Coding and Transformations in the Olfactory System

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Erratum

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Abstract

How is sensory information represented in the brain? A long-standing debate in neural coding is whether and how timing of spikes conveys information to downstream neurons. Although we know that neurons in the olfactory bulb (OB) exhibit rich temporal dynamics, the functional relevance of temporal coding remains hotly debated. Recent recording experiments in awake behaving animals have elucidated highly organized temporal structures of activity in the OB. In addition, the analysis of neural circuits in the piriform cortex (PC) demonstrated the importance of not only OB afferent inputs but also intrinsic PC neural circuits in shaping odor responses. Furthermore, new experiments involving stimulation of the OB with specific temporal patterns allowed for testing the relevance of temporal codes. Together, these studies suggest that the relative timing of neuronal activity in the OB conveys odor information and that neural circuits in the PC possess various mechanisms to decode temporal patterns of OB input.

Contents

INTRODUCTION

Cracking the Code

Neurons transmit information using sequences of discrete events: action potentials (spikes). A central question in neuroscience is how trains of action potentials represent specific information. That is, what is a neural code in the brain? Understanding a neural code requires tackling four issues. First, to identify potential neural codes for sensory systems, one must observe which aspects of stimuli cause discernible changes in neural activity (e.g., by determining tuning curves). One critical question is which aspects of the neural activity (e.g., firing rates, spike timing) carry reliable information about the stimulus (representations)? However, understanding the first issue is not sufficient to establish a neural code (or representation) (deCharms & Zador 2000). Second, one needs to understand the mechanisms by which relevant information is transformed into such activity patterns (encoding). Third, for a neural representation (or a neural code) to be functional, it must be read out by downstream neurons (decoding). Ultimately, a given neural code should be read out by animals to guide behavior. Finally, one should ask why a given code is used by the system. That is, what are the computational advantages of a particular coding method (computational merits)? Different brain regions may benefit from different coding methods depending on their evolutionary, structural, and functional constraints.

To understand the fourth issue discussed above, we need to understand the goals of the system as well as the complexity and challenges that the system faces in the real world. For instance, imagine a rat in the wild trying to scavenge for food. The rat must detect and recognize a particular scent by comparing incoming sensory input with the memorized scents of several previously learned food odors (odor memory and recognition). To locate the food source successfully, the rat must also recognize the food odor across a wide concentration range (concentration-invariant recognition) and isolate (or segment) the target odor from complex background odors. These computations must be performed in the presence of various other perturbations (e.g., sensory and neural noise). In addition, the rat might be required to make a very fast decision. Which coding method may be the most advantageous, considering the constraints of the olfactory system and the complexity of natural odor scenes? Furthermore, from an evolutionary perspective, Barlow (1961) proposed that the goal of sensory systems is to encode the maximum amount of relevant information with a small number of spikes (the efficient coding hypothesis). Ultimately, one should be able to explain why a given neural code is suited to fulfill all these requirements over other codes.

Recent experiments as well as computational approaches have begun to address these questions in the olfactory system. Here we review these recent studies and synthesize emerging ideas, focusing mainly on odor coding in the mammalian olfactory system. Note, however, that studies using other animals including insects and fish have contributed significantly to developing the ideas discussed below. Although we discuss some of these studies, readers are encouraged to refer to previous reviews (Friedrich 2013, Laurent 2002, Wilson 2013) for further information.

Olfaction as a Pattern Recognition Problem Across ~1,000 Input Channels

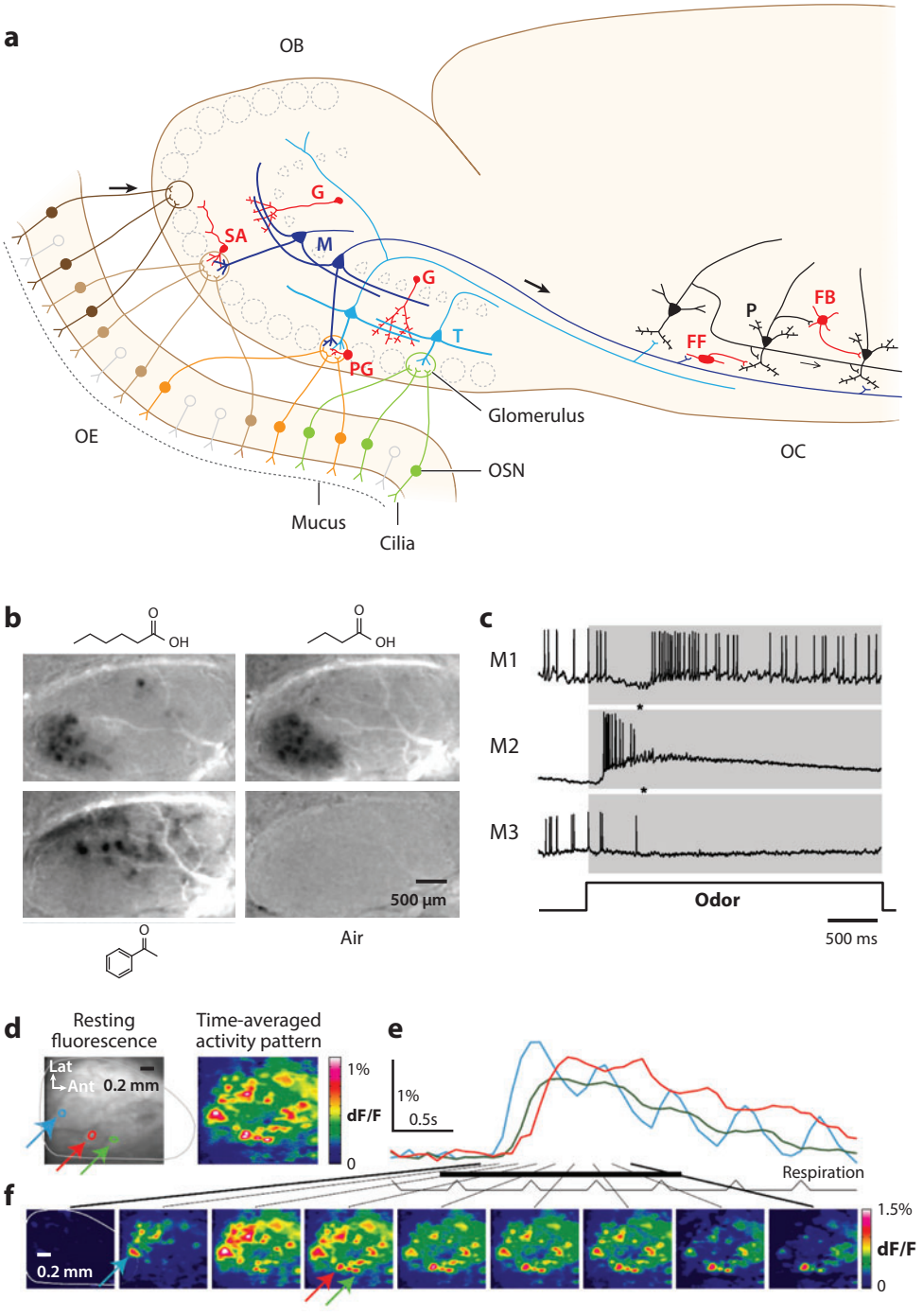
Identification of odorant receptors and elucidation of the remarkable wiring patterns of early olfactory circuits have laid out the basic logic of odor information processing in the brain (Axel 1995, Mori et al. 1999) (**Figure 1*a***). Almost all volatile chemicals, even newly synthesized molecules, can be perceived and discriminated from other molecules. To handle such diverse molecular inputs, the olfactory system has developed a unique strategy. It uses a large array of odorant receptors (ORs) (Buck & Axel 1991) whose tuning specificity varies: Some ORs are broadly tuned, whereas others are strongly activated by only a very specific set of molecules (Hallem & Carlson 2006, Nara et al. 2011, Saito et al. 2009). The number of functional ORs varies across species and has been estimated to be ~1,000 in rodents, ~300 in humans, and ~60–350 in insects (Go & Niimura 2008, Olender et al. 2013, Touhara & Vosshall 2009).

