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Central taste anatomy and physiology

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Abstract

The gustatory system contributes to the flavor of foods and beverages and communicates information about nutrients and poisons. This system has evolved to detect and ultimately respond to hydrophilic molecules dissolved in saliva. Taste receptor cells, located in taste buds and distributed throughout the oral cavity, activate nerve afferents that project to the brainstem. From here, information propagates to thalamic, subcortical, and cortical areas, where it is integrated with information from other sensory systems and with homeostatic, visceral, and affective processes. There is considerable divergence, as well as convergence, of information between multiple regions of the central nervous system that interact with the taste pathways, with reciprocal connections occurring between the involved regions. These widespread interactions among multiple systems are crucial for the perception of food. For example, memory, hunger, satiety, and visceral changes can directly affect and can be affected by the experience of tasting. In this chapter, we review the literature on the central processing of taste with a specific focus on the anatomical and physiological responses of single neurons. Emphasis is placed on how information is distributed along multiple systems with the goal of better understanding how the rich and complex sensations associated with flavor emerge from large scale, systems-wide, interactions.

Keywords

taste; gustatory; brainstem; thalamus; cortex; limbic system; hedonic value; reward; cross-modal; expectation

INTRODUCTION

The function of the gustatory system is to detect, identify, and establish the palatability of specific chemicals present in foods and beverages, herein termed “tastants”. Sugars, salts, acids, alkaloids, and amino acids can dissolve in saliva, bind to specific receptors, and activate taste receptor cells located in the taste buds. Activation of different receptors initiates the chain of events that leads to the perception of different taste qualities: sweet, salty, sour, bitter and umami (savory). Information processed in the taste buds is relayed to afferent fibers from three cranial nerves, the facial (CN VII), glossopharyngeal (CN IX), and

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vagus (CN X). The cell bodies of these afferent fibers are located in the cranial nerve ganglia, whose central branches enter the central nervous system in the brainstem. Signals pertaining to the chemical identity of taste stimuli are processed by brainstem nuclei before ascending to the gustatory thalamus and ultimately reaching the gustatory cortex. This pathway has been extensively studied for its role in analyzing chemical information present in the mouth (Carleton et al., 2010; Spector and Glendinning, 2009; Spector and Travers, 2005). With regard to this function, two main theories have been formulated, each postulating a different strategy for encoding chemosensory signals (Lemon and Katz, 2007). The first theory, the labeled line theory, proposes that information about different taste qualities is encoded by distinct groups of neurons that must be narrowly tuned to encode exclusively a single taste quality(Chandrashekar et al., 2006; Hellekant et al., 1998). In this view, each structure, region or nucleus along the central gustatory pathway contains distinct neurons for signaling sweet, salty, sour, bitter, and umami sensations. According to the most extreme view of labeled-line theory, the same coding strategy applies from the tongue to the cortex (Chen et al., 2011). A second theory, historically rooted in the across-neuron pattern theory (Erickson, 1963), postulates that taste qualities are encoded by the combined and dynamic activity of large ensembles of neurons (Katz et al., 2002). Each taste quality can engage the same group of neurons but evokes different patterns of activity. Thus, single gustatory neurons do not need to be narrowly tuned but can encode information about multiple taste qualities. For several decades, the contraposition between these two theories has monopolized the debate on the function of the gustatory system. While the exact coding scheme has been a matter of contention, neither theory has challenged the view of the gustatory system as being solely devoted to representing taste qualities.

However, recent data have opened the door for a more integrative perspective on the gustatory system(Jones et al., 2006; Simon et al., 2006; Vincis and Fontanini, 2016b). According to this view, neurons in the gustatory system are not only concerned about encoding tastants, but also process non-gustatory information related to the experience of food and eating(Small, 2012). For instance, stimuli of sensory modalities distinct from taste, like texture, temperature, and odor, can effectively recruit neurons in the gustatory system (Escanilla et al., 2015; Li and Lemon, 2018; Maier et al., 2015; Vincis and Fontanini, 2016a; Wilson and Lemon, 2013). In addition to other sensory modalities, neurons in the gustatory system are also sensitive to visceral signals concerning the post-ingestive effects of food (Oliveira-Maia et al., 2012), as well as homeostatic signals conveying the metabolic state of the subject (de Araujo et al., 2006). Finally, neurons throughout the gustatory system can encode psychological, affective, and cognitive states associated with the present and past experience of eating (Simon et al., 2006; Vincis and Fontanini, 2016b). This function of the gustatory system relies on its tight relationship with areas devoted to processing interoceptive signals and reward-related functions (Haley et al., 2016; Livneh et al., 2017).

While numerous theories of chemosensory coding have been proposed, less attention has been paid to how gustatory areas represent and integrate information from non-gustatory sources. Evidence from electrophysiological recordings suggests that individual neurons may encode multiple gustatory and non-gustatory variables (Escanilla et al., 2015; Gardner and Fontanini, 2014; Liu and Fontanini, 2015; Livneh et al., 2017; Vincis and Fontanini, 2016a), a feat known as “multiplexing”. Multiplexing of information is believed to occur via

time-varying changes in firing rates (Katz et al., 2002; Parabucki and Netser, 2014). This ability to represent multiple signals is modulated and enhanced by learning (Grossman et al., 2008; Moran and Katz, 2014; Vincis and Fontanini, 2016a). According to this relatively recent perspective, the gustatory system is not just simply an analyzer of chemical information but is an adaptive system that integrates all of the information necessary for properly forming and contextualizing the experience of food.

In this chapter we review the basic organization of the gustatory system, its connectivity, and its ability to represent purely gustatory information and complex signals related to food consumption. Of necessity, the focus is largely on non-human mammalian forms, primarily rodents, although, when possible, information from humans and other primates is provided.

NUCLEUS OF THE SOLITARY TRACT (NST)

Inputs, Outputs, and Internal Connectivity

Gustatory inputs from the mouth make their first central synapse in the nucleus of the solitary tract (NTS) (Aström, 1953). As noted above, gustatory information reaches the NTS via axonal fibers of the facial, glossopharyngeal, and vagus nerves (Beckstead and Norgren, 1979; Hayakawa et al., 2001; Nomura and Mizuno, 1981; Torvik, 1956; Whitehead and Frank, 1983). The terminal fields of these cranial nerves project to the NTS in a coarse rostro-caudal topographical organization (Contreras et al., 1982; Corson et al., 2012; Hamilton and Norgren, 1984). The two branches of the facial nerve, namely the chorda tympani (CT) and the greater superficial petrosal, send their axons to the most rostral part of the NTS and carry gustatory information from the anterior tongue and palate, respectively (Whitehead and Frank, 1983). The glossopharyngeal nerve, with its lingual-tonsillar branch, carries sensory information from taste buds located in caudal parts of the tongue; its terminal fields project both to the rostral (where they partially overlap with the axons of the facial nerve) and caudal NTS. The vagus nerve, with its laryngeal branch, transmits gustatory information from the epiglottis (Hamilton and Norgren, 1984) and projects mainly to the caudal portion of the NTS with just a few axonal fibers arriving in the rostral part (Hamilton and Norgren, 1984). The NTS also receives somatosensory inputs from the lingual branch of the trigeminal nerve, which projects to the lateral edges of the rostral NTS just lateral of the glossopharyngeal projections (Hanamori and Smith, 1989; Whitehead and Frank, 1983). The trigeminal nerve transmits sensory information from the oral epithelium (Hamilton and Norgren, 1984). Despite the weak rostro-caudal topographical organization of peripheral input, gustatory responses in the NTS do not necessarily reflect the cranial nerve axonal projections. For example, when the taste buds located in the more anterior portion of the tongue are stimulated with tastants, neural activity is evoked not only in the more rostral NTS, but also in the caudal region (Travers and Norgren, 1995; Travers et al., 1986).

