first explicit statements of labeled line coding were by Sir Charles Bell (1811; see Bell and Shaw 1868), and Johannes Müller (1835), who coined the concept, Law of Specific Nerve Energies (LOSNE), according to which "each type of sensory nerve ending, however stimulated (electrically, mechanically, etc.), gives rise to its own specific sensation; moreover, each type of sensation depends not upon any special character of the different nerves but upon the part of the brain in which their fibers terminate" (Müller 1836). Since then, it has become clear that each modality is indeed "labeled" insofar as touch, temperature, taste, olfaction, vision, hearing, and so forth are each transmitted along separate neural pathways. The question, now, is whether such "labeling" extends to different qualities *within* a sensory modality, such as red versus green color, rose versus geranium scent, or sweet versus salty taste. That is the crux of the current debate. In certain sensory systems, such as vision and olfaction, the answer is clearly "no"; colors and odors unarguably display combinatorial quality coding.

In this review, we examine the evidence, primarily derived from electrophysiological and imaging studies at different levels of the taste system, of the responses of receptors and neurons to stimuli representing different taste qualities. We discuss what the responses at each level suggest about the logic of coding taste quality.

The detectors: coding taste quality in taste bud cells

A strict peripheral labeled line coding for taste qualities (sweet, salty, sour, etc.) has been strongly promoted by some researchers (Barretto *et al.* 2015; Chen *et al.* 2011b; Yarmolinsky *et al.* 2009). The strongest evidence for such a hard-wired logic for taste quality coding comes from the observation that taste bud cells express primarily or only one type of taste receptor. Some cells express a few to several members of the Tas2R family of receptors which are activated by bitter-tasting compounds (Behrens *et al.* 2007; Mueller *et al.* 2005). Other TRCs may express heterodimeric Tas1R family receptors, which are activated by either sweet- or umami-tasting compounds (Dando *et al.* 2012;

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Nelson *et al.* 2002; Nelson *et al.* 2001). Yet other cells are dedicated for sour taste sensing (Huang *et al.* 2006). However, some fraction of taste cells do express taste receptors for more than one quality (Dando et al. 2012). The relatively non-overlapping pattern of receptor expression led to the proposal that, similar to insects, mammals use a hard-wired logic for coding taste quality (Yarmolinsky *et al.* 2009). That is for example, Tas2R-expressing TRCs, when stimulated, activate a dedicated subset of afferent fibers which would encode the bitter taste quality. Other dedicated TRCs and nerve fibers would convey sweet and so on. This taste quality-dedicated TRCs constitute the beginning of a labeled line for "bitter" or "sweet", respectively, that is maintained along the taste axis to the gustatory cortex.

The question is how well do the responses of individual taste bud cells mirror the seemingly compartmentalized, non-overlapping pattern of expression of the various taste receptors. The taste quality sensitivity and selectivity of specific populations of taste bud cells have been examined through both, electrophysiological and Ca^{2+} imaging methods (Tomchik *et al.* 2007; Yoshida *et al.* 2009; Yoshida *et al.* 2018), using several distinct *ex vivo* preparations. Using the combination of transgenically identified taste bud cell types and apical stimulation with a variety of taste stimuli, the response profiles of taste bud cell types have been studied electrophysiologically (Yoshida *et al.* 2009) and via Ca^{2+} imaging (Caicedo et al 2002; Tomchik et al 2007). Very consistently, Type II cells respond best to sweet, bitter or umami taste stimuli. "Bitter-best" taste cells are the most narrowly tuned and respond almost exclusively to bitter compounds (Yoshida et al. 2009b). In contrast, some "sweet-best" TRCs are more broadly tuned such that, in addition to sucrose, some also respond to salt (NaCl) and/or umami stimuli (monosodium glutamate, MSG). Type III cells from fungiform taste buds consistently respond to acid (sour) stimuli, and each cell typically responds to multiple acids (citric, acetic or HCl). Thus, tuning, measured in the electrical responsivity of cells from fungiform taste buds (Yoshida *et al.* 2009), is generally similar to that measured by the Ca^{2+} responses of Type II cells from mouse circumvallate taste buds (Tomchik *et al.* 2007). Further, in both studies, responses to acids were limited to Type III cells.

Type III cells in mouse fungiform papillae fell into 2 groups with. approximately 75% responding only to acids, the rest being broadly tuned, with responses to salty, umami, and/or bitter stimuli in addition to acids. This observation differed conspicuously the Ca^{2+} imaging study which reported that all or most Type III cells in mouse circumvallate taste buds were both sour-responsive and broadly tuned (Tomchik *et al.* 2007). Whether these differences are attributable to differences in methodology or in the taste bud fields examined (fungiform vs. circumvallate) remains to be determined.

Another question that has been explored electrophysiologically in mouse fungiform taste bud cells is how diverse stimuli that produce similar taste perception are represented in the initial receptor cells.