Each olfactory sensory neuron (OSN) expresses only one type of OR, and axons of OSNs expressing a given type of OR converge onto typically two small (~50–100 μm) spherical structures in the OB called glomeruli, where axons relay information about the activation level of each receptor type to neurons in the OB. As such, each odor activates an odor-specific pattern of glomeruli (Friedrich & Korsching 1997, Meister & Bonhoeffer 2001, Rubin & Katz 1999, Uchida et al. 2000) (**Figure 1*b***). Thus, odor recognition or discrimination can be seen as the process of deciphering activity patterns across the two-dimensional sheet of glomeruli in the OB. Odor recognition is a pattern-recognition problem defined by ~1,000 input channels (odorant receptors or glomeruli in rodents).

Whereas our understanding of peripheral olfactory processing has shown great progress, our understanding of how the brain deciphers patterns of glomerular activation remains elusive and a matter of hot debate. One salient issue has been which features of neural activity (firing rates, spike timing, etc.) are important in conveying odor information. It has long been known that odors elicit distinct temporal spike patterns that are not directly related to the dynamics of the olfactory stimulus. These observations have led to the idea that the exact timing of spikes can be a

Figure 1

(*a*) Olfactory system. Abbreviations: OE, olfactory epithelium; OSN, olfactory sensory neuron; OB, olfactory bulb; OC, olfactory cortex; PG, periglomerular cell; SA, short axon cell; M, mitral cell; T, tufted cell; G, granule cell; P, pyramidal cell; FF, feedforward inhibitory interneuron; FB, feedback inhibitory interneuron (after Shepherd 2001). (*b*) Odor-evoked activity in the rat OB measured using intrinsic signal imaging (Uchida et al. 2000). (*c*) Odor-evoked spiking activity of mitral cells in zebrafish OB (Friedrich & Laurent 2001). (*d–f*) The time course of glomerular activation in the rat OB measured using voltage-sensitive dyes (Spors et al. 2006). The changes in the fluorescent signals in three glomeruli marked in circles in panel *d* are shown in panel *e*.



neural code for nontemporal features of stimuli such as odor identity or concentration. However, the functional importance of various temporal coding mechanisms remains to be established.

ODOR REPRESENTATIONS IN THE OLFACTORY BULB

Theories of Temporal Coding in Olfaction

Odor stimulation evokes odor- and cell-specific temporal patterns of activity in the OB. These include modulation of firing rates across various timescales and synchronous oscillations at different frequencies (Bathellier et al. 2010, Wilson & Mainen 2006) (**Figure 1*c–e***). Two models have sought to describe the role of temporal coding in olfaction.

Hopfield model: latency coding. Hopfield (1995) proposed a theoretical model for pattern recognition. The model assumes common oscillatory inputs to a population of neurons. When these neurons receive different levels of constant input, those receiving stronger input fire early in each oscillation cycle compared with those receiving weaker input (**Figure 2*a–c***). Using this simple principle, the model converts input strength into spike timing (latency). This model has been particularly attractive to the field of olfaction for several reasons. First, as mentioned above, the olfactory system can be seen as a pattern-recognition mechanism using ~1,000 input channels. The Hopfield model provides a mechanism by which the strengths of 1,000 glomerular inputs can be transformed into a pattern of spike times across postsynaptic neurons [mitral (M) and tufted (T) cells]. Second, oscillations are prominent in the olfactory system. Third, this model, in principle, allows rapid encoding of complex input patterns in just one oscillation cycle using one spike per neuron. Fourth, when odor concentration changes, the timing of each neuron's spiking shifts together and the relative timing across neurons remains unchanged, providing a mechanism for concentration-invariant odor recognition.

Brody & Hopfield (2003) extended the Hopfield model, discussed above, to include a mechanism that reads out a specific pattern of inputs (Brody & Hopfield 2003). The model assumed varying strengths of biases that make each M/T cell easy or difficult to fire (**Figure 2*d***). The spike timing of each M/T cell is determined by the sum of OSN inputs and a bias term. When a specific set of M/T cells receives the same amount of the summed input (OSN and bias inputs), these M/T cells fire synchronously, and neurons receiving inputs from these M/T cells are effectively activated (**Figure 2*e***). This model also achieved concentration-invariant recognition as well as odor segmentation.

