



A gustocentric perspective to understanding primary sensory cortices

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Most of the general principles used to explain sensory cortical function have been inferred from experiments performed on neocortical, primary sensory areas. Attempts to apply a neocortical view to the study of the gustatory cortex (GC) have provided only a limited understanding of this area. Failures to conform GC to classical neocortical principles have been implicitly interpreted as a demonstration of GC's uniqueness. Here we propose to take the opposite perspective, dismissing GC's uniqueness and using principles extracted from its study as a lens for looking at neocortical sensory function. In this review, we describe three significant findings related to gustatory cortical function and advocate their relevance for understanding neocortical sensory areas.

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Introduction

Historically, sensory physiologists interested in understanding the computations performed by cortical circuits have focused their attention on neocortical areas [1–3]. The ability to precisely control the physical variables of a stimulus, as well as the ease of experimental access have contributed to rendering visual, somatosensory and auditory cortices primary models for investigating sensory processing. Electrophysiological studies from these areas started earlier and engaged larger communities than studies on chemosensory cortices. As a result, many of the fundamental principles of sensory, cortical physiology have been defined by results obtained in these cortices. The cortical organization in sensory maps [2,4,5], the presence of columns [1] and stereotyped circuits [6]

and the hierarchical organization of sensory streams (i.e. ‘lower’ order areas devoted to signal processing and ‘higher’ order areas involved in integration) [7] are just few among the many principles established in neocortical areas. Albeit never explicitly theorized, the knowledge accumulated on neocortical areas has influenced the way in which chemosensory areas have been approached. Multiple attempts have been made to adapt general principles of neocortical processing to either olfactory or gustatory cortices [8–10]. Failures to fit some of such principles to chemosensory areas have been interpreted as evidence for the uniqueness of these cortices. However, many of the results initially deemed as specific to chemosensory cortices have proven to generalize to neocortical areas. For instance, studies of oscillations and their links to sensory coding and cognition have been pioneered in the olfactory system [11–14]. Similarly, the importance of sensorimotor rhythms has been first established by looking at sniffing and respiration [15–18]. The recent rise in attention toward the olfactory cortex has brought into focus its relevance for understanding general computational principles. However, a similar process has not yet occurred for the gustatory cortex (GC). In the case of GC, the results have been either viewed as confirmatory of known neocortical principles [8,9], or, if unique and unprecedented, treated as an exotic peculiarity. In this review, we will discuss recent developments in understanding the function of the gustatory cortex, with the goal of showing how many of the findings on this area can help us gain an original perspective on neocortical sensory areas.

Coding of chemosensory information: the importance of time and dynamics

Neurons in the gustatory cortex are responsible for mediating the perception of different taste qualities: sweet, salty, sour, bitter and umami (just to name the best studied). GC neurons encode chemosensory information via time-varying changes in firing rates [19,20]. Initial analyses of the time course of firing rate activity revealed a great richness in single neuron responses to intraorally delivered tastants [20]. Most of the firing rate modulations revolved around three temporal epochs that encode different aspects of sensory information and unfold on the relatively long-lasting period of 2.5 s from taste delivery [20] [19,21*,22,23].

The temporal evolution of taste-evoked activity in GC has also been analyzed at the neural ensemble level. Use of the Hidden Markov Model (HMM) to extract specific

patterns of ensemble activity revealed that upon gustatory stimulation populations of neurons in GC go through different states of partially coordinated activity [24–27,28^{••}]. Each state can last from few to hundreds of milliseconds and suddenly end, leading the network to a rapid transition into another state. Multiple lines of evidence prove the importance of this regime of activity. Analysis of responses to multiple tastants revealed that each taste quality is associated with a specific sequence of states [26]. While the duration of each state and the times at which transitions occur vary from trial-to-trial, each particular sequence of states is specific to a certain taste. The sequences generated by a HMM analysis allowed for a very effective decoding of stimulus identity, showing that this conceptual and analytical framework successfully captures how GC encodes sensory information [25,26]. This approach to understanding how GC encodes gustatory information goes beyond the traditional single cell perspective, based on tuning curves computed from averaged data (Figure 1a), and suggests that sensory cortical processing entails the concerted activity of populations of neurons.