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For example, many sugars (sucrose, fructose, etc.), artificial sweeteners (saccharin, sucralose, etc.) and certain proteins (Monellin, Thaumatin, Brazzein, etc.) all elicit sweet taste. Similarly, there are numerous chemically diverse compounds, all of which elicit bitter taste. To test whether TRCs respond identically to diverse stimuli of a given quality (for example "bitter") or can discriminate among perceptually similar compounds, responses were recorded to a battery of bitter-tasting compounds (Yoshida *et al.* 2018). Type II TRCs from fungiform and circumvallate taste buds showed considerable heterogeneity in their responses to this battery of bitter chemicals. Some bitter stimuli elicited responses in 5-8 times as many taste cells as did other bitter compounds. That is, taste compounds that are perceived as having similar taste may produce very different patterns of activation among taste bud cells

Yoshida et al (2018) also demonstrated that bitter-sensitive cells as a population displayed considerable heterogeneity. When tested with 10 bitter compounds, some were selective for only a single stimulus while others responded broadly to as many as 9 of the 10 stimuli tested. Such heterogeneous responses among bitter-sensitive taste cells had also been demonstrated using functional imaging of rat and mouse circumvallate taste bud cells (Caicedo *et al.* 2002; Caicedo and Roper 2001). The family of bitter taste receptors Tas2Rs, includes ≈35 diverse members and each of these Tas2Rs is activated by a different complement of bitter compounds (Lossow *et al.* 2016). In both, human and mouse, some Tas2rs are narrowly tuned and others that can be activated by large numbers of bitter tasting compounds (Lossow *et al.* 2016; Meyerhof *et al.* 2010). Thus, the selectivity of bitter sensitive TRCs would be defined by the expression of different combinations of Tas2Rs.

All molecular receptors for bitter tastants, Tas2Rs, were reported to be co-expressed in some TRCs with the interpretation that discrimination among bitter stimuli could not occur (Adler *et al.* 2000), More comprehensive analyses showed that only limited numbers of Tas2Rs are expressed per TRC, and in various combinations (Behrens *et al.* 2007; Matsunami *et al.* 2000). The electrophysiological and Ca^{2+} imaging results above also demonstrate that the initial hypothesis (Mueller et al 2005) for how bitter taste quality is coded in the periphery was likely incorrect. Combinatorial expression of Tas2Rs in individual TRCs could, in principle, form a basis for discriminating among different bitter compounds, but it is unclear whether such discrimination exists along the taste neural axis or even behaviorally.

Taken together, electrophysiological and Ca^{2+} imaging data indicate that taste buds contain many taste receptor cells dedicated to detect one of 5 basic taste qualities. These may provide the basis for discrimination across basic taste qualities. However, taste buds also contain TRCs that respond to multiple taste qualities (Caicedo *et al.* 2002; Tomchik *et al.* 2007; Yoshida *et al.* 2009). These multiply-responsive cells may reflect information processing (divergence and convergence of signals) that occurs within taste buds via cell-cell synaptic interactions (Chaudhari 2014; Dando and Roper

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2009; Huang *et al.* 2009; Huang *et al.* 2007). Moreover, some taste cells express multiple types of taste receptors. For instance, a subset of taste cells expresses all three T1R subunits and responds to both sweet and umami compounds (Dando *et al.* 2012; Kusuhara *et al.* 2013). Whether broadly tuned TRCs serve a distinct role from narrowly tuned TRCs as well as the contribution of broadly-tuned TRCs to coding of taste signals remain, however, still unclear.

Taste quality coding begins with the sensitivities of individual receptor cells within taste buds. The synaptic connections between these cells and gustatory nerve fibers is a major unknown at present. Understanding convergence or divergence at these peripheral synapses will be key to understanding the initial coding of taste signals in the periphery.

Quality coding in the first neurons of the taste pathway

How do primary sensory afferent neurons transmit taste information to the central nervous system (CNS; see Figure 1) and how does activity in primary afferents represent taste quality (sweet, salty, sour, etc.)?

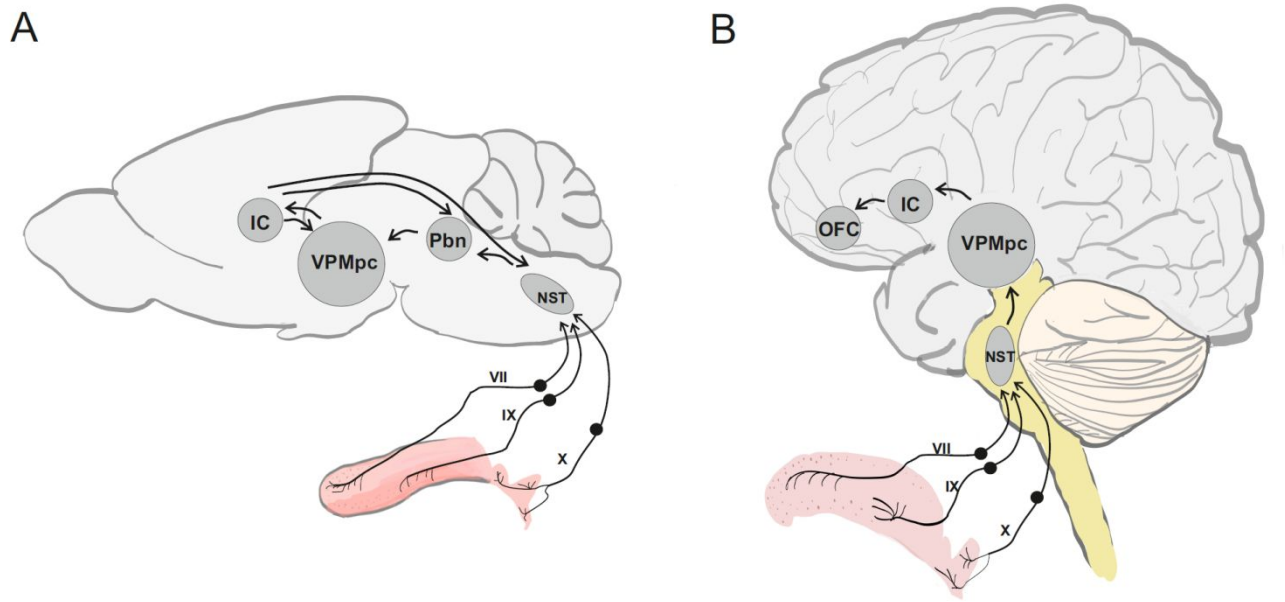

Figure 1. Schematics of the rodent (A) and human (B) gustatory pathways with a focus on peripheral and thalamo-cortical relays. In both species, information is conveyed via cranial nerves VII, IX, and X from the tongue to the brainstem. NST: nucleus of the solitary tract, PbN: parabrachial nucleus, VPMpc: parvicellular portion of the ventroposteromedial nucleus of the thalamus, IC: insular cortex, OFC: orbitofrontal cortex.