Experimental results have provided some support for the Hopfield model. In rodents, investigators have shown that the latency of glomerular activations shows stimulus-specific patterns (Spors et al. 2006, Spors & Grinvald 2002), and M/T cell spike timing with respect to respiration cycle at the theta frequency range (7–12 Hz) is advanced with increased odor concentrations (Cang & Isaacson 2003, Fukunaga et al. 2012, Margrie & Schaefer 2003). In larva, *Xenopus laevis*, which do not sniff, latency from stimulus onset across M/T cells (on the order of tens to hundreds of milliseconds) reliably conveyed stimulus information about odor identity and concentration (Junek et al. 2010). These studies suggest that spike latency with respect to slow oscillations (e.g., respiration cycle) or latency from odor onset on the order of hundreds of milliseconds can convey reliable odor information. However, in many of these cases, shorter spike latency is accompanied by increased spike counts. Furthermore, one study in locusts showed that spike timing with respect to fast oscillations (15–30 Hz, or beta frequency) does not appear to support coding of odor concentration (Stopfer et al. 2003). Which of these two (latency or spike counts) sends more reliable information, or is used by the system, remains to be examined.

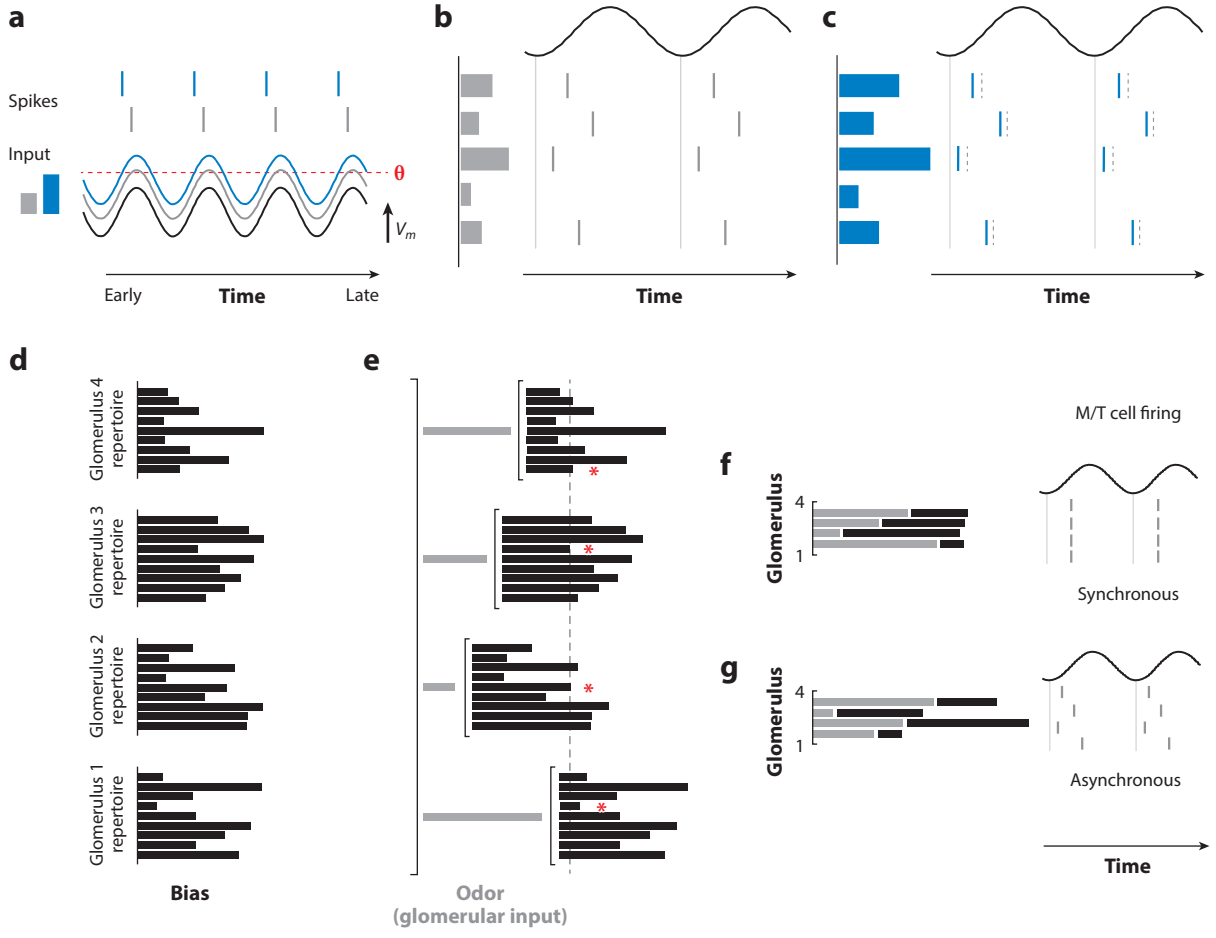


Figure 2

(*a–c*) Hopfield model (Hopfield 1995). A pattern of inputs (*gray bars*) is transformed into the timing of spikes in an oscillation cycle (panel *b*). (*a*) The neuron membrane potential has an internal rhythm (*black*). Two stimuli (*gray and blue*) increase membrane potential. The neuron spikes when the membrane potential crosses a certain threshold (θ). Higher-intensity stimulation shifts the timing of spikes toward early time points while the overall pattern is preserved (panel *c*). (*d–g*) Brody & Hopfield model (Brody & Hopfield 2003). Each black bar represents bias received by each mitral (M)/tufted (T) cell (panel *d*). Upon odor stimulation, each M/T cell receives the sum of odor-evoked inputs (panel *e*, *gray*) and bias input (panel *e*, *black*). When a set of M/T cells (*red asterisk* in panel *e*) receives the same amount of total inputs, these M/T cells fire synchronously (panel *f*). When these M/T cells are stimulated with a different odor, the total inputs do not match, and the neurons thus fire asynchronously (panel *g*).

Laurent model: slow-evolving temporal coding, decorrelations. The Hopfield model provided one way to look at activity patterns across a population of neurons using spike latency. But temporal dynamics of neural responses in the olfactory system goes beyond the first spikes. Work by Laurent and colleagues in locusts has provided a different way to look at more complex temporal patterns (Laurent 2002, Laurent et al. 2001).

Principal neurons in insect antennal lobes (ALs) [called projection neurons (PNs)] (Laurent et al. 1996, Wehr & Laurent 1996) or M/T cells in the zebrafish OB (Friedrich & Laurent 2001) respond to odors with complex, odor- and cell-specific temporal patterns over hundreds of milliseconds or a few seconds. These responses consist of successive periods of up- and downmodulations

of firing rates. Populations of neurons exhibit synchronized oscillatory activity, but each neuron only transiently participates in this population activity. The identities of neurons that participate in the oscillatory ensemble change over time.