Overall, gustatory inputs reach a well-defined area of the NTS, which extends from the rostral part to the caudo-medial portion of the nucleus. It is worth emphasizing that this area does not exclusively receive gustatory inputs, but also integrates thermal and tactile somatosensory information from the oral cavity as well as information from several other brain regions. The cranial nerves that send gustatory input to the rostral NTS also carry orofacial tactile information. Both the glossopharyngeal and the vagus nerve transmit

somatosensory tactile information to the rostral NTS (Ogawa et al., 1984). Furthermore, the lingual branch of the trigeminal nerve sends tactile information from the oral cavity to the NTS (Whitehead and Frank, 1983).

In addition to peripheral inputs, multiple central brain regions project to the NTS. These fibers carry signals that can impact the response profile of gustatory NTS neurons and can modulate gustatory processing as early as the first central synapse. One of the main sources of afferents to the NTS is the brainstem (Whitehead and Frank, 1983). Indeed, the rostral part of the NTS receives inputs from the caudal NTS as well as from the parabrachial nucleus (PBN) in murine rodents. Inputs from the caudal NTS originate from a region of the nucleus that integrates viscerosensory information (Whitehead et al., 2000); this connection is likely important for the integration of oral gustatory and visceral information within the NTS (Karimnamazi et al., 2002).

The gustatory NTS also receives, in addition to brainstem inputs, inputs from forebrain regions involved in sensory processing, cognition, reward processing, and energy homeostasis. For example, the gustatory cortex (GC) sends bilateral feedback projections to the rostral NTS (Shipley, 1982). These cortico-NTS projections modulate both the sensory input within, and the efferent output from, the nucleus (Cho et al., 2003; Di Lorenzo and Monroe, 1995). Other central brain regions that send inputs to the rNTS are the central nucleus of the amygdala (CeA) (Halsell, 1998; Veening et al., 1984) and the lateral hypothalamus (LH) (Moga et al., 1990; Norgren, 1976; van der Kooy et al., 1984). Neurons in the CeA can be differentially modulated by the hedonic value of taste stimuli (Nishijo et al., 1998), and electrical stimulation of the CeA has been shown to modulate gustatory processing in NTS (Di Lorenzo and Victor, 2003). In the LH there are neurons that have been described to respond to taste stimuli(Norgren, 1970; Yamamoto et al., 1989). Stimulation of the LH induces feeding behaviors (Hoebel and Teitelbaum, 1962), while lesion of the LH leads to a reduction of food intake (Hoebel and Teitelbaum, 1962). Given that the modulation of NTS neurons by LH stimulation causes primarily a facilitation of gustatory responses (Di Lorenzo and Victor, 2003), it is possible that LH-NTS inputs are crucial in enhancing the gain of NTS taste neurons during feeding (Di Lorenzo and Victor, 2003).

With regard to its outputs, the NTS disseminates gustatory and orofacial sensory information to other brain areas involved in sensory perception, sensory-motor feedback, and behavioral responses. The neural pathways originating from the NTS can be generally classified in two groups. The first group features taste-related direct projections to the pons, while the second group has both direct and indirect projections to medullary motor nuclei. The main gustatory output of the NTS (i.e., the ascending gustatory pathway) differs in different species. In rodents, NTS neurons send axons to the caudal parabrachial nucleus (PBN) in the pons (Moga et al., 1990; Travers, 1988). These efferents arise mainly from the rostral part of the NTS (Halsell et al., 1996), are primarily ipsilateral (Travers, 1988) and their terminal fields are located in the external region and waist area of the PBN (Karimnamazi et al., 2002). It has been estimated that in the rat, up to 80% of rostral NTS taste-responsive neurons project to the PBN (Di Lorenzo and Monroe, 1995). In primates, it is believed that NTS gustatory efferents bypass the pontine relay and directly project to the parvicellular portion of the

ventroposteriormedial thalamic nucleus (VPMpc) (Beckstead et al., 1980; Rolls, 1989). The second group of rostral NTS projections target brain areas that are not part of the ascending gustatory sensory pathways but send crucial information to drive and modulate oromotor responses to gustatory and tactile stimuli. Among those, the major efferent is the descending pathway that from the rostral NTS reaches the parvicellular reticular formation (PCRt) located in the pontomedullary reticular core (Shammah-Lagnado et al., 1992). This intramedullary projection is likely involved in oro-motor activity, since the PCRt contains neurons that project to oro-motor brainstem nuclei (Streefland and Jansen, 1999). Other descending rostral NTS projections are ones that directly target the brainstem oro-motor nuclei (Beckman and Whitehead, 1991). Among those, the denser projection seems to target the hypoglossal nucleus (Karimnamazi et al., 2002). Finally, the rostral NTS sends intranuclear output to the caudal NTS (Halsell et al., 1996); this projection is thought to be important for the integration of gustatory, orosensory, and visceral information.

Coding of Gustatory Information

Studies employing electrophysiological methods to record single neuron activity have provided fundamental information on how NTS neurons encode taste information. Studies on taste coding in the NTS have assessed responsiveness to taste by either averaging the number of spikes over the entire time of taste delivery or by analyzing the fine temporal structure of spiking following stimulation. Both approaches, applied to extracellular recordings in anesthetized and awake rodents, show how gustatory stimulation strongly modulates the average number of spikes produced by NTS neurons (Di Lorenzo and Victor, 2003; Doetsch and Erickson, 1970; Lemon and Smith, 2005; Roussin et al., 2012; Yokota et al., 2014) as well as the precise temporal structure of spiking activity (Di Lorenzo and Victor, 2003; Hallock and Di Lorenzo, 2006; Roussin et al., 2012).