Electrophysiological recordings and Ca^{2+} imaging studies from primary sensory afferent neurons (single fibers or ganglion neuron somata) have been carried by several groups. Some form of combinatorial coding in taste was originally suggested by Pfaffmann (1941) based on early electrophysiological recordings from afferent fibers that innervated taste buds in the cat. Single units were found that responded to lingual stimulation with more than one taste compound (for example quinine or HCl or both). That many fibers were not limited to excitation by a single taste quality, was inconsistent with a labeled line coding scheme. This led Pfaffmann (ibid) to conclude "[…] sensory quality does not depend simply on the" all or nothing" activation of some particular fiber group alone, but on the pattern of other fibers active." Other investigators elaborated and extended this model to encompass the widespread co-activation of a large number of sensory afferent fibers, with different combinations of the same fibers constituting the code for different taste qualities. This was termed "cross-fiber coding" and was held as the polar opposite of labeled line coding (Erickson 2008). According to cross-fiber coding, activity in any single fiber on its own does not convey information about sweet, sour, salty, etc. Only the combined activity of many fibers generates the code. Some resolution of these two opposite concepts—labeled line versus combinatorial coding—was obtained by Frank and Pfaffmann (1969). They recorded from single sensory afferent fibers from the tongues of hamsters and observed that although many fibers did indeed respond to multiple taste stimuli, the most effective stimulus of a fiber was predictive of the relative effectiveness of the other stimuli. These observations suggested that there were fiber "types" organized according to the stimulus that evoked the "best" response. They termed these "sweet-best", "salt-best" etc. fibers. Although this has been interpreted as a form of labeled line coding, the fact is that activity in a single fiber could not unambiguously distinguish between (strong) excitation by the "best" stimulus versus (weak) excitation by other, less effective stimuli.

The observation of "best stimulus" for individual taste afferent fibers has been widely replicated in different laboratories, and in mammalian species ranging from mice to monkeys (Danilova *et al.* 1999; Hellekant and Ninomiya 1994; Sato *et al.* 1975; Tonosaki and Beidler 1989). A further refinement of the distinctions between taste afferents was the recognition that some neurons respond principally or exclusively to one stimulus type, usually sugars – the so-called "specialist" neurons; other neurons responded to a variety of electrolytes that might produce sour, bitter or salty tastes (reviewed by Frank *et al.* 2008). Specialist and generalist neurons have been detected electrophysiologically as single-fiber recordings on afferent nerves and by extracellular recordings in geniculate ganglia. A method applied more recently is functional imaging of sensory afferent neuron activity using genetically encoded Ca2+ indicators such as GCaMP. Barretto *et al.* (2015) and Wu *et al.* (2015) carried out functional imaging on geniculate ganglion neurons in the mouse and cataloged responses to a battery

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of different taste stimuli presented at different concentrations. Those studies verified that about half the ganglion neurons were “specialists” that responded best (and some solely) to a single taste compound, such as sucrose. Specialist neurons could be detected for each of the five “basic” taste qualities (sweet, sour, salty, bitter, umami). The geniculate ganglion also had “generalist” sensory neurons that responded much more broadly to taste stimuli, mirroring the electrophysiological recordings from the primary afferent axons (above).

The relative proportion of specialist and generalist neurons varied strongly depending on the concentrations of stimuli tested (Wu *et al.* 2015). Importantly, neurons that displayed a specialist profile with a low concentration stimulus were transformed to generalists when the same stimuli were tested at higher concentrations. At concentrations that produced maximal responses, half the neurons exhibited responses to multiple distinct stimuli. Unless half the information from the periphery is discarded, which seems unlikely, a resolution to the question of taste coding is that a cross-fiber code involving a combination of primary afferent axons that vary in their “tuning”, from specialists to generalists, encode taste.

In addition to the encoding the basic taste qualities, there is a question of how stimuli which produce a similar quality may be discriminated from one another. For instance, in primates, individual afferent fibers that responded to one sweet stimulus typically also responded to several other sweets, and minimally to bitter or sour tastants (Hellekant and Ninomiya 1994; Wang *et al.* 2009). This type of narrow tuning is much less prevalent for taste qualities other than sweet: individual neurons respond quite variably to different salts (Frank *et al.* 2008). However, this feature remains incompletely explored in the periphery as most studies have utilized only limited panels of taste stimuli.

Whether sensory afferent fibers and their parent ganglion neurons employ patterns of action potentials to encode stimulus identity has been explored to only a limited extent. Different taste stimuli appear to cause primary afferent fibers to fire action potentials with somewhat different patterns, though these differences are not marked (Lawhern *et al.* 2011; Nagai and Ueda 1981; Ogawa *et al.* 1974). Thus, spike discharge pattern may augment and refine the combinatorial coding described above (Nagai and Ueda 1981). Taste coding in the periphery most likely involves activating a combination of afferent fibers having varying tuning capabilities (from specialists to generalists) and subtly different firing patterns. All these factors together play a role in the transmission of information needed to discriminate sweet, sour, salty, bitter, and umami.