Does the temporally evolving ensemble provide any computational merit? The data in zebrafish OB demonstrate that ensemble activity patterns become gradually decorrelated: The patterns of odor-evoked activity across neurons initially reflect the similarity (or classes) of odors (thus odor representations for similar odors are correlated); however, over the time course of hundreds of milliseconds to seconds, these correlations are gradually reduced and the ensemble activity patterns become less similar (Brown et al. 2005, Friedrich & Laurent 2001, Mazor & Laurent 2005). In addition to examining the similarity (correlation) of the trial-averaged responses, the authors also quantified the reliability of the neural response at each time point by estimating how well an unbiased observer can classify neural responses on a trial-by-trial basis using a simple linear decoder (decoding analysis). Using this analysis, the rate of successfully classifying odors indeed improved over a similarly slow timescale. PNs in locusts also have similar slow temporal dynamics; however, classification success is highest 200–300 ms after odor onset (Stopfer et al. 2003). In contrast, *Drosophila* PNs have weak temporal dynamics and the ensemble activity patterns do not show decorrelations (Olsen et al. 2010). The significance of slow temporal decorrelation remains to be clarified in the future (Friedrich 2013).

Studying Odor Representations in Behaving Animals

Humans' sense of smell relies on inhalation of odor molecules into the nose. In awake animals, sniffing patterns change dramatically depending on behavioral contexts. During active exploration, rodents sniff at the theta frequency range (6–10 Hz). Behavioral experiments in rodents have shown that fine odor discrimination can be made with just one sniff or 250 ms (Abraham et al. 2004, Rinberg et al. 2006b, Uchida & Mainen 2003, Zariwala et al. 2013). How is odor information encoded in such a short time period? Do the temporal dynamics of neural responses evolve that quickly? Furthermore, investigators have suggested that during rapid sniffing, OB neurons lose their phase locking to respiration (Carey et al. 2009, Kay & Laurent 1999). With these constraints, can either latency coding or slow temporal coding work at the level of M/T cells in awake rodents? Recent studies have begun to address these questions (Cury & Uchida 2010, Shusterman et al. 2011). Studies in anesthetized animals using new techniques (e.g., optogenetics and in vivo whole-cell recording) have also provided insights into mechanisms of temporal dynamics of OB neurons. In the following sections, we review these studies.

Respiration Coupling of Spontaneous Activity in the Mammalian OB

In awake rodents, spontaneous firing of M/T cells is generally high (on average 10–25 spikes per second) compared with those under anesthesia (Rinberg et al. 2006a). A recent study in behaving rats compared spontaneous firing patterns across different respiration frequencies (Cury & Uchida 2010) (**Figure 3**). This study found that spontaneous firing of many M/T cells is locked to the respiration cycle. Each M/T cell fired maximally at a particular latency from inhalation onset, and the timing was conserved across various respiration frequencies. Latency to spike varied among M/T cells, such that they tiled the entire cycle of rapid respiration (sniffing) (**Figure 3**). In anesthetized mice, M/T cells that innervate the same glomeruli (sister M/T cells) tend to fire with similar latencies when compared with M/T cells that were connected to different glomeruli (Dhawale et al. 2010). Using whole-cell recording in anesthetized mice, a recent study found that T cells consistently fired earlier in the respiratory cycle relative to inhalation than did M cells

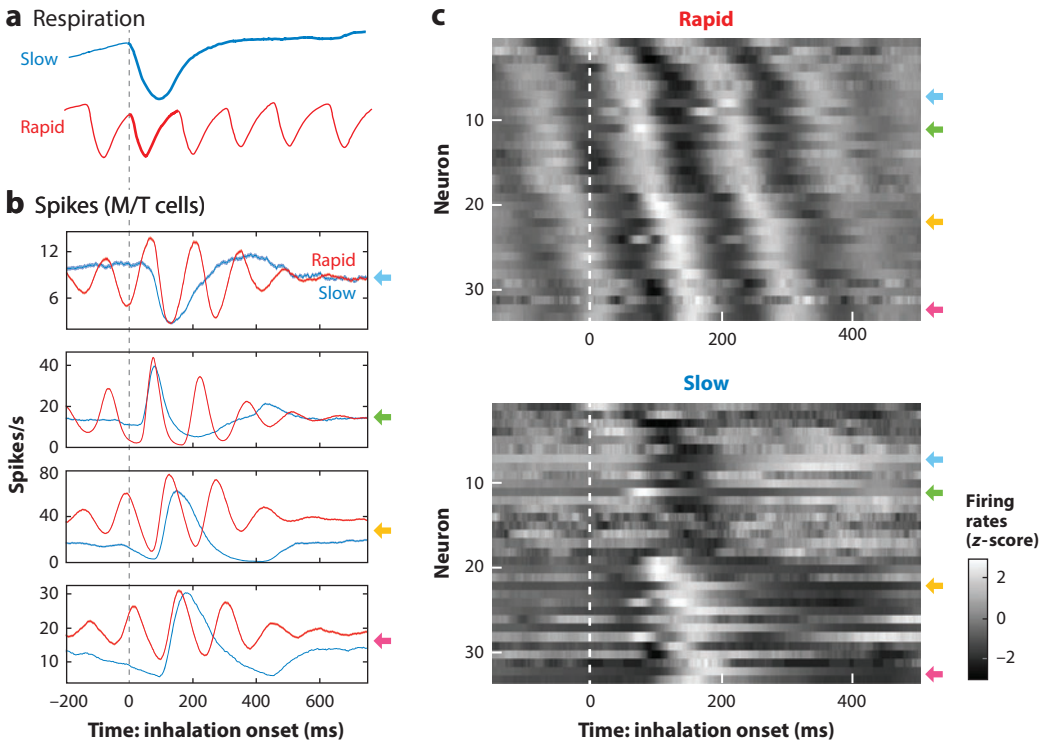


Figure 3

Spontaneous activity of mitral/tufted (M/T) cells (Cury & Uchida 2010). (*a*) Example respiration patterns during slow (*blue*) versus rapid (*red*) breathing; downward change, inhalation; upward change, exhalation. (*b*) Firing patterns of 4 M/T cells during slow (*blue*) and rapid (*red*) respiration. The traces are aligned by inhalation onset. (*c*) Firing patterns of 33 M/T cells. Firing rates are normalized using *z*-scores, calculated over rapid sniffing events, and plotted using the color scale at right. In both graphs, neurons are sorted from bottom to top by increasing latency to the peak firing rate observed in rapid sniffing peri-event time histograms (PETHs) (0–160 ms following inhalation onset). The four neurons in panel *b* are indicated by colored arrows.