NTS recordings have been extensively analyzed in search of evidence for either labeled line or population coding. A labeled line strategy might be favored by the spatial distribution of cranial nerve terminal fields and their differences in sensitivity across the basic gustatory qualities. Indeed, while all cranial nerves within the oral cavity are responsive to all taste modalities (Hallock and Di Lorenzo, 2006), the chorda tympani is activated mostly by salt and acid (Frank, 1973; Frank, 1974), the glossopharyngeal by bitter-tasting stimuli (Hanamori et al., 1988), and the superficial petrosal branch of the facial nerve by sweet-tasting agents (Travers and Norgren, 1991). However, electrophysiological recordings demonstrate that label line logic is not sufficient to account for taste coding in NTS. Both in primates and rodents, NTS gustatory neurons appear to be broadly tuned, where the same neuron is modulated by more than one of the classical taste modalities (sweet, salt, acid and bitter). In rats, half of the gustatory NTS neurons are tuned to two or more tastants (Di Lorenzo and Monroe, 1995; Travers and Norgren, 1995). Recordings performed in primates have found that more than 80% of NTS gustatory neurons respond to more than 3 basic taste stimuli (Scott et al., 1986). The breadth of gustatory tuning of NTS neurons may arise from intra-NTS interactions (Rosen and Di Lorenzo, 2012) and from the convergence onto the same neurons of peripheral axonal fibers originating from separate taste bud populations (Travers and Norgren, 1991; Vogt and Mistretta, 1990). Employing an analysis of entropy (a metric used to assess breadth of tuning), Smith and Travers (1979) demonstrated that NTS

neurons are systematically more broadly tuned than chorda tympani neurons (Smith and Travers, 1979). The breadth of tuning of NTS gustatory neurons is evidence for a population-based coding scheme (Scott and Giza, 2000), with gustatory information being carried by heterogeneous ensembles of NTS neurons. Recent data, relying on recordings from individual NTS neurons for multiple days, further demonstrate that taste responses and tuning are highly plastic (Sammons et al., 2016), a finding that is hard to reconcile with a strict labeled line logic.

Beyond coding of gustatory information

Neurons in the NTS do not only code for gustatory information. An increasing number of studies provides evidence for the convergence of olfactory, somatosensory and lick related information in NTS. Escanilla et al. (2015) found that, in awake rats, half of taste-responsive NTS neurons are also modulated by odorants. In addition, they showed that olfactory stimuli modulate taste-evoked activity of NTS neurons in the form of attenuation, enhancement, and changes in the temporal profile of spike activity (Escanilla et al., 2015).

With regard to somatosensory information, neurons in NTS can respond to tactile stimulation of the mouth (Travers and Norgren, 1995) and encode temperature (Lemon, 2017; Wilson and Lemon, 2013). Analysis of the relationship between neural activity and licking unveiled a significant fraction of neurons that were modulated by licking rhythmicity (Roussin et al., 2012). In addition to firing rhythmically, neurons in NTS can also reduce their firing during licking and show changes in firing rates before the initiation of a licking bout and after its termination (Roussin et al., 2012). These data emphasize the tight relationship between taste processing and sensorimotor signals. Altogether, evidence from the literature supports a view of the NST as a nucleus capable of integrating multiple gustatory, olfactory, and somatosensory signals.

Gustatory Thalamus

Inputs, Outputs, and Internal Connectivity—The parvicellular portion of the ventropostero-medial nucleus of the thalamus (VPMpc) is the main thalamic gustatory relay to cortex (Mufson and Mesulam, 1984). Gustatory information reaches the VPMpc via projections from the NST in primates (Beckstead et al., 1980) and the parabrachial nucleus (PBN) in rodents (Holtz et al., 2015; Karimnamazi et al., 2002). In primates, no gustatory connection to the PBN has been demonstrated so far. The VPMpc receives inhibitory inputs from the gustatory portion of the reticular thalamus (Hayama et al., 1994) and a strong contingent of excitatory fibers from the GC (Allen et al., 1991; Holtz et al., 2015). The GC projects to the VPMpc directly (Allen et al., 1991; Holtz et al., 2015) and indirectly via the RT (Hayama et al., 1994). As is the case for many other sensory thalamic nuclei, the VPMpc also receives fibers from neuromodulatory centers. The efferent fibers from the VPMpc target mostly the GC and the amygdala (Turner and Herkenham, 1991). However, this latter projection does not originate from the same neurons that target the GC (Nakashima et al., 2000).

Coding of Gustatory Information—Neural responses to gustatory stimulation have been studied in the VPMpc of both anesthetized and alert animals (Liu and Fontanini, 2015;

Nomura and Ogawa, 1985; Ogawa and Nomura, 1988; Pritchard et al., 1989; Verhagen et al., 2003). Early studies demonstrate that neurons in the VPMpc can respond to gustatory, tactile and thermal stimuli (Nomura and Ogawa, 1985; Verhagen et al., 2003). These modalities are not segregated in the VPMpc; indeed, more than 40% of VPMpc neurons can encode a combination of tactile, thermal, and chemosensory information (Verhagen et al., 2003). Taste responses are, as in the entire gustatory system, broadly tuned, with neurons typically encoding more than one taste quality (Liu and Fontanini, 2015). In addition, analysis of the time-course of responses to the delivery of tastants reveals time-varying dynamics (Verhagen et al., 2003), with complex modulations in firing rates for the first two seconds following stimulus onset (Liu and Fontanini, 2015). These dynamics are believed to reflect the exchange of information between the VPMpc, PBN, RT, and GC.

Beyond coding of gustatory information—According to classic view of the gustatory system, upstream of the NTS (or in the case of murine rodents, the PBN) the taste pathway bifurcates into two branches: a thalamic branch and a limbic branch. This view conceives the VPMpc as a purely sensory relay, which carries chemosensory and orosensory signals to the cortex. Inactivation studies, showing that silencing the VPMpc greatly reduces taste processing in the GC, are in apparent agreement with this view (Samuelsen et al., 2013). However, recordings and behavioral studies suggest a more complex functional role for the VPMpc. Extracellular recordings in anesthetized and alert rodents demonstrate that VPMpc neurons also carry information regarding the hedonic value of taste (Liu and Fontanini, 2015; Verhagen et al., 2003). Despite coding for hedonic value, behavioral experiments revealed that the VPMpc is not necessary for learning a conditioned taste aversion (CTA), leaving its role in hedonic processing and learning still to be fully explored (Arthurs and Reilly, 2013; Liang et al., 2012). A second function of the VPMpc involves its ability to modulate the state of cortical networks. Inactivating the VPMpc induces slow oscillations in the GC, an effect that is likely to alter the GC's ability to process any type of stimulus (Samuelsen et al., 2013). Finally, a third potential role of the VPMpc involves taste expectation. Taste processing in the VPMpc is dramatically affected by expectation (Liu and Fontanini, 2015). Indeed, the same stimuli are encoded differently depending on whether they are unexpected or expected following an anticipatory cue (Liu and Fontanini, 2015).

Recordings in primates suggest that VPMpc neurons are capable to change their firing rates in anticipation of a delivery of fluid (Pritchard et al., 1989). The role of the VPMpc in expectation is further confirmed by behavioral experiments (Reilly and Trifunovic, 1999).

In summary, the VPMpc plays a fundamental role in the gustatory system. It is not only necessary for transferring chemosensory signals to the GC, but it also plays a central role in mediating the effects of expectations.