Understanding sensory cortical activity in terms of metastable states allowed for insights beyond sensory coding. The description of sudden transitions between states lead to the suggestion that a stochastic, jumping model of decision making could account for ingestive decisions more accurately than the traditional diffusion-to-bound model, particularly in conditions of noisy signals [29^{••},30] (Figure 1). Recent data confirmed this suggestion in both GC [31[•]] and lateral intraparietal area (LIP) [32]. Finally, recent work unveiled that metastability is not limited to evoked activity, but can also be observed during spontaneously ongoing activity [28^{••}] (Figure 1d). Populations of neurons in GC undergo sudden jumps between states even in the absence of any overt stimulation. Analysis of firing rates of single neurons revealed that metastability is not simply caused by neurons alternating between two regimes of firing rates. Rather, neurons can produce multiple (i.e. more than two) firing rates depending on the state (a feature called multistability). Spontaneous metastability and multistability result from network interactions, as demonstrated by theoretical analysis and simulations with a network model of spiking neurons [28^{••}]. Such a model features balanced excitation/inhibition and a clustered architecture and generates an attractor landscape that spontaneous activity explores (Figure 1e). The model built to explain spontaneous activity could reproduce fundamental features of stimulus-evoked activity [27,28^{••}], indicating that the elusive relationship between spontaneous and evoked cortical activity [33] is grounded in the dynamics internally generated by a network with clustered architecture [34].

GC represents the first primary cortical sensory area for which the study of metastable ensemble dynamics provides a unifying view that explains sensory coding, decision-making and the relationship between evoked and spontaneous

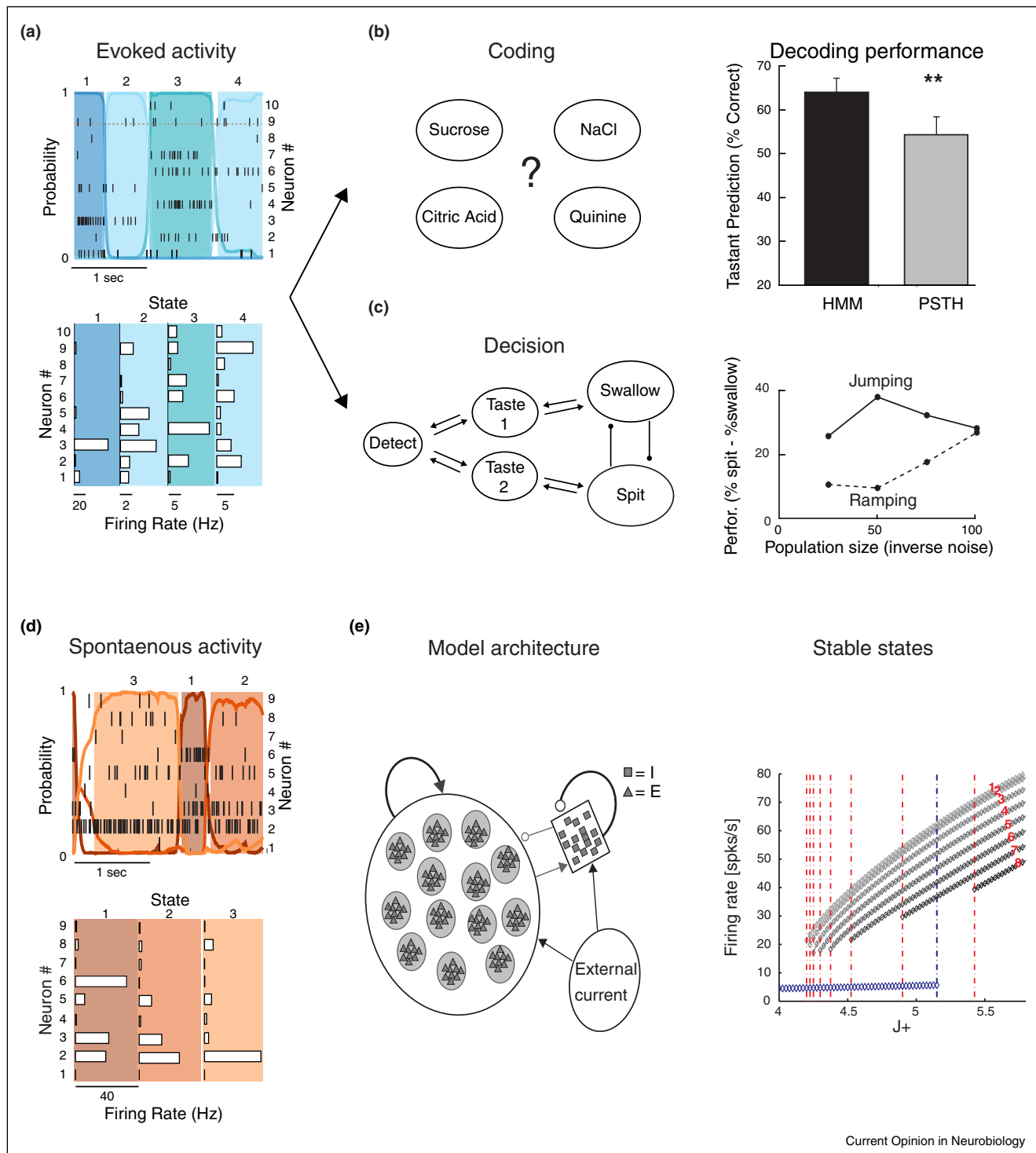
activity. We believe that this approach could also be productively adopted to study other primary sensory areas, beyond taste and olfaction [35].