(Fukunaga et al. 2012). Together, these studies revealed a highly organized temporal pattern of spontaneous firing of M/T cells at the population level, which can serve as a temporal frame of specific coding mechanisms. For instance, respiration-coupled sequential activation of M/T cells can provide a reference time frame for odor-evoked responses.

Odor-Evoked Responses in the Mammalian Olfactory Bulb

Odor-evoked responses have often been detected as a gross firing rate change over time. Studies found that fewer M/T cells changed their average firing rate in response to odors in awake animals compared with anesthetized animals (Davison & Katz 2007, Rinberg et al. 2006a), suggesting that odor responses are sparse in awake animals. However, neurons can also change their spike timing in addition to the overall frequency. Indeed, recent studies in awake animals show that many neurons change their spike timing in an odor-specific manner (Cury & Uchida 2010, Gschwend et al. 2012, Shusterman et al. 2011) (**Figure 4*b***). These responses consisted of transient changes in firing rate within a respiratory cycle, which is often obscured in analyses examining average firing rates. Sister M/T cells that fire at similar respiratory phases prior to odor stimulation become

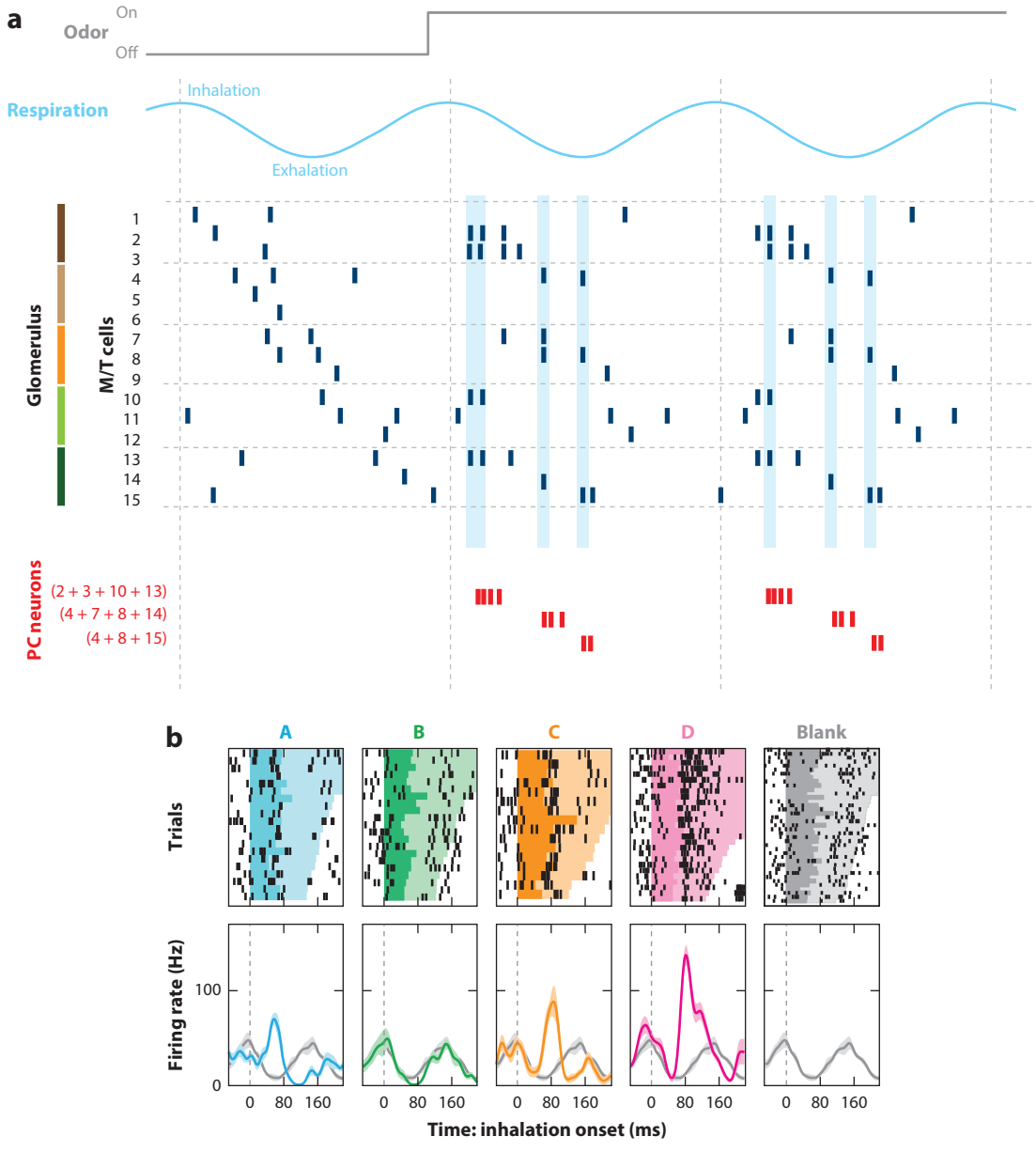


Figure 4

(*a*) A model of respiration-coupled, spike-timing-based odor coding. Modified from Wilson & Mainen (2006). The PC neurons act as coincidence detectors of specific M/T cell firing patterns. (*b*) Odor-evoked activity of an example mitral/tufted (M/T) cell in the OB to four odors and blank airstream [also overlaid on all odor responses (*gray*)] (Cury & Uchida 2010).

coupled to different respiratory phases with odor stimulation (Dhawale et al. 2010). Taking into account these temporal changes in M/T cell spikes, odor-evoked responses are not sparse in the OB of awake animals (15–60% of M/T cells responded to a given odor) (Cury & Uchida 2010, Gschwend et al. 2012, Shusterman et al. 2011).

Do fine temporal structures within a respiratory cycle convey odor information? A recent study addressed this question by comparing the ability to identify an odor from the neural response when taking into account subsniff temporal structures versus only the firing rate over entire sniff cycles (Cury & Uchida 2010). The authors found that odor-decoding performance improved significantly when subsniff temporal structures were considered. Furthermore, most of the information was conveyed within the first 100 ms after inhalation onset. These initial fine-scale temporal patterns were found to be well preserved between slow and rapid modes of odor sampling, whereas patterns based on the overall firing rates in the entire sniff cycle were poorly conserved (Cury & Uchida 2010). Decoding using the first spike latency from inhalation onset performed poorly compared with decoding using entire subsniff temporal patterns. This result is in part because high spontaneous firing rates prevent reliable detections of the onset of odor-evoked activity. In this study, activity from all recorded M/T cells was included for decoding. As discussed above, Fukunaga et al. (2012) suggests that the firing of M cells occurs later in the respiration cycles. A specific subset of OB neurons may still be able to encode reliable odor information by latency alone. Nevertheless, these studies demonstrate that subsniff temporal patterns, in particular initial portions of the dynamic response, can reliably convey odor information.