Parenthetically, a key point that should be noted is that to date, recordings from the primary afferent neurons have only been obtained in anesthetized animals. It is possible that some of the distinctions noted below in the response properties of higher level neurons may be attributable to anesthesia.

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Hindbrain neurons: evidence for temporal coding

Gustatory afferents from the periphery project directly to the NTS in the brainstem where there is substantial convergence (Whitehead and Frank, 1983; Whitehead, 1986). Cells in the brainstem, NTS and PbN (the main target of projections from the NTS), are generally more broadly tuned than peripheral fibers in both anesthetized (see Spector and Travers 2005, for a review) and awake (see Roussin et al. 2012, but see Nakamura and Norgren 1991) rodents, though there are still groups of neurons in each structure that are narrowly tuned to a single taste quality. Like fibers/cells in the periphery, neurons in the brainstem can become more broadly tuned with changes in stimulus concentration. Moreover, response profiles, defined as the subset of taste qualities that evokes a response, of NTS and PbN cells can change over time (Sammons et al., 2016). This may be due to the changing inputs to these cells as taste receptor cells die and are replaced. Despite such turnover, the network obviously needs to remain stable in its output. It is possible that extensive convergence from neurons with different profiles of sensitivities may support this stability; that is, the loss or addition of a few inputs with different taste sensitivities would have minimal impact on the target cells if there were enough variety in the array of inputs. Further, simultaneous recordings from taste-responsive NTS and PbN cells have shown that NTS with a particular best stimulus are more effective in driving PbN cells with a similar best stimulus, though the same PbN cells receive input from NTS cells with all types of best stimulus preferences (Di Lorenzo and Monroe, 1997; Di Lorenzo et al. 2009). As a changing array of inputs to NTS cells shift their response profiles from one best stimulus to another, simultaneous activation of enough inputs responding to a given best stimulus may also cause PbN cells upstream to shift their best stimulus in kind, as well as modifying the effectiveness of inputs that were activated. Thus, response profiles may change but the overall proportions of the constituents of the network encoding taste stimuli may remain consistent.

With a variety of response profiles in the taste-responsive portion of the NTS and PbN, there remains the problem of how confusion among similar-tasting, but not identical, tastants is resolved. As discussed, the across-fiber/neuron patterns may offer one solution, but another might be response dynamics, that is, temporal coding. Variation in the temporal pattern of taste-evoked firing offers a way to disambiguate two tastants that evoke similar response magnitudes within the same cell (Di Lorenzo et al. 2009).

Both specialist and generalist neurons have been described in brainstem taste areas in electrophysiological studies with anesthetized animals. Perceptually similar stimuli evoke similar patterns of neuronal population activity, lending support to the combinatorial coding model discussed

above (Geran and Travers 2009; Simon *et al.* 2006; Smith *et al.* 2000). However, unlike taste bud cells and sensory afferent neurons, gustatory neurons of the brainstem do exhibit evidence of temporal coding. “Metric space analysis” (MSA; Victor and Purpura 1996; 1997) has been used to quantify this. MSA begins by determining a “distance” between spike trains in terms of the “cost” of making them identical, via adding, deleting, or moving spikes. Adding or removing a spike costs one arbitrary unit. The cost of moving a spike in time by an amount t is given by qt, where q is a parameter that controls the sensitivity of the distance to spike timing. Based on these distances, calculated from repeated neural responses to presentations of several tastants, one can determine two information-theoretic quantities: H^{count} and $H^{spike}[q]$. H^{count} is the amount of information about taste quality conveyed by spike count alone, and $H^{spike}[q]$ is the amount of information about taste quality when spike timing is taken into account.

In early work using anesthetized rats, spike timing was shown to convey a significant amount of information about taste stimuli in both the Nucleus of the Solitary Tract (NTS; Di Lorenzo and Victor 2003) and the Parabrachial Nucleus of the pons (PbN; (Rosen *et al.* 2011), respectively the first and second synapses in the central gustatory pathway in rodents. Specifically, in about half of the taste-responsive cells in NTS (Di Lorenzo and Victor 2003) and PbN (Rosen *et al.* 2011), spike timing contributes to taste quality discrimination – and in both NTS and PbN this contribution was largest in neurons that would appear to be broadly tuned if only spike count were considered. In addition, in the NTS, spike timing contributes significant amounts of information to distinguishing among responses to the components of binary mixtures (Di Lorenzo *et al.* 2009b), between tastants of different concentrations (Chen *et al.* 2011a) and tastants of the same taste quality but different chemical compositions (Roussin *et al.* 2008).

While evidence for temporal coding of taste stimuli in brainstem structures has been obtained in the anesthetized animal, further studies asked whether there was similar evidence of temporal coding of taste in the alert animal (Roussin *et al.* 2012; Weiss and Di Lorenzo 2012). To that end, rats were implanted with 8-channel microwire electrode bundles aimed at either the NTS or PbN. Following recovery from surgery, mildly water-deprived rats were placed in an experimental chamber with a drinking spout that allowed control of various fluids on a lick-by-lick basis. Taste responses in the NTS and PbN of awake freely licking rats differed in several ways from those recorded under anesthesia. For example, in addition to the typical phasic-tonic time course of response seen under anesthesia, brief lick-by-lick responses were also apparent in many NTS and PbN cells recorded in awake rats. Of these, some cells had responses that progressively increased with successive licks. There were also many cells with very long latency (>2 sec) taste responses that began long after the licks were

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completed (Roussin *et al.* 2012), which might be the result of stimulation of post-oral receptors during swallowing.