Integration between sensory and reward processing

Taste coding is intimately linked with reward processing. Gustatory stimuli have hedonic valence, they are either palatable or aversive. The reward value of taste can be easily measured relying either on consummatory behaviors [36,37] or orofacial reactions [38,39]. The ability to assess objectively different dimensions of reward with specific behavioral tests has allowed researchers in the field to explore the involvement of GC in processing reward. Spatio-temporal patterns of neural activity in GC account for the palatability and/or aversiveness of taste. Imaging experiments in rodents revealed that the spatial representations of taste qualities are plastic and can track changes in the valence of gustatory stimuli [40]. Extensive analysis of single neuron responses showed that valence is encoded by the temporal structure of firing rate changes [21[•],23,41]. Specifically, it has been demonstrated that valence coding emerges with a slow latency (i.e. ~1 s) compared to stimulus onset. Population analyses with HMM confirmed this observation and provided further evidence indicating that, at a single trial level, valence coding emerges as a sudden and rapid change in the state of ensemble activity [31[•]]. Recent ensemble recordings in rat GC showed that gapes (i.e. orofacial reactions of aversion) were reliably preceded by a state change, suggesting a causal role of GC in evaluating the palatability of gustatory stimuli. Results from optogenetic studies confirm GC's involvement in mediating appetitive and aversive responses [42]. The sources of valence-related information in GC could be multiple, given its connectivity with limbic regions [43]. However, clear evidence points at the amygdala as one of the main synaptic inputs to GC [44,45] and a fundamental source of reward-related signals [41,46,47].