Odor Representations by Dynamic Neural Assemblies (Trajectories)

As discussed above, odors trigger evolving dynamics in an ensemble of neurons. Rather than looking at single neurons one by one, analyzing the behavior of the ensemble as a whole can provide useful insights. The pattern of time-varying activity of N neurons can be described as a trajectory in N-dimensional activity space. Using this multidimensional space, investigators can quantify the dynamics of neuron ensembles (e.g., velocity, acceleration). Furthermore, using appropriate dimension reduction methods (e.g., principal component analysis), investigators can visualize the dynamics of a neuron ensemble (Stopfer et al. 2003). With prolonged odor stimulation, an ensemble activity of PNs in locust AL changed immediately after odor onset and, after about 1 s, reached a steady attractor-like state (Mazor & Laurent 2005). When an odor stimulus was terminated, the ensemble activity moved quickly again and returned to its steady-state baseline activity. Remarkably, decoding analyses showed that discriminability of odors was highest at the time of maximum velocity rather than during an attractor-like, steady state (Mazor & Laurent 2005). A similar analysis applied to OSNs produced a contrasting result: The highest level of odor discriminability was achieved during the steady state, and odor termination caused much less movement in the ensemble trajectory than at odor onset (Fdez Galán et al. 2004). Thus, compared with OSNs, PNs emphasize more sharp changes in odor stimuli in odor stimulation. Similar observations were made in the rat OB during both rapid sniffing and slow breathing, although a steady state was not achieved during the timescale of a single inhalation period, and the speed at which ensemble patterns changed was much faster (in ~35 ms, ensemble patterns became substantially different) (Cury & Uchida 2010). These results suggest that the ensemble activity evolves not necessarily to gradually reach a more informative steady state but to establish that temporal dynamics itself (or its trajectory) is informative or can be a carrier of information.

Why would transient dynamics be more suitable than steady-state neural responses in representing information? First, computational analysis suggests that information can be coded by a change in the ensemble activity or by the time derivative of ensemble trajectories (Moazzezi &

Dayan 2008, 2010). Changes evoked by odor stimulation can be largely invariant to changes in the initial set point of a neuronal ensemble caused by background odors or a slow context-dependent change in baseline activities. Second, in locust, investigators showed that ensemble trajectories evoked by varying concentrations of the same odor change continuously and fall onto a specific manifold (or low-dimensional space) despite the fact that individual neurons often respond nonlinearly across changing concentrations (Stopfer et al. 2003). This emerging property of ensemble dynamics may provide a basis for concentration-invariant odor recognition. Furthermore, reaching a steady state might require a relatively long constant stimulus (Fdez Galán et al. 2004, Mazor & Laurent 2005). Such a slow process may not be adaptive given the various time pressures in natural environments.

ENCODING: HOW ARE TEMPORAL PATTERNS OF MITRAL/TUFTED CELLS GENERATED?

So far, our discussion has focused on which features of neural activity contain reliable stimulus information and are computationally attractive. We now turn to the neural mechanisms that generate these activities (encoding).

Temporal Dynamics During Spontaneous Activity

The spontaneous spiking of M/T cells (or PNs in AL) in response to clean, nonodorous air is driven primarily by inputs from OSNs. Closing the nostril in mammals or cutting antennae in insects greatly reduces spontaneous activity of OB (or AL) neurons (Joseph et al. 2012, Onoda & Mori 1980, Sobel & Tank 1993). OSNs can likely be activated by pressure or mechanical stimulation, and this type of activation mechanism shares the same signaling pathway as that used for odor-evoked activation (Grosmaitre et al. 2007). Knocking out the cyclic nucleotide–gated channel CNGA2 eliminated respiration-coupled spontaneous activity of M/T cells. However, it is unclear how ordered, yet diverse, respiratory-phase preferences of M/T cells are generated. Different phase preferences among nonsister M/T cells can be explained by different levels of activations among glomeruli as observed in various imaging experiments. M/T cells have different levels of hyperpolarization-activated current (I_h or "sag" potential) that makes M/T cells difficult to fire. These I_h currents are more similar among sister M/T cells than among nonsister pairs (Angelo et al. 2012). In addition, sister M/T cells are connected with gap junctions (Schoppa & Urban 2003). These mechanisms can explain the similar phase preferences in sister M/T cells and the diversity seen in nonsister cells. Further diversities in respiratory-phase preferences can be attributed to differences in intrinsic properties of M/T cells (Padmanabhan & Urban 2010) as well as neural circuits within the OB. For example, recent studies have shown that inhibitory inputs play a role in delaying M cell firing compared with T cells (Fukunaga et al. 2012), in shaping their odor tuning (Kikuta et al. 2013), or in making their responses more transient (Olsen et al. 2010).

Odor-Evoked Temporal Dynamics

Odors increase OSN activity and add more complex temporal dynamics on top of spontaneous activity. First, odor molecules pass through a rather complex environment (or filter) of mucosae, which contain various odor-binding proteins and enzymes that modify odor molecules. Odor molecules then bind to ORs with different affinities, resulting in various latencies and temporal dynamics of OSN firing and glomerular activations (Spors et al. 2006, Spors & Grinvald 2002). OB circuits that are engaged with increased OSN input also add more complex temporal dynamics.

For example, some evidence indicates that inhibition determines respiratory-phase preferences of M versus T cells (Fukunaga et al. 2012), and deep short axon cells provide feedforward inhibition onto granule cells that limit the time window of granule cell spikes (Boyd et al. 2012).

In the visual system, relatively simple models have been successfully used to describe the relationship between sensory inputs and spiking outputs (Meister & Berry 1999). One successful model consists of linear filtering of incoming inputs followed by a nonlinear spike-generating mechanism [linear-nonlinear (L-N) model]. Geffen et al. (2009) presented locust ALs with flickering odor stimuli. Although recorded neurons showed diverse response dynamics, a simple L-N model with just three parameters could predict odor-evoked responses. The linear filters obtained had diverse time-varying waveforms but could be described as a superposition of two filters. These two waveforms were thought to represent direct excitatory inputs (ON-filter) from OSNs and inhibitory inputs (OFF-filter) from inhibitory interneurons. The shape and the time course of the ON-filter can be determined in part by odorant-receptor interactions, whereas the OFF-filter reflects complex, indirect inputs from inhibitory interneurons. It remains to be seen how these filters change with different odor concentrations or with odor mixtures. In rodents, Khan et al. (2008) showed that M/T cell responses to odor mixtures could be predicted by simple linear combinations of filters extracted from responses to component odorants. These approaches are very useful in quantifying relative contributions of different factors that generate seemingly complex temporal patterns of M/T cell activities.