Parabrachial nucleus (PBN)

Inputs, Outputs, and Internal Connectivity—In such rodents as mice, rats, and hamsters, the PBN is the second synapse of the ascending central gustatory pathway (Barnard, 1936; Norgren and Leonard, 1973). Whether this nucleus plays any role in primate taste function is presently uncertain but seemingly unlikely. The PBN is a complex of nuclei

located in the brainstem that extends from the dorsolateral region of the pontine tegmentum to the most caudal mesencephalic region (Bianchi et al., 1998). The PBN is composed of ten subnuclei characterized based on the size, shape and staining characteristics of the constitutive neurons (Fulwiler and Saper, 1984). Despite this subnuclear parcellation, a more general cytoarchitectural organization divides the PBN in three main regions: the ventral region (also known as the Kolliker-Fuse nucleus), the medial region (mPBN) and the dorsolateral region (lPBN) (Bianchi et al., 1998; Saper and Loewy, 1980).

The main gustatory afferent to the PBN is represented by ascending fibers from the NTS (Halsell et al., 1996; Moga et al., 1990; Norgren and Leonard, 1971; Whitehead, 1990). The rostral, and to a lesser extent the caudal NTS, send axonal projections that largely terminate in the caudal and ventral portions of the medial PBN (waist area)(Cho et al., 2002; Moga et al., 1990). From an anatomical point of view, it is interesting to note that while the rostral NTS-PBN projections are mostly ipsilateral, the terminal fields of the caudal NTS-PBN afferents are also found in the contralateral PBN (Tokita et al., 2009). In addition to anatomical data, multiple electrophysiological studies confirm the functional significance of the NTS-PBN taste pathways. Indeed, PBN neurons are modulated by gustatory stimulation in a way that strongly resembles taste modulation in the NTS (Perrotto and Scott, 1976; Scott and Perrotto, 1980). Furthermore, NTS neurons projecting to the PBN are more likely to be taste responsive than those that do not project to the PBN (Di Lorenzo and Monroe, 1995), suggesting a flow of taste information from NTS to PBN.

In addition to taste, the PBN also receives inputs conveying orosensory tactile information and a variety of central autonomic visceral signals, such as those pertaining to nociception (Hammond and Proudfit, 1980; Li and Lemon, 2018), respiration (Cohen, 1971), blood flow (Mraovitch et al., 1985), blood pressure (Mraovitch et al., 1982) and gastrointestinal function (Karimnamazi et al., 2002). Anatomical studies have shown that the orosensory and visceral input reaching the PBN also originate in the NTS. Earlier reports have suggested an overall spatial segregation of gustatory and visceral inputs (Moga et al., 1990; Norgren, 1978). However, neurophysiological data showed that the same PBN neurons in the waist area could be activated by both oral and gastric stimulation (Karimnamazi et al., 2002).

The PBN does not receive inputs exclusively from the NTS; multiple other brain areas thought to play a role in taste processing and feeding behaviors send centrifugal afferents and modulate spontaneous and taste-evoked activity in the PBN. Different studies have indeed demonstrated that the CeA, LH and GC send afferents to the PBN (Di Lorenzo and Monroe, 1995; Li et al., 2005; Lundy and Norgren, 2004; Moga et al., 1990). Stimulation of the CeA can induce both inhibitory as well as excitatory modulation on taste -responsive PBN neurons (Lundy and Norgren, 2001). Similarly, stimulation of the GC and LH bilaterally modulates gustatory processing in the PBN. It is interesting to note that, while CeA, GC, and LH centrifugal projections can distinctly influence PBN taste-evoked responses, they often converge on the same PBN neurons (Lundy and Norgren, 2004).

With regard to the projections out of the PBN, the two major taste-related PBN targets are the thalamus and the CeA (Bernard et al., 1993; Fulwiler and Saper, 1984; Halsell, 1992; Holtz et al., 2015; Ogawa et al., 1984; Tokita et al., 2010). Anterograde tracing studies have

shown that PBN-thalamic projections mainly terminate in the ipsilateral gustatory thalamus (Halsell, 1998). Fewer axonal terminal fields are also present in the central-medial thalamic nucleus (Halsell, 1998). While most of the PBN taste responsive neurons preferentially project to the gustatory thalamus relative to the CeA (Fulwiler and Saper, 1984; Halsell, 1992; Holtz et al., 2015), injections of anterograde tracer targeting exclusively the waist area of the PBN show dense projections in the CeA. These two main gustatory-related PBN efferents, the parabrachial-thalamic and the parabrachial-amygdalar pathways, may serve to transmit to higher brain areas different features of taste: pure sensory information via the thalamic pathway and hedonic information via the amygdalar pathway (Lundy and Norgren, 2015).

Other important PBN projections target the LH (Tokita et al., 2014), the bed nucleus of the stria terminalis, and to a lesser extent the diagonal band of Broca and the lateral preoptic areas (Lundy and Norgren, 2015). In addition, some PBN neurons directly project to the GC, mainly targeting the granular and dysgranular region (Saper, 1982; Zhang et al., 2011).

Coding of Gustatory Information—The role of PBN neurons in coding gustatory information has been extensively studied in both anesthetized and awake rodents. Electrophysiological evidence from anesthetized rats suggest that a general topographical organization might be present in the PBN with caudal neurons more responsive to tastants presented in the anterior oral cavity than to stimuli presented in the posterior portion of the mouth (Halsell and Travers, 1997). Mapping of taste qualities onto different subdivisions of the mouse PBN revealed signs of a topographic organization with overlaps in taste quality representation (Tokita and Boughter, 2012; Tokita and Boughter, 2016). Some regions of the PBN appeared to respond preferentially, albeit not exclusively, to certain stimuli, while others showed no such a bias. Analysis of the breadth of tuning of PBN neurons responding to taste yielded heterogeneous results. Some reports have found evidence for narrowly tuned responses (Geran and Travers, 2009), while others have demonstrated the existence of broadly tuned neurons (Di Lorenzo, 1988). Even in the case of alert rodents, the results show a mix of narrow and broad tuning, with a bias toward the latter. Nishijo and Norgren, using stimuli directly delivered into the mouse of alert rats via intraoral cannulae, found that 40% of PBN neurons respond exclusively to a single taste quality (Nishijo and Norgren, 1990). More recent evidence from experiments analyzing the temporal structure of taste responses in licking rats reported a larger proportion of broadly tuned neurons (Weiss et al., 2014). Direct analysis of the temporal structure of taste responses in the PBN underscored the importance of time and dynamics in the coding of gustatory information (Baez-Santiago et al., 2016). Time-varying patterns of spiking activity in the PBN are likely the result of dynamic inputs from the NTS (Roussin et al., 2012; Weiss et al., 2014) and from other regions like the GC (Parabucki and Netser, 2014).

Beyond coding of gustatory information—Neurons in the PBN do not process only gustatory information. Similarly to what has been described for the NTS, neurons in the PBN can be modulated by somatosensory (Li and Lemon, 2018; Schwartzbaum, 1983) and olfactory stimuli (Di Lorenzo and Garcia, 1985). Somatosensory modulation is particularly visible in recording from freely licking animals. Under these conditions, PBN neurons show

rhythmic responses that covary with licking (Schwartzbaum, 1983; Weiss et al., 2014). Processing of multisensory signals has been demonstrated in different contexts. For instance, a recent study from Sammons et al. (2016) found that naturalistic stimuli with multiple gustatory, olfactory, and somatosensory components (i.e. clam juice, lemon juice, coffee, grape juice, and cream) can be encoded by the PBN more effectively than prototypical gustatory solutions (Sammons et al., 2016).