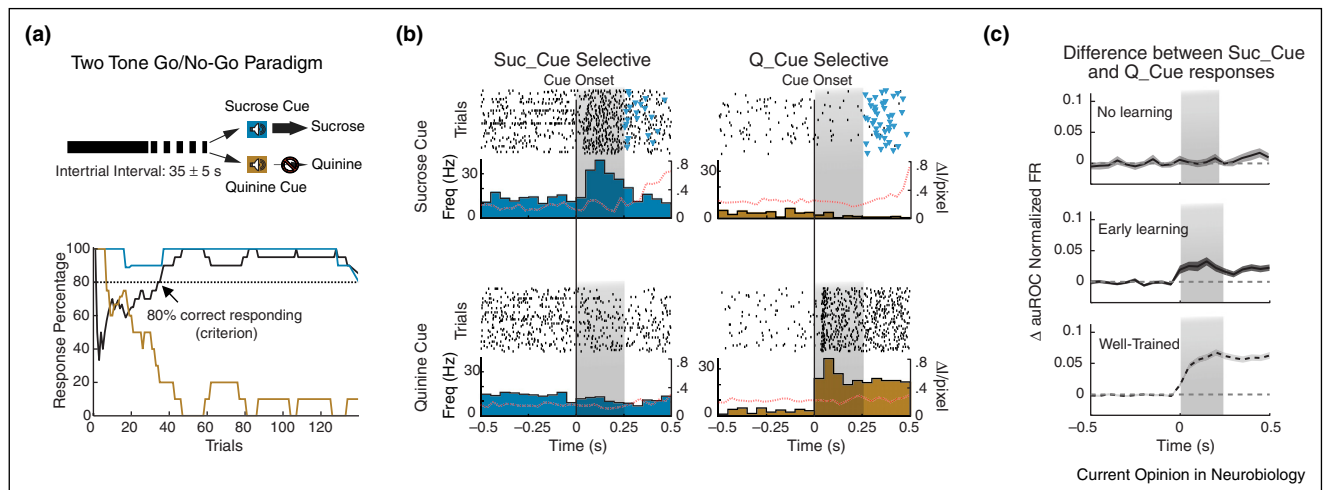
The intimate relationship between taste and reward implies that gustatory stimuli can also be used as outcomes. Using tastants as unconditioned stimuli in learning paradigms led to the discovery that GC plays a role in encoding reward-predictive stimuli [46,48,49^{••},50]. Training rats to associate a predictive cue with the availability of multiple tastants unveiled that GC neurons can be modulated by non-gustatory, anticipatory cues. The appearance of cue responses, a phenomenon observed so far only in limbic areas depends on learning, and can be observed with both classical and instrumental conditioning paradigms [46,48,49^{••}]. In addition, neurons in GC can encode both the general expectation of taste, that is, the expectation that a general gustatory stimulus is going to be available regardless of its identity, and the specific expectation of tastants with opposite valence [49^{••}] (Figure 2). The obvious question, at this point, is whether this cue-related

Figure 1



Metastable dynamics in the gustatory cortex of awake animals. **(a)** Representative ensemble showing taste-evoked metastable dynamics. Top: population raster with overlaid the HMM fit; each color represents a different state. Bottom: histograms showing firing rate vectors for each HMM state. **(b)** Metastable dynamics and taste quality coding. Left: schematic showing the four different tastants delivered. Right: histogram showing that an HMM-based classification can outperform a PSTH-based classification. **(c)** Metastable dynamics and decision-making. Left: schematic showing the architecture of the decision-making network used to test the role of reproduce metastable in ingestive decisions. Right: Comparison of the performance for two models of decision-making: deterministic integration ('ramping') and stochastic ('jumping'). The plot shows how performance depends on network size and internal noise. For a complete analysis of the differences between the two models of decision-making see Miller and Katz [30]. **(d)** Representative example of metastable dynamics during spontaneous activity. Top: population raster with overlaid the

Figure 2



Cross-modal cue responses in the gustatory cortex can encode specific expectations of rewarding or aversive tastants. **(a)** Go/no go paradigm. Top: schematic of the behavioral paradigm; one auditory cue predicts the availability of sucrose; the other cue predicts the availability of quinine. Rats press a lever following the sucrose predicting cue (Suc_Cue) and self-deliver sucrose directly into their mouth. On the contrary, rats refrain from pressing following the quinine-predicting cue (Q_Cue). Bottom: representative behavioral record a session. The plot shows the percentage of trials for Suc_Cue (cyan) and Q_Cue (gold) followed by a lever pressing. The solid black line indicates the average performance. **(b)** Selectivity of cue responses. Raster plots and peri-stimulus histograms (PSTHs) for two representative units, one selective for Suc_Cue (blue, left) and one selective for Q_Cue (right, gold). The dotted line overlaying the PSTHs shows the time course of the magnitude of mouth movements. Time 0 represents the onset of the auditory cue. Triangles markers represent lever-presses. The gray shading indicates the temporal window in which only the cue was present, without any lever-press. **(c)** Emergence of cue selectivity with learning. The three plots depict the difference in normalized firing between responses to Suc_Cue and Q_Cue averaged across neurons. A flat line indicates no difference between cue responses (hence no cue selectivity). Each plot features data from animals at different stage of learning. Top: rats not showing any sign of learning in the first few sessions; middle: rats showing learning in the first few sessions; bottom: rats extensively trained. Notice how the difference between cue responses (i.e. the selectivity) increases with learning. Time 0 and gray shadow as in panel b. Dotted horizontal line represents zero difference. Panels (a)–(c) modified from Gardner and Fontanini [49**].

activity plays any role in guiding behavior, or is just a byproduct of GC's connectivity with limbic areas. Behavioral studies relying on pharmacological manipulations of the activity in GC suggested its involvement in guiding behavioral choices [51]. A recent study was specifically designed to investigate the role of cue-related activity in GC [52]. Mice were trained to associate the delivery of a food pellet at a food-port with a 10 s long anticipatory cue. Upon successful training, mice responded to the cue with a series of conditioned, food-port entries. Inactivation of GC selectively during the presentation of the cue significantly reduced the number of food-port entries, indicating that cue-related activity in GC affects behavior.