DECODING: HOW DO DOWNSTREAM NEURONS READ OUT INPUTS FROM THE OB?

To establish which features of the observed neural activity in the OB actually constitute a neural code, it is essential to understand how downstream neurons read out these activity patterns and how they are used by the animal. We now discuss odor coding and decoding in downstream neurons.

Odor Representations in the Olfactory Cortex

M/T cells in the mammalian OB project to several areas, including the anterior olfactory nucleus (AON), the piriform cortex (PC), the tenia tecta, the olfactory tubercle, the cortical amygdala, and the entorhinal cortex (Haberly 2001). These areas are traditionally called the olfactory cortex (OC), although some of these areas do not contain pyramidal neurons that form distinct layers (and thus are not cortical). In insects, PNs in the AL, analogous to M/T cells in the OB, project to the mushroom body (MB) and the lateral horn.

In insects, neural activity in the MB, which is thought to be involved in associative learning, is quite distinct from neural activity observed in the AL (Perez-Orive et al. 2002). First, spontaneous activity of MB neurons (called Kenyon cells) is nearly nonexistent [mean: 0.052 spikes per second, median: 0.011 spikes per second (Jortner et al. 2007)]. Second, an odor activates many fewer neurons in the MB than it does in the AL. Third, odor-evoked responses consist of a burst of a few spikes (often a single spike). Fourth, MB neurons respond to odors in a more concentration-invariant manner. These results thus showed that odor representations in insects are drastically transformed from dynamic and dense representations in the AL to sparse and simple representations in the MB. Sparse representations in the MB provide more explicit information about odor identity, which appears to be suitable for their roles in the formation, storage, and recall of associative memories (Perez-Orive et al. 2002).

Fewer studies have recorded neural activity in the mammalian olfactory cortices, particularly in awake animals. However, recent studies have begun to document basic characteristics of both spontaneous and odor-evoked activities in olfactory cortices. For example, the anterior part of the PC, the most studied among the mammalian olfactory cortices, has relatively low, but not quite silent, spontaneous activity [in awake animals, 6.15 ± 9.01 spikes per second, mean ± standard deviation (Miura et al. 2012)]. Neurons that respond to an odor are broadly distributed in space without apparent spatial organization (Illig & Haberly 2003, Miura et al. 2012, Poo & Isaacson 2009, Rennaker et al. 2007, Stettler & Axel 2009). A single odor activates about 10–30% of neurons (Miura et al. 2012, Poo & Isaacson 2009, Stettler & Axel 2009). The breadth of odor tuning varies among neurons; although most neurons select to a small number of odors, some neurons are broadly activated by many (Miura et al. 2012, Poo & Isaacson 2009, Zhan & Luo 2010). Recording in awake rats showed that temporal responses of anterior PC neurons are simple, consisting mainly of transient burst spiking that is tightly locked to sniff onset (Miura et al. 2012), and the spike counts in this sniff-locked neural activity convey reliable odor information (Gire et al. 2013b, Miura et al. 2012). In contrast, spike timing conveyed little additional information about odor identity compared with information provided by total spike counts over the entire sniff cycle (Miura et al. 2012). Furthermore, the overall firing rates of ensemble neurons correlated with the trial-by-trial accuracy of perceptual decisions in a psychophysical odor-discrimination task. These results suggested that there is a profound transformation in the way odors are represented in the OB and the anterior PC: In the PC, odor representations are distributed and do not show odor-specific spatial patterns as seen in the vertebrate OB (Friedrich & Korsching 1997, Meister & Bonhoeffer 2001, Rubin & Katz 1999, Uchida et al. 2000). Furthermore, the importance of spike timing–based coding is much reduced in the anterior PC compared with the OB.

Convergence and Divergence of Olfactory Bulb Projections to Piriform Cortex

Anatomical tracing studies have shown that neighboring M/T cells, including M/T cells belonging to the same glomerulus, project broadly across the PC without apparent spatial order (Ghosh et al. 2011, Igarashi et al. 2012, Nagayama et al. 2010, Sosulski et al. 2011). Conversely, a small cortical region receives input from M/T cells belonging to a distributed set of glomeruli (Miyamichi et al. 2011). A recent study in *Drosophila* demonstrated quantitatively that individual Kenyon cells receive information from a nearly random set of glomeruli (Caron et al. 2013). These results show that spatially segregated channels of odor information become integrated in the PC (or the MB). In brain slice experiments, investigators found that coincident inputs from multiple M/T cells are required to activate PC neurons (Apicella et al. 2010). Measuring the response of the PC population to odor mixtures revealed interactions between odors, exhibiting cross-odor suppression as well as supralinear excitation (Stettler & Axel 2009, Wilson & Sullivan 2011, Yoshida & Mori 2007). Additionally, recent studies in intact animals used glutamate uncaging and optogenetic photostimulation of glomeruli and recording in anterior PC to show that anterior PC neurons respond to activation of a specific and dispersed set of glomeruli (Davison & Ehlers 2011, Haddad et al. 2013). These experiments are consistent with the long-held view that PC neurons integrate information across dispersed glomeruli and act as combination detectors (**Figure 4*a***). However, a recent study using optogenetic stimulation in behaving mice showed that mice can detect the activation of a single glomerulus using light (Smear et al. 2013). These results suggest that even though naturalistic glomerular activity that is spread across the OB is integrated to activate anterior PC neurons, the animal could also detect strong activation of a single glomerulus.

Can Neurons in the Piriform Cortex Read Out Temporal Patterns in the Olfactory Bulb?