Finally, it is important to mention that neurons in the PBN can be involved in representing the palatability of a gustatory solution. Lesions and pharmacological manipulations of the PBN can impact the perceived palatability of food and alter consumption (Söderpalm and Berridge, 2000; Spector and Travers, 2005), demonstrating the importance of this nucleus in hedonics. Electrophysiological recordings from alert rats have further confirmed this observation, showing that PBN neurons can encode hedonics with dynamics not dissimilar from those observed in the gustatory cortex (Baez-Santiago et al., 2016).

In summary, the data on the PBN demonstrate that the murine gustatory system, even at the level of the brainstem, integrates information from multiple sources. Gustatory signals are processed together with somatosensory, olfactory and affective signals, de facto suggesting that high level of integration can occur even at early stages of gustatory processing.

Gustatory Cortex

Inputs, outputs and internal connectivity—The gustatory cortex occupies a portion of the insular cortex and, in primates, also part of the operculum (Benjamin and Burton, 1968; Kosar et al., 1986; Mufson and Mesulam, 1982; Yamamoto et al., 1980). The insular cortex can be divided in three subdivisions on the basis of its cytoarchitectural structure. Based on the presence and the morphology of layer 4, one could identify a granular subdivision with a typical neocortical architecture, a dysgranular subdivision with a dysmorphic and progressively fading layer 4, and finally an agranular subdivision characterized by the absence of an identifiable layer 4 (Allen et al., 1991; Maffei et al., 2012). These subdivisions are adjacent and smoothly transition into one another on the dorsoventral axis in rodents and on the anteroposterior axis in primates.

The gustatory cortex receives inputs from a series of sensory and limbic areas (Allen et al., 1991). These afferents distribute differentially across the three subdivisions (Maffei et al., 2012). For instance, in rodents, thalamic afferents from the VPMpc target the granular and the dysgranular portions of the GC (Allen et al., 1991). A similar distribution can be seen for gustatory fibers arriving directly from the PBN (Allen et al., 1991). Inputs from limbic structures, like the amygdala, lateral hypothalamus, and prefrontal cortices, target the dysgranular and agranular subdivisions of the GC (Allen et al., 1991; Mufson and Mesulam, 1982). These are not the only inputs to the GC, afferent fibers arrive also from neuromodulatory nuclei (locus coeruleus and the nucleus basalis of Meynert) (Linster and Fontanini, 2014), olfactory areas (Shipley and Geinisman, 1984) and from other portions of the insular cortex (Adachi et al., 2013; Fujita et al., 2010; Shi and Cassell, 1998). In rodents, these intra-insular afferents come from both the anterior and the posterior portions of the insular cortex. Fibers from the anterior insular cortex may carry nociceptive information (Jasmin et al., 2004), whereas afferents from the posterior insula relay visceral,

somatosensory, and auditory signals (Rodgers et al., 2008). A similar level of interconnectivity has also been observed in primates (Rolls, 2016). In addition to inputs from other regions of the ipsilateral insula, the GC also receives projections from contralateral GC.

Besides receiving multiple sensory, visceral and limbic inputs from other nuclei and areas, the GC also shows a degree of internal interconnectivity. The three subdivisions of GC are not isolated from each other; anatomical and electrophysiological studies have demonstrated that they are interconnected (Adachi et al., 2013; Fujita et al., 2010; Shi and Cassell, 1998). This is an extremely important organizational feature, as it can subtend a high degree of integration of the different, and anatomically separated inputs within the GC.

As for the circuits within the various subdivisions of the GC, much less is known compared to the general connectivity. It is known that the laminar distribution of inputs and outputs is less localized relative other neocortical and paleocortical sensory areas (Allen et al., 1991). In most neocortical sensory cortices, layer 4 is the main recipient of thalamic inputs, layer 2/3 the site of cortico-cortical connections, and layer 5 is the main output. In the GC, thalamic afferents target multiple layers, with only a mild preference for layer 4. Similarly, inputs from the amygdala show differences in density, but do not appear to exclusively target specific layers (Haley et al., 2016). The interlaminar redistribution of afferent signals is further favored by the strong connectivity across different layers of the GC (Sato et al., 2008).

We are aware of only few studies characterizing the distribution of inputs onto intralaminar circuits and cell types. Amygdalar inputs can target pyramidal neurons, parvalbumin positive inhibitory interneurons, and somatostatin positive interneurons located in different layers. The probabilities of connection, as well as the strength of inputs, vary for different layers and cell types (Haley et al., 2016). Cell type specificity has been observed also for the effects of adrenergic and cholinergic stimulation (Koyanagi et al., 2010; Yamamoto et al., 2010). With regard to the outputs, GC efferents target cortical and subcortical regions belonging to the limbic network, to the gustatory system, and to other sensory systems. Interestingly, many targets of the GC are also sources of afferent inputs to the GC. Limbic outputs (Allen et al., 1991) target the amygdala (Shi and Cassell, 1998), lateral hypothalamus (Allen et al., 1991), mediodorsal thalamus (Allen et al., 1991), nucleus accumbens (Wright and Groenewegen, 1996), anterior cingulate cortex (Gabbott et al., 2003) and the orbitofrontal cortex (Baylis et al., 1995; Cavada et al., 2000). Gustatory outputs target the PBN (in rodents), the reticular nucleus of the thalamus (Hayama et al., 1994), and the VPMpc (Allen et al., 1991; Holtz et al., 2015). Beyond gustatory regions, the main sensory recipient of GC fibers is the endopiriform nucleus (Fu et al., 2004) which integrates gustatory and olfactory information. Altogether, the anatomical data available converge in showing that the GC receives projections from multiple sensory, visceral, homeostatic, and limbic areas. These inputs are partly segregated to the different subdivisions of GC, however, a high degree of internal interconnectivity ensures the wide redistributions of signals across all the subdivisions. The outputs are sent to multiple sensory and reward related regions, which are frequently engaged in feedback loops whose significance still has to be explored.

Coding of Gustatory Information—Experiments from rodents demonstrate that all three of the subdivisions of GC (granular, dysgranular and agranular) can respond to gustatory stimulation (Kosar et al., 1986; Ogawa et al., 1992). This is to be expected given the connectivity outlined above. In primates, taste appears to be coded mostly by the granular and dysgranular subdivisions of the anterior insular cortex (Ogawa, 1994).