While one might argue that taste is unique among the senses for its intimate relationship with reward, this is

certainly not the case. Stimuli of all sensory modalities can have an affective dimension, either innately or upon experience. Alas, only a few studies have focused on such an important dimension of perception in primary sensory areas other than GC [53*,54–57].

Multisensoriality in a primary sensory cortex

Neurons in GC are not devoted exclusively to processing the physiochemical and affective dimensions of taste. Multiple studies demonstrate that GC can effectively process non-gustatory, cross-modal stimuli encountered either during the consumption of food or even before [19,46,49**,58–62].

Evidence for multisensory integration during consumption comes from experiments showing that single neurons in

(Figure 1 Legend Continued) HMM fit; each color represents a different state. Bottom: histograms showing firing rate vectors for each state. **(e)** Model and theory of spontaneous activity. Left: schematic of the clustered spiking network capable of reproducing spontaneous metastability and multistability. Right: Attractor landscape of the spiking network model. The plot shows the number of active clusters and relative firing rates of neurons inside clusters as a function of the strength of relative intracenter synaptic connections (J_+). Vertical dotted lines indicate values of intracenter connections at which new clusters are recruited. The numbers of activated clusters in each configuration are indicated in red (configurations with larger clusters have lower firing rates, due to the overall inhibition). Panel (a) and (b) modified from Jones *et al.* [26]; panel (c) modified from Miller and Katz [29**]; panel (e) modified from Mazzucato *et al.* [28**].

GC can encode tactile, thermal and olfactory information coming from the oral cavity [61,63]. The integration of these multimodal, intraoral signals relates to the ability of perceiving flavor [64–66], the unitary, multisensory percept associated with food consumption. A second form of multisensory processing, fundamental for forming expectations, can occur in GC before the consumption of food and triggered by extraoral stimuli [46,49**]. The sight of food, for instance, successfully activates GC in human subjects [67]. In alert rats, GC neurons can respond to sounds, or odors, predicting either the general availability of taste or specific gustatory stimuli [46,49**] (Figure 2). Single unit recordings and immediate early gene analysis demonstrated that cross-modal responses are present before learning and increase in prevalence and specificity after stimulus-taste associations [46,49**,50].

While one might argue that the multimodality of GC is a direct consequence of the intrinsic relationship of tastants with tactile and odor stimuli, or a consequence of taste being always preceded by other sensory stimuli, this is not the case. In the real world, each unimodal sensory stimulus is perceived against the background of other stimuli. Perception is inherently associated with multisensory integration. While few studies have indeed investigated cross-modal responses in primary sensory areas [56–68], we believe not enough attention has been devoted to this fundamental issue.

Conclusion

In this brief overview, we discussed three lines of investigation on the function of GC. These approaches have not been directly influenced by existing theories of neocortical sensory function. Rather, these were efforts directed at understanding GC's relationship to gustatory perception and taste-related behaviors. These research directions have contributed to: Firstly, demonstrate that a single computational framework can link sensory coding, sensory-based decisions and spontaneous activity; secondly, unveil the intimate links between perception and reward; and finally, define sensory processing in primary cortices as an inherently multisensory process. Altogether, this research has shown that the primary gustatory cortex is not simply an analyzer of physiochemical information, but rather an area that integrates perception, emotion and actions. Of course, one could dismiss all the results from GC as peculiarities of a 'unique' cortex. After all, one might argue, GC is part of the insula (an area known to be integrative), has a unique cytoarchitecture and deals with atypical stimuli. Here we contend that the opposite attitude may be more productive and could lead to original insights on the function of neocortical sensory areas. Time might have come to stop imposing a neocortical view on all the sensory cortices and begin to be inspired by the chemical senses.

Conflict of interest statement

Nothing declared.

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