Recordings from the NTS (Roussin *et al.* 2012) and PbN (Weiss *et al.* 2014) of awake freely licking rats revealed a rich variety of cell types in addition to those that respond solely to taste. For example, many cells fire in phase with licking, with peak firing rates just at the time of the lick, or between licks. In addition, there are cells that significantly decrease their firing rate during a lick bout. The relative silencing of such cells when the rat engages in consummatory behavior suggests that they may set the initial conditions for the network to acquire sensory information. Moreover, these data underscore the idea that sensory and motor components of gustation are inextricably linked.

In a separate series of experiments, the effects of pairing olfactory stimuli with tastants were tested (Escanilla *et al.* 2015). Widespread modulation of taste responses was observed, including changes in response magnitude and latency following taste-odor pairing. MSA of taste- and odor-evoked responses showed that NTS cells were more competent at discriminating tastants when they were presented with odors than when presented alone. This applied for all taste qualities, and whether or not spike timing was taken into account, leading to the hypothesis that brainstem neurons may be most keenly tuned to respond to naturalistic stimuli, that is food, rather than pure chemical exemplars of taste qualities (Escanilla *et al.* 2015). This was tested by presenting complex, natural stimuli such as grape juice (sweet), clam juice (salty), lemon juice (sour) and coffee (bitter). Evoked spike trains in the PbN of awake freely licking rats displayed conveyed significantly more information to naturalistic stimuli than those associated with single compounds (Weiss *et al.* 2014).

In conclusion, data from electrophysiological recordings from awake, freely licking rats, underscores the role of the gustatory brainstem as an important node in the neural circuit that controls food identification and ingestion. In addition, dynamics – both intrinsic to the spike trains and related to the lick cycle – are prominent and functionally significant aspects of neural responses.

From the gustatory brainstem, afferents target the most medial portion of the ventral posteromedial thalamus. Taste-responsive thalamic neurons in this nucleus form an important source of input to gustatory cortex. Although this small region has been understudied relative to other taste areas, there is recent evidence that the gustatory thalamus may play important roles in taste quality and palatability coding, as well as stimulus expectation (Liu and Fontanini 2015).

Patterns of activity in the rodent gustatory cortex

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Within gustatory cortex (GC), physiological studies demonstrate that taste-responsive cells are often multimodal, responding to other sensory stimuli in addition to taste (for review, see Maffei *et al.* 2012). When recordings are made in in either anesthetized or awake animals probed with only sapid stimuli, both narrowly and broad taste-responsive neurons are found, similar to those found in both peripheral and other central taste areas (e.g. Katz *et al.* 2001; Ogawa *et al.* 1992a; Ogawa *et al.* 1992b; Sadacca *et al.* 2016; Spector and Travers 2005; Stapleton *et al.* 2006a; Yamamoto *et al.* 1989; Yamamoto *et al.* 1984; Yamamoto *et al.* 1985). The roles of these cell types are still ambiguous in terms of function, although there is evidence that some cortical taste neurons may respond broadly to sets of stimuli that can be classified as sharing a hedonic value (Fontanini and Katz 2006; Yamamoto *et al.* 1989).

An important and related, yet not well-understood aspect of taste coding, involves the spatial organization of taste neurons – are cells responsive to particular taste stimuli clustered together? Other sensory systems differ in this mode of organization; from the well-known somatotopy of barrel cortex, to the apparent random overlap of odorant responses in piriform cortex (Petersen 2007; Stettler and Axel 2009). Chen and colleagues (2011b) used 2-photon imaging to describe a sharply segregated quality representation in mouse GC. Here, quality-specific clusters of singly responsive neurons were separated in space along the cortical surface, by areas with only sparse taste-evoked activity. In contrast, the vast majority of work on taste cortex is entirely consistent in suggesting that there is little to no stimulus topography in how taste qualities are represented in the gustatory cortex. Across the anterior – posterior expanse of GC, mapping studies using different techniques have yielded very different conclusions. For instance, studies using either in vivo recordings, or intrinsic imaging, show a large degree of overlap among the basic taste stimuli, with bias towards overrepresentation of individual qualities at the anterior and posterior extremes (Accolla *et al.* 2007; Bahar *et al.* 2004; Carleton *et al.* 2010; Yamamoto *et al.* 1985). A genetically encoded trans-synaptic tracer similarly suggested that neurons receiving input for different taste qualities are intermingled in the gustatory cortex (Sugita and Shiba 2005).

More recently, 2-photon imaging was used to investigate taste responses to stimuli representing four primary qualities (acid, bitter, salty and sweet) in an area of mouse gustatory cortex defined by taste thalamic input (Fletcher *et al.* 2017). This “central” area, located just posterior to the landmark middle cerebral artery, possessed thalamic terminal labeling concentrated in the dysgranular subdivision. Using a virally expressed calcium indicator (GCaMP6s), taste imaging responses were collected in anesthetized mice in this delineated area. Not surprisingly, cortical taste cells were found to respond either best to individual stimuli, or combinations of stimuli. Spatial mapping demonstrated that taste quality responses overlapped in this region, with no evidence of segregation of cells responding to a single quality. Principle components analysis of this aggregate data suggested that the primary taste

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qualities were distinctly represented in the population response, providing a basis for discrimination despite spatial overlap. Moreover, the stimuli were ordered along the first component in a way that suggested hedonic character may also be represented in the response.