Analyses of neural spiking activity obtained in awake rodents revealed that neurons in the GC are broadly tuned. Indeed, the majority of GC neurons are modulated by more than one tastant. This result, which has been reproduced by multiple laboratories and in multiple species, supports an ensemble coding scheme rather than a labeled line logic (Hanamori et al., 1998; Jezzini et al., 2013; Katz et al., 2002; Simon et al., 2006; Stapleton et al., 2006). This view has been challenged by a 2-photon calcium imaging study performed in anesthetized rodents showing the presence of “hot spots” of narrowly tuned neurons and the virtual absence of broadly tuned neurons in the GC (Chen et al., 2011). The discrepancy in these results could largely arise from the differences in the neural activity readouts: calcium signals represent only an indirect and partial measure of neural spiking. However, a recent 2-photon study performed by Fletcher and colleagues showed, that when using a more sensitive calcium reporter (GcAMP6), even under anesthesia, GC neurons are broadly tuned and lack specific spatial organization (Fletcher et al., 2017).

Classically, in order to establish if GC neurons are modulated by gustatory stimuli, spike responses or calcium transients are averaged over multiple seconds after taste delivery. While studies averaging neural activity over long intervals have been fundamental in providing a general picture of how the GC encodes chemosensory information, more recent experiments have focused on the importance of temporal dynamics (Jones et al., 2006). The majority of these studies have been performed in alert rodents receiving tastants either via an intraoral cannula or by intentionally licking a spout. Analysis of the time course of single neuron activity reveals rich temporal structures in the firing patterns in response to tastants. Intraoral delivery of tastants leads to modulations in firing rates that can last for longer than 2.5 seconds. In this context, chemosensory coding has a slow onset (between 250 and 500 ms after taste delivery) and can last for longer than a second (Katz et al., 2001). The dynamic nature of gustatory coding has been demonstrated by also looking at how ensemble activity changes over time (Jones et al., 2007; Mazzucato et al., 2015). Populations of neurons in the GC undergo periods of time (defined as “states”) in which firing activity is coordinated (Jones et al., 2006; Jones et al., 2007; Mazzucato et al., 2015). States can last for hundreds of milliseconds and suddenly end and give way to new states, in which the patterns of coordinated activity change. States and changes of state can occur spontaneously or can follow gustatory stimulation (Mazzucato et al., 2015) (Mazzucato et al., 2015). Sequences of states appear to have specific characteristics during taste processing (Mazzucato et al., 2015; Mazzucato et al., 2016) and have been shown to encode the chemosensory identity of different tastants (Jones et al., 2006). Rich and complex temporal dynamics have also been observed in rodents actively licking a spout to get taste stimuli (Stapleton et al., 2007; Stapleton et al., 2006). As in the case of intraoral deliveries, GC neurons are broadly tuned and represent information pertaining to multiple taste qualities (Stapleton et al., 2006). Different from intraoral deliveries, however, encoding is faster and paced by licking

rhythmicity (Stapleton et al., 2007; Stapleton et al., 2006). This is likely related to the ability of licking, both its motor component as well as the associated tactile stimulation, in driving chemosensory processing (Gutierrez et al., 2010). This interaction will be further examined in the next paragraph.

The overall picture emerging from these studies in alert animals is that chemosensory coding in the GC is not just a matter of either activating labeled lines or recruiting static ensembles of neurons, but a matter of a time varying and dynamic processes.

Beyond time, space is another dimension that has been neglected in classical theories of taste coding that appears to be relevant (Accolla et al., 2007; Chen et al., 2011; Fletcher et al., 2017; Yoshimura et al., 2005). Initial electrophysiological studies suggested some differences in the spatial distribution of neurons (Yamamoto et al., 1985a), with different sub regions of the gustatory cortex being more sensitive to some taste qualities than others. Similar results were demonstrated in both rodent and human imaging experiments (Accolla et al., 2007; Accolla and Carleton, 2008; Chen et al., 2011; Fletcher et al., 2017; Schoenfeld et al., 2004). The exact organization of this spatial map is still debated. Some studies show a high degree of overlap between parts of the cortex with preferential responses to different tastants (Accolla et al., 2007; Accolla and Carleton, 2008; Fletcher et al., 2017), while other studies indicate little overlap (Chen et al., 2011). This discrepancy is likely due to a combination of factors including experimental conditions, different reporters of neural activity (intrinsic signals, OGB, GcAMP6), and levels of anesthesia. Regardless of the specific features of the spatial organization, electrophysiological experiments show that nearby neurons can have both similar and different taste tuning properties (Yokota et al., 2007; Yokota and Satoh, 2001). These results demonstrate that only some of the neurons in the GC are organized according to a spatial map. The functional significance of a spatial map for taste coding in alert animals still needs to be fully explored.

Few experiments have attempted to correlate differences in taste coding with positioning in different subdivisions of the GC (i.e., granular, dysgranular and agranular), different layers, and different neuron types (Kosar et al., 1986; Ogawa et al., 1992; Yokota et al., 2011). Evidence points to differences in tuning and responsiveness across divisions and layers, but more work is required to ultimately understand this issue.

Beyond coding of gustatory information—Evidence from electrophysiological and imaging studies in rodents and primates shows that the GC integrates information from a multitude of sensory, affective and cognitive sources (Veldhuizen et al., 2011; Vincis and Fontanini, 2016a; Vincis and Fontanini, 2016b; Yamamoto et al., 1981). GC neurons can respond to somatosensory (Yamamoto et al., 1981), olfactory (Maier, 2017; Samuelsen and Fontanini, 2017; Vincis and Fontanini, 2016a), visual (Vincis and Fontanini, 2016a), auditory (Samuelsen et al., 2012; Vincis and Fontanini, 2016a), and visceral stimuli (Hanamori et al., 1998). In addition to responding to these sensory sources, GC neurons can also process the affective value of taste (i.e., hedonic value) (Grossman et al., 2008; Piette et al., 2012; Yamamoto et al., 1985b; Yamamoto et al., 1985a), expectations (Gardner and Fontanini, 2014; Samuelsen et al., 2012; Vincis and Fontanini, 2016a) , and other cognitive states (Fontanini and Katz, 2005).

Responses to somatosensory stimuli can be seen as changes in firing rates for fluids of different temperatures and textures and changes in activity following tactile stimulation of the tongue, whisker and oral region in general (Cerf-Ducastel et al., 2001; Vincis and Fontanini, 2016a; Yamamoto et al., 1981). This type of activity has been observed in anesthetized as well as alert animals. In alert animals, somatosensory responses appear as fast and phasic changes of activity following the delivery of a fluid into the mouth (Katz et al., 2001). Strong somatosensory activity can also be seen in relation to licking (Gutierrez et al., 2010; Stapleton et al., 2006). Licking a spout results in strong rhythmic (6-12 Hz) activity in GC neurons. Whether this activity is entirely the result of somatosensory stimulation of the tongue following its contact with licking spout, or also features motor components, is not presently known.

Neurons in the gustatory cortex can also be activated by odorants (Maier, 2017; Samuelsen and Fontanini, 2017; Vincis and Fontanini, 2016a). Similar results have been observed with imaging work in humans; Cerf-Ducastel et al. has demonstrated odor stimuli delivered both orthonasally as well as retronasally elicit neural activity in the gustatory cortex (Cerf-Ducastel et al., 2001).