Are PC neurons also sensitive to the temporal patterns of inputs? As discussed above, a neural recording experiment suggested that odor representations are transformed from spike timing–based to firing rate–based representations between the OB and anterior PC. A recent study tested this idea directly by recording from neurons in anterior and posterior parts of the PC while varying the timing of optogenetic stimulation of two foci of glomeruli or M/T cells in anesthetized mice (Haddad et al. 2013). This study showed that firing rate responses of PC neurons depended on the order and the lag of input activations. Information conveyed by the firing rate increased in more central brain regions, and conversely, information conveyed by temporal patterns decreased. PC neurons' sensitivity to relative timing of activation did not depend on the time at which photostimulation was given with respect to the respiratory cycle. These results demonstrate that neurons in the PC can read out relative timing of activation across glomeruli and M/T cells. This study, however, used a relatively long duration of stimulation (~80 ms) to activate each spot, and the relative timing was varied on the order of tens of milliseconds. Whereas this stimulation protocol was aimed to mimic the time course of glomerular activation, M/T cells exhibit much faster dynamics. Furthermore, this study examined interactions between only two foci. It remains to be examined whether PC neurons are also sensitive to finer and more complex temporal and spatial patterns.

In contrast, a recent study in zebrafish showed that responses of neurons in the posterior zone of the dorsal telencephalon (Dp) did not depend on whether a set of M/T cells is activated synchronously or asynchronously, suggesting that Dp neurons effectively discard information about synchrony in the OB (Blumhagen et al. 2011). Although it is difficult to compare the Haddad and Blumhagen studies directly because each study used different stimulation protocols, it is possible that the difference in temporal sensitivity is the result of the difference in these neural circuits. For instance, feedforward inhibition in zebrafish Dp is relatively weak, whereas that in rodents plays a major role in shaping responses of PC neurons. Furthermore, temporal modulation in zebrafish OB is much slower (seconds) than that in the mouse OB (tens of milliseconds). Therefore, temporal sensitivity of neural circuits may be different between these species.

Can Animals Read Out Temporal Patterns in the OB?

The mere presence of the neural activity that contains reliable stimulus information does not prove its functional importance. The encoded stimulus information needs to be read out by downstream brain regions and ultimately utilized by the animal to discriminate sensory stimuli successfully. Recording neuronal activity in animals performing a psychophysical task is therefore critical for understanding the functional importance of neural codes. For example, discrimination of sensory stimuli in a behaving animal should cofluctuate with information content of the neural code used on a trial-by-trial basis. Such correlations can provide additional evidence that a given neural code is used by the animal (Britten et al. 1996, Luna et al. 2005, O'Connor et al. 2013). Cury & Uchida (2010) observed that the firing rates of subsniff, short epochs, but not the firing rates over the entire sniff cycle, cofluctuated with an animal's decisions (whether the animal decided to make a choice after one sniff or to take another sniff).

The importance of neural activation timing at the behavioral level was studied more directly by activating the olfactory circuit electrically or optogenetically in behaving animals (Monod et al. 1989; Smear et al. 2011, 2013). An earlier study showed that rats could not discriminate electrical stimulation of the OB delivered during inhalation versus exhalation (Monod et al. 1989). However,

it was later shown that mice can discriminate optogenetic stimulation of OSNs given at certain times in the respiration cycle (sniff phase) with a precision of ~10 ms (Smear et al. 2011). This study, however, could not examine the role of relative timing because the same OSN population was activated at different times relative to inhalation onset without changing the relative timing across neurons. This limitation raises the question of whether perceived differences are due merely to the timing of stimulus onset with respect to the respiration cycle or to changes in perceived quality or intensity of the stimuli. It remains to be examined whether the animal can discriminate more complex stimulus patterns (e.g., relative time code). Nevertheless, these experiments demonstrate that optogenetic activation (or electrical stimulation) can provide a powerful means to directly test the functional relevance of specific coding schemes.

The Role of Inhibitory and Recurrent Circuits in Decoding Olfactory Bulb Inputs

Which mechanisms generate the activity patterns of PC neurons? How are spatiotemporal activity patterns in the OB recognized by the neural circuits in the PC? Principal excitatory neurons in the PC receive inputs directly from M/T cells. However, PC principal cells also receive prominent inhibitory connections as well as excitatory recurrent connections, which shape their responses (**Figure 5*a***). The functional properties of cortical circuits play a critical role in the representations of sensory stimuli. The time course and strength of synaptic inputs primarily determine the timing and selectivity of spike output of PC neurons. These synaptic circuits have been studied using anatomical methods and brain slice in vitro electrophysiology.

Inhibition in the PC is provided by a local network of interneurons. Feedforward inhibitory inputs onto PC principal neurons are mediated by superficial layer 1 (L1) GABAergic interneurons that are directly activated by M/T cells. They selectively target the apical dendritic compartments of principal neurons in the PC and provide inhibition with a short latency (<10 ms) relative to the onset of M/T cell excitation (Stokes & Isaacson 2010, Suzuki & Bekkers 2012). Complementary to feedforward inhibition, feedback inhibition is mediated by deep L2/3 interneurons that target the soma and basal dendrites of PC principal neurons. Recruitment of these deep L2/3 interneurons requires the activation of PC neurons and therefore provides inhibition at a later onset (tens of milliseconds) (Stokes & Isaacson 2010, Suzuki & Bekkers 2012). The relative time course of cortical inhibition and OB input can restrict integration of specific synaptic inputs to a limited time window. Thus cortical inhibition can play a role in increasing PC neurons' sensitivity to synchronous synaptic inputs as well as in generating order sensitivity (**Figure 5*b*,*c***).

PC principal neurons also make excitatory connections with each other; these recurrent inputs are restricted to L2/3 and basal dendritic compartments (Haberly & Price 1978, Johnson et al. 2000). Recurrent connections may play an important role in shaping odor-evoked responses (Haberly 2001; Haberly & Presto 1986; Hasselmo & Bower 1990; Johnson et al. 2000; Ketchum & Haberly 1993a,b; Luskin & Price 1983a,b). Indeed, studies using in vivo whole-cell recordings as well as optogenetics demonstrated that excitatory recurrent activity functionally influences whether PC principal neurons are recruited by OB M/T cell inputs (Franks et al. 2011, Poo & Isaacson 2011). Temporally, recurrent excitation comes at a delay (10–50 ms) relative to direct M/T cell excitation (**Figure 5*c***). Together with cortical inhibition, these cortical circuits in the PC provide a mechanism for PC neurons to detect temporally patterned OB inputs.

In addition to synaptic delays, other properties of the cortical circuit such as short-term synaptic plasticity and location of the targeted dendritic compartment also contribute to the activation of neurons embedded in a cortical circuit (Behabadi et al. 2012, Branco et al. 2010, Gabernet et al. 2005, Higley & Contreras 2006, Larkum et al. 2009). In PC, feedforward inhibition decays rapidly