The finding of an area of quality overlap in the center of mouse GC fits in nicely with the previously mentioned mapping studies in the rat (Accolla *et al.* 2007; Yamamoto *et al.* 1985), and other recent 2-photon approaches in mice (Lavi *et al.* 2018; Livneh *et al.* 2017). Still, these papers and the Chen et al. (2011b) study leave open the possibility that bitter taste responses and sweet taste responses may be overrepresented posteriorly and anteriorly, respectively, in GC. If so, any topographic representation of taste quality likely stems from the source of peripheral input. The glossopharyngeal (IX) nerve, which innervates posterior taste buds, is known to be more responsive to bitter-tasting stimuli than branches of the facial nerve (VII), which innervate taste buds on the anterior tongue and palate (Frank 1991; Frank *et al.* 1983). In rat taste cortex, information from the chorda tympani branch of VII projects to the anterior GC, while information from IX targets the posterior GC (Hanamori *et al.* 1998; Yamamoto *et al.* 1980). A similar "gradient" of taste quality representation that follows peripheral input has also been described in the parabrachial nucleus in the rodent brainstem (Geran and Travers 2006; Halsell and Travers 1997). In this discussion, however, it is important to consider the multimodal nature of GC, as well as surrounding cortical areas. For example, there is also a prominent viscero-sensory representation found in posterior insular cortex, adjacent to GC (Cechetto and Saper 1987). Perhaps correspondingly, the hotspot for conditioned taste aversion learning is also found in posterior insular or GC (Schier *et al.* 2016; Schier *et al.* 2014). Furthermore, Hanamori and colleagues (1998) found that over 75% of taste-responsive neurons in posterior GC in rat were also responsive to a nociceptive stimulus (tail pinch).

In summary, reports (Chen *et al.* 2011b; Peng *et al.* 2015) from a single laboratory notwithstanding, the evidence is now quite strong that gustatory signals for taste quality are distributed and intermingled in the gustatory cortex.

Patterns of gustatory activity in the human cortex

While taste processing in the periphery and also the central nervous system has gained considerable attention in animal models, these processes are still to be investigated in humans. Of particular interest are questions on how, when, and where taste information, in general, and specific taste attributes such as taste quality, intensity, and hedonics, in particular, are processed in the human brain. Human neuroimaging studies have shown that taste consistently activates a range of cortical areas including the anterior insula and frontal operculum (FOP), mid-dorsal insula and overlying Rolandic operculum, posterior insula and POP, as well as the postcentral gyrus (cf. Veldhuizen *et al.*

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2011; Yeung *et al.* 2018). Evidence suggests that the mid-dorsal insula and the adjacent FOP form GC (Bender *et al.* 2009; Iannilli *et al.* 2012; O'Doherty *et al.* 2001; Small 2010; Small *et al.* 1999), while the posterior insula and POP have been implicated in oral somatosensation and attention to the mouth rather than gustation (Veldhuizen *et al.* 2007). These findings are in line with macaque anatomy, where the anterior and mid insula and the FOP, but not the POP, receive taste afferents from the thalamus (Pritchard *et al.* 1986) but may not directly translate to human physiology. Observations that taste sensations can be elicited by electrical stimulation of the mid-dorsal insula (Mazzola *et al.* 2017) further corroborate its role as GC. Consistent with the anatomical evidence, scalp-level electrophysiological studies found pronounced activation of the bilateral anterior in mid insula and adjacent frontal operculum in response to electric (Ohla *et al.* 2010) and sapid taste (Crouzet *et al.* 2015; Tzieropoulos *et al.* 2013) within 150 ms of taste delivery.

Functionally, insular activation has been linked with sensory taste features, such as taste intensity (Grabenhorst and Rolls 2008; Guest *et al.* 2007; Ohla *et al.* 2010; Spetter *et al.* 2010; Tzieropoulos *et al.* 2013) and taste quality (Crouzet *et al.* 2015; Schoenfeld *et al.* 2004); taste pleasantness and valuation, on the other hand, have been mostly associated with activity in the OFC, the anatomically later, secondary taste area (Grabenhorst and Rolls 2008; Guest *et al.* 2007). However, it has also been proposed that the GC jointly encodes both the chemical identity and palatability of a tastant (de Araujo *et al.* 2006) thereby suggesting a role of the insula in the evaluation of taste or its precursors beyond mere sensory processing. This notion is corroborated by observations that expectations about the value of a taste, induced by visual cues, modulate taste-related processing in the rodent (Grossman *et al.* 2008) and in the human (Nitschke *et al.* 2006; Ohla *et al.* 2012) insula.

In contrast to animal models, the mechanisms underlying taste quality coding have received little attention in humans mostly due to the limited spatial resolution of noninvasive brain imaging techniques such as functional magnetic resonance imaging (fMRI) yielding a spatial resolution of a few millimeters at best. Accordingly, only a few fMRI studies have addressed the question of a gustotopic organization of the human GC and their results failed to provide evidence for a clear spatial segregation of taste qualities but rather suggest a partial overlap of insular representations for different tastes (Dalenberg *et al.* 2015; Prinster *et al.* 2017; Schoenfeld *et al.* 2004). However, cortical activation patterns change rapidly, within milliseconds, rendering temporal information a candidate variable for taste quality coding. In fact, neuronal response patterns obtained from electrophysiological recordings at the scalp allow deciphering which taste participants tasted on a given trial. The onset of this discriminability coincided with the earliest taste-evoked responses that were localized in GC signifying that quality is among the first attributes of a taste represented in the central gustatory system (Crouzet *et al.* 2015) in strong accord with electrophysiological studies in awake rodents (Graham *et al.* 2014;

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Pavao *et al.* 2014; Stapleton *et al.* 2006b). The results also align with and add to observations that neuronal response patterns along the rodent gustatory neuroaxis, including the nucleus of the solitary tract (Di Lorenzo *et al.* 2009a), parabrachial nucleus (Geran and Travers 2013), and insula (Jezzini *et al.* 2013), code taste quality.

More recent evidence linked the predictive value of gustatory neural response patterns and taste-related decision-making. For this, behavioral reports from different tasks were combined with multivariate analyses of large-scale electrophysiological recordings in a series of studies. Specifically, Crouzet and co-workers (2015) showed that the more alike the neural response patterns of any two tastes were, as indicated by poorer discriminative performance of a classifier, the more these tastes were confused by the participants. The results were surprising for the taste domain because they provide evidence for a mapping between neural and phenomenological rather than between neural and chemical spaces. Whether the information encoded in gustatory neural response patterns drives actual behavior was addressed in two further studies. In the study by Wallroth and Ohla (2018), participants were to detect the presence of a taste as quick as possible. They found that the onset of taste decoding (discriminable brain response patterns) indeed predicted *when* participants detected a given taste by button press and linked neuronal response patterns to the speed of simple gustatory perceptual decisions – a vital performance index of nutrient sensing. Interestingly, the onset of taste decoding was earlier in this study, where participants responded speedily, compared to the previous study, where participants performed a delayed response task suggesting that the timing of gustatory coding is in a way flexible and dependent on behavioral goals.

While the mere detection of a taste in the oral cavity may prepare a non-specific response, the regulation of nutrient uptake and expulsion of potential toxins calls for quick and reliable taste detection and identification. Whether taste detection and discrimination are sequential or parallel processes, that is whether you know what it is as soon as you taste it, was addressed in another study (Wallroth and Ohla in press). To uncover the sequence of processing steps involved in taste perceptual decisions, participants performed taste-detection and -discrimination tasks. Irrespective of taste quality and task, neural decoding onset and behavioral response times were strongly linked, demonstrating that differences between taste judgments are reflected early during chemosensory encoding. Moreover, neural and behavioral detection times were faster for the iso-hedonic salty and sour tastes than their discrimination time. No such latency difference was observed for sweet and bitter, which differ hedonically. These results indicate that the human gustatory system detects a taste faster than it discriminates between tastes, yet hedonic computations may run in parallel (Perez *et al.* 2013) and facilitate taste identification.

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Together these studies clearly show that the information encoded in taste-related neural response patterns is also the foundation for gustatory decision-making and that the timing aligns with task-specific goals.

Cortical population coding of taste decisions and behavior

Taste quality is tightly linked to taste palatability or pleasantness. While sweet taste is typically liked, bitter taste is commonly aversive to most mammals. Accordingly, the gustatory neuroaxis needs to represent both features as they, together, drive food-related decisions and allow adaptive behavior. In awake rats, taste administration is represented by complex temporal coding in single neurons: a brief period of non-specific firing is followed by approximately 500 msec of identity-related firing, which is in turn replaced by firing that is reliably related to taste palatability (Katz *et al.* 2000; Sadacca *et al.* 2012). A series of studies have demonstrated that the palatability "epoch" can be independently manipulated, validating the characterization: changes in perceived palatability, such as that observed at the transition from an attentive to "withdrawn" state (Fontanini and Katz 2005; 2006) and across conditioned taste aversion learning (Grossman *et al.* 2008; Moran and Katz 2014), change palatability epoch coding while having no impact on the earlier ~800 ms of taste-induced activity.

CNS neural responses provide information about the identity of tastes on the tongue. Countless studies have demonstrated that sapid stimuli, flowing across the tongue of anesthetized animals, induce responses in neurons across the gustatory neuroaxis (for just a few examples, see (Azuma *et al.* 1984; Di Lorenzo 1988; Di Lorenzo and Victor 2003; Erickson *et al.* 1994; Li *et al.* 2013; Nishijo and Norgren 1990; Yamamoto 1984; Yamamoto *et al.* 1989). Perhaps the most discussed facet of these studies is the fact that taste responses vary vastly in breadth; a great deal of energy has been devoted to debating theories of gustatory coding that turn on these breadths of responsivity (e.g., Di Lorenzo 2000; Lemon and Katz 2007; Scott 2004; Smith and St John 1999; Spector and Travers 2005). Neural circuitry in general, and taste circuits in particular, are rife with cross-talk and feedback at both micro- (within region) and macro-circuit (between region) level (Jones *et al.* 2006). Empirical and theoretical work makes it clear that neural responses in such interactive networks should contain functionally interpretable dynamics that are most meaningful when examined at the ensemble rather than at the single cell level (e.g., see Abarbanel and Rabinovich 2001).

An independent set of studies have made use of analytic techniques specialized to interpret the real-time firing of multiple simultaneously-recorded neurons (hidden Markov modeling, or HMM). This work reveals that firing rate modulations within taste responses, which appear gradual in across-trial averages of single-neuron firing, are in fact not gradual at all. Rather, they reflect sudden coherent

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shifts between ensemble states: at particular time points within individual trials, the firing rates of (on average) ~50% of the recorded neurons will change simultaneously; across-trial averages "smear" these changes, making them look more gradual, because they happen at different latencies in different trials (Jones *et al.* 2007; Miller and Katz 2010). Together, these two sets of results suggest the testable hypothesis that GC neural ensembles, far from simply coding what the taste IS, may process that information to directly drive action. If in fact palatability-related firing appears suddenly in single trials (a possibility implied by but not directly demonstrated in the above-described work), it is possible to hypothesize that this appearance predicts the onset of consumption behavior. Our testing (Sadacca *et al.* 2016) proves this to be the case, in that analyses keyed to the onset of the ensemble state dominant during the palatability epoch (rather than to stimulus onset time, as is more typical) reveal that palatability coding does emerge suddenly—more suddenly than a range of ramping models (including the model used to explain primate perceptual decision-making (see Gold and Shadlen 2001; Shadlen *et al.* 1996) can explain, and as fast as models assuming instantaneous state transitions (Sadacca *et al.* 2016).

Armed with the knowledge of precisely *when* decision-related information appears in GC on individual trials, the authors were then able to compare this information to within-trial latencies of palatability-related behavioral responses, measured through electromyography. This analysis specifically reveals that the sudden emergence of the "palatability-related state" in GC neural ensembles predicts both *whether* the rat will gape in response to taste stimulation and precisely *when* that gape will occur, in single trials, with correlation values of ~ 0.75 (Sadacca *et al.* 2016).

The above results, while robust, are phenomenological. Li and co-workers (2016) performed two types of perturbation experiments to test whether GC ensemble transitions are causally linked to consumption behavior. In one experiment, arrival of an aversive taste was cued: as the rats learned the meaning of the cue across a full session, the latency with which they gaped in response to the taste decreased by ~150 ms; recordings showed that the cue had an almost identical impact on neural coding of that aversive taste. In the second experiment; optogenetic silencing of GC neurons was shown to change the likelihood of gaping. Together, these experiments confirm the general hypothesis that GC is a part of a distributed system responsible for transforming an incoming identity code into a taste decision.

These results, while perhaps surprising within the field of taste research, are consistent with a great deal of work on sensorimotor systems—and, more specifically, on work describing the top-down modulation of multi-rhythmic central pattern generators (Marder 2012).

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Conclusion

When examined at each level of the nervous system – periphery, brainstem, and cortex – it is evident that individual taste-responsive receptor cells or neurons may respond either selectively or broadly to stimuli of different taste qualities. Recent approaches to rodent and human central taste also emphasize the importance of temporal response patterns, which likely underlie the progression of taste behavior, from detectability to discrimination. This response complexity supports the notion of combinatorial coding along the gustatory neuroaxis. The flexibility inherent in this type of coding for the sense of taste may be necessary for animals to exhibit adaptive behavior in food selection and consummatory behavior.

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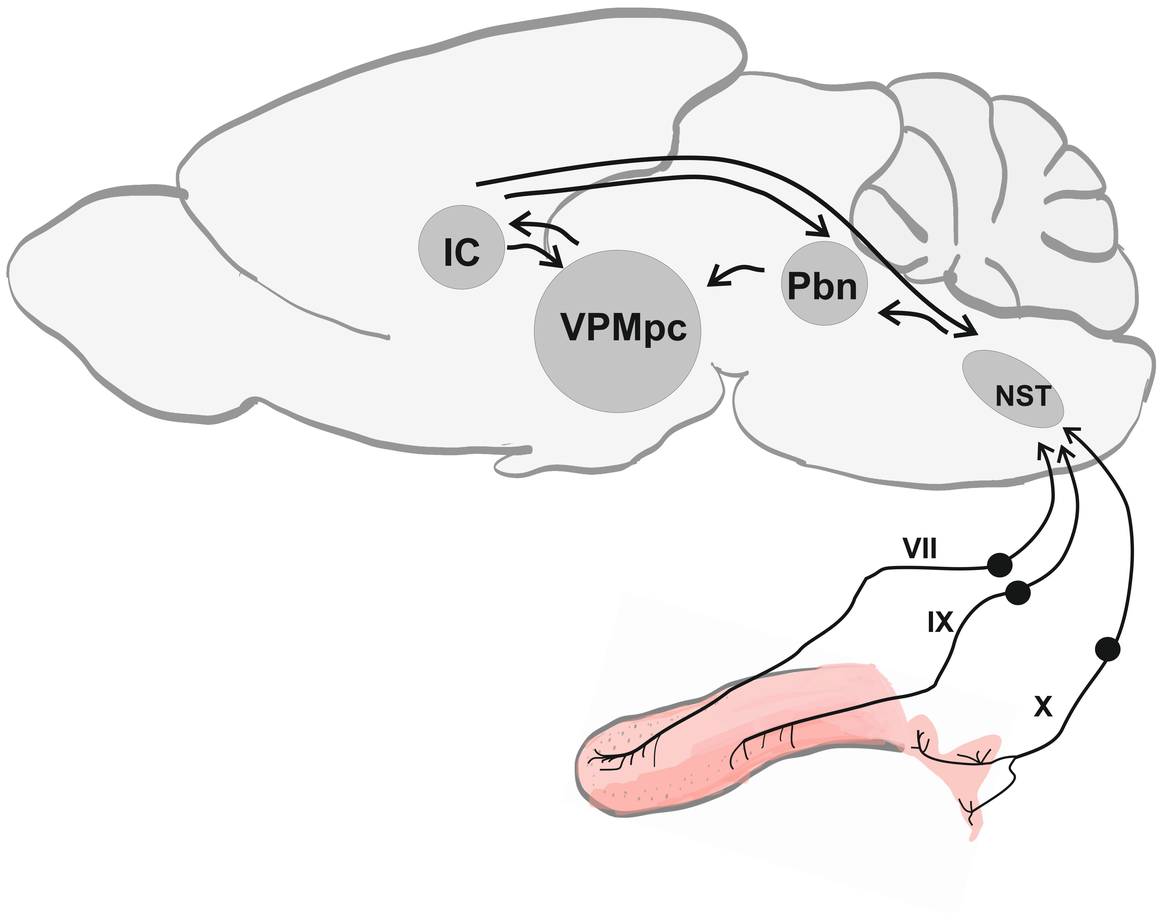

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