In addition to somatosensory stimuli and odors, the GC can also represent visual and auditory information (Vincis and Fontanini, 2016a). The ability to represent stimuli of different sensory modalities, particularly somatosensation and olfaction, is particularly relevant to the GC's function in processing flavor (Small, 2012; Verhagen, 2007). Indeed, the experience of food requires the ability to integrate mouthfeel, aromas, and taste. While initial proposals suggested that this integration would take place in the orbitofrontal cortex (Rolls and Baylis, 1994), novel evidence suggests that flavor is processed by a network of sensory and associative areas (Small, 2012; Verhagen, 2007). The evidence described above points at the GC as one of the neural hubs in the flavor-processing network.

Beyond their function in flavor, the existence of cross-modal responses for sensory modalities represents a substrate for building associations with taste and for endowing predictive stimuli with the ability to trigger anticipatory activity in the GC. Indeed, multiple lines of evidence show that the fraction of GC neurons responding to stimuli of various sensory modalities is increased by associative learning (Gardner and Fontanini, 2014; Saddoris and Holland, 2009; Samuelsen et al., 2012; Vincis and Fontanini, 2016a). Learning that cross-modal stimuli can predict gustatory stimulation leads to the development of anticipatory responses. Initially, it was shown that these responses mediate the general expectation of taste and enhance the coding of the expected stimuli (Samuelsen et al., 2012). In this regard, these responses are interpreted as the neural signature of attentional signals. More recently, however, it has been found that GC neurons can also encode specific expectations and differentially respond to cues that predict different gustatory outcomes (i.e., sucrose and quinine) (Gardner and Fontanini, 2014).

The GC can also encode the valence of taste, i.e., whether a tastant is palatable or aversive. Initial reports showed that some neurons can produce similar responses to pairs of stimuli that share hedonic value (i.e., sucrose and NaCl or quinine and citric acid) and different responses to pairs of stimuli with opposing palatability (Katz et al., 2002; Yamamoto et al.,

1985a) (Katz et al., 2002; Yamamoto et al., 1985b). GC activity covaries with the palatability of a gustatory stimulus. Pairing a specific tastant with gastric malaise, a learning paradigm called conditioned taste aversion (CTA), changes GC responses to that stimulus (Grossman et al., 2008). Imaging studies have shown that pairing sucrose with malaise changes the spatial representation of sucrose, making it more similar to that of quinine (Accolla and Carleton, 2008). Analysis of the temporal structure of firing activity revealed that hedonic valued is encoded in a specific temporal epoch following taste delivery (Grossman et al., 2008; Moran and Katz, 2014).

Limbic circuits involved in taste processing—Analysis of the organization of the gustatory system reveals a great deal of convergence and divergence. Each region along the ascending gustatory pathway (i.e., NTS, PBN, VPMpc and GC) receives converging inputs from multiple sources. At the same time, each station, besides feeding into the next link in the gustatory pathway, projects to multiple sensory, limbic, and associative areas. In this paragraph we briefly review the main areas whose function is not primarily gustatory, but that contribute significantly to taste processing.

Amygdala—Two nuclei of the amygdala are particularly interconnected with the gustatory system: the basolateral nucleus (BLA) and the central nucleus (CeA). The BLA receives gustatory inputs from the VPMpc (Turner and Herkenham, 1991) and the GC (Allen et al., 1991; McDonald, 1998). As for the CeA, its main gustatory inputs come from the brainstem (Fulwiler and Saper, 1984; Halsell, 1998) and GC (Allen et al., 1991; McDonald, 1998). The CeA may also receive taste-related information from the BLA (McDonald, 1998).

Neurons in both the BLA and CeA can encode the physiochemical properties of taste(Fontanini et al., 2009; Nishijo et al., 1998; Sadacca et al., 2012; Scott et al., 1993). However, the main taste-related function attributed to the amygdala pertains to the coding of the reward value of taste (Grossman et al., 2008; Piette et al., 2012). The BLA contains at least two subpopulations of taste-processing neurons: one group has phasic and short-lasting responses to gustatory stimulation, while the second features long-lasting responses (Fontanini et al., 2009). The first group is involved in coding the reward value of taste and possibly prediction errors. Indeed, when a cue is paired to the availability of a taste, phasic responses to taste disappear and are transferred to the cue. On the other hand, long-lasting responses resemble similar taste-evoked neural dynamics in GC and encode the hedonic value of taste. With regard to the CeA, studies using increasing concentrations of NaCl unveiled the role of CeA in processing taste intensity and hedonic value (Sadacca et al., 2012). The CeA, similarly to the BLA, encodes palatable and aversive stimuli with different groups of neurons, which appear tuned to either one or the other property. Regardless of the specific function of individual neurons in amygdala, it is important to mention that a large group of those neurons is broadly tuned and can respond to multiple tastants as well as multiple stimuli (e.g., taste and orosensory information or taste and auditory/visual information) (Nishijo et al., 1998).

What is role of the amygdala in taste processing? The amygdala exerts its function through outputs to the GC (Haley et al., 2016) and to the brainstem (Li et al., 2005). The function of these outputs is best studied by the BLA to GC connection. Studies have demonstrated that

this connection is important for coding hedonic value in the GC (Piette et al., 2012). This function can be seen both in naive animals as well as animals that have learned a conditioned taste aversion (Grossman et al., 2008). In addition, BLA inputs play a fundamental role in the formation of anticipatory responses in the GC (Samuelsen et al., 2012). Inactivating BLA greatly reduces GC responses to auditory cues predicting taste. This role can be related to (the) BLA's function in associative learning as well as its ability to relay information about multiple sensory modalities.

Mediodorsal Thalamus—The mediodorsal thalamus (MD) has typically been studied as part of the limbic system (Wolff et al., 2015) and, in the case of the chemical senses, as a thalamic nucleus relevant for relaying olfactory information to the orbitofrontal cortex (Courtiol and Wilson, 2015). However, the connectivity of the MD supports its potential role in modulating activity in the gustatory system. The MD receives inputs from the olfactory system (Courtiol and Wilson, 2015), basal ganglia, PBN, frontal and insular cortices, amygdala and a series of other subcortical structures (Allen et al., 1991; Delevich et al., 2015; Groenewegen, 1988; Krout et al., 2001). The MD may receive gustatory-related information from the GC, PBN, or reward-related areas. The main gustatory target for the outputs of the MD is the GC (Allen et al., 1991). Projections from the MD to frontal cortices (Delevich et al., 2015; Giguere and Goldman-Rakic, 1988; Groenewegen, 1988; Ray and Price, 1993) can also lead to modulation of gustatory regions.

The activity recorded in the MD reflects its role in processing olfactory stimuli and associative learning (Courtiol and Wilson, 2016; Kawagoe et al., 2007). In this regard, the MD may be responsible for relaying olfactory information to GC as well as cooperating with the amygdala in conveying reward related signals. These signals may involve responses to anticipatory cues and coding of hedonic value.

Frontal cortices—The orbitofrontal cortex (OFC) as well as the anterior cingulate cortex (ACC) can be viewed as higher order gustatory cortices (Rolls, 2016). The orbitofrontal cortex receives afferents carrying gustatory information from GC, amygdala, and MD (Baylis et al., 1995). MD inputs are also the main source of olfactory information for the OFC (Courtiol and Wilson, 2015). The anterior cingulate cortex is connected to the GC, MD, and LH (Gabbott et al., 2003). For both OFC and ACC, the connections with GC are reciprocal.

The OFC and ACC have been extensively studied for their role in decision-making and reward-based behaviors (Laubach, 2011; Stalnaker et al., 2015). In addition to processing rewards and expectations, these areas also represent the sensory identity of rewarding and aversive stimuli. In monkeys and rodents, neurons in the OFC and ACC can differentiate among different tastants (Gutierrez et al., 2006; Gutierrez et al., 2010; Jezzini et al., 2013; Rolls, 2016). For instance, in the rodents' ACC neurons can encode gustatory stimuli of the four different qualities. Interestingly, ACC neurons appear to respond more vigorously to aversive stimuli compared to palatable tastants (Jezzini et al., 2013).

In these areas, coding of sensory information does not follow the labeled line logic. Indeed, neurons are broadly tuned to different taste qualities and can also respond to other sensory

modalities (Rolls, 2016). For instance, somatosensory stimuli – i.e., touch, texture of food and temperature – change firing rates in OFC neurons of primates. A large fraction of neurons encoding somatosensory information is also responsible for processing taste. The intimate relationship between somatosensation and taste can be observed in recordings from rats licking a spout (Gutierrez et al., 2006; Gutierrez et al., 2010). In these experimental conditions, OFC neurons modulate their firing rates before the initiation of a licking bout, during a bout, and after the termination. A group of neurons shows that rhythmic firing is tightly correlated with licking. Licking-related activity increases with learning of a gustatory go/no-go paradigm (Gutierrez et al., 2010). In this task, one tastant predicts reward and another tastant anticipates an aversive stimulus; rats learn to continue to lick for the reward-predicting tastant and refrain from licking for the other gustatory cue. Increase of lick-related activity was not independent of taste coding; in fact, increased licking improved a neuron's ability to discriminate gustatory cues. Licking modulated neurons have also been demonstrated in the ACC (Horst and Laubach, 2013). This activity is not simply reflective of somatosensory stimulation concurrent with licking but is also instructive of licking. Indeed, inactivation of the OFC and ACC disrupts normal licking in rats (Gutierrez et al., 2006; Parent et al., 2015).

The importance of the OFC in chemosensation is further emphasized by its role in flavor perception (Rolls, 2016). Neurons in the OFC can concurrently integrate gustatory, somatosensory, and olfactory information. Early theories suggested that the OFC could be the area where the perception of flavor is formed (Rolls and Baylis, 1994). This hypothesis was largely based on the lack of neurons responding to taste and olfaction in the GC of monkeys and their presence in OFC. However, recent work in humans and rodents reporting gustatory and olfactory responses in piriform cortex and GC, respectively, suggest that flavor processing is coordinated and distributed across a network of multiple areas (Maier et al., 2015; Small et al., 2004; Veldhuizen et al., 2011).

In summary, both the OFC and ACC play a fundamental role in perception of food. They represent multiple sensory stimuli, process rewards and are involved in associative learning. As such, they are well poised to link multiple stimuli to taste and rewards and form multisensory representations of food objects.

Lateral Hypothalamus—The lateral hypothalamus (LH), a zone of the hypothalamus that contains multiple subnuclei, plays a central role in controlling energy balance and regulating feeding behaviors (Stuber and Wise, 2016). It receives inputs from multiple sensory, cortical, limbic and interoceptive regions (Castro et al., 2015; Norgren, 1970; Scott and Leonard, 1971; Scott and Pfaffmann, 1967). With regard to taste and chemosensation, the LH receives projections from the the PBN, GC, olfactory cortex, and other olfactory areas (Berthoud and Münzberg, 2011; Niu et al., 2010; Tokita et al., 2010). Afferents to the LH also come from frontal cortices and from the amygdala (Berthoud and Münzberg, 2011; Niu et al., 2010; Norgren, 1976; Tokita et al., 2010). LH connections with the gustatory system are reciprocal, indeed different groups of neurons in the LH send orexinergic projections to GC and GABAergic projections to the PBN (Wu and Palmiter, 2011).

Activity in the LH is modulated by multiple events related to feeding: hunger and satiety change the firing rates of neurons in the LH (Burton and Jones, 1976; Sternson et al., 2013).

Pioneering work has demonstrated that neurons in the LH respond to palatable and aversive stimuli (Nakamura et al., 1989; Norgren, 1970; Schwartzbaum, 1983; Yamamoto et al., 1989) and to cues that predict them (Mora et al., 1976; Nakamura and Ono, 1986). Neurons excited by rewards are located in the caudal portion of the LH, while neurons in the rostral portion appear to be biased toward aversive stimuli (Schwartzbaum, 1988). Responses to cues are associative and are generally coherent in sign with responses to rewards (Schwartzbaum, 1988). A neuron that is excited by sucrose is also likely to be excited by the cue predicting sucrose as opposed to the cue predicting quinine. Careful analysis of the time course of firing activity revealed that after an initial (i.e. the first 250 ms) nonspecific response to taste delivery, LH neurons begin to encode palatability (Li et al., 2013). Two groups of neurons were described: neurons with phasic responses, preferentially activated by palatable tastants, and neurons with more prolonged responses, more strongly modulated by aversive tastants. The function of the LH in feeding and ingestive behaviors has been studied extensively and the subject is beyond the scope of this chapter. With regard to the LH's role in modulating the central processing of taste, it is likely that the LH sends information related to reward and anticipatory cues to the GC and taste brainstem. However, unlike the other limbic areas projecting to taste regions, the LH may be more involved in regulating processing of hedonic value and expectations depending on the energy requirements of the animal. Studies manipulating LH circuits while recording neural activity in taste regions of alert animals under different levels of hunger and satiety will be necessary to fully understand the role of the LH in taste processing. Classic studies that have found that electrical stimulation of LH alters taste tuning in the PBN and NTS of anesthetized rodents further support the importance of this area in modulating taste.

Conclusions

The act of savoring food and beverages is more than just detecting and analyzing chemicals dissolved into saliva. It involves integrating multiple sensory modalities and interpreting the resulting percept against the background of the psychological state of the subject. Attention, emotions, expectations, and memories can all shape our tasting experience. The relationship between taste and psychological state is mutual, as gustatory information can trigger emotions and motivate decisions. A similar reciprocal relationship exists between taste and homeostatic signals. Hunger, satiety, and visceral signals can affect, and can be affected by, savoring food and beverages. This level of perceptual complexity and psychophysiological integration arises from the interweaving between gustatory, sensory, visceral, and limbic pathways. In this chapter, we reviewed the anatomical basis for this relationship and presented evidence showing how neural responses throughout the gustatory axis reflect this high degree of integration.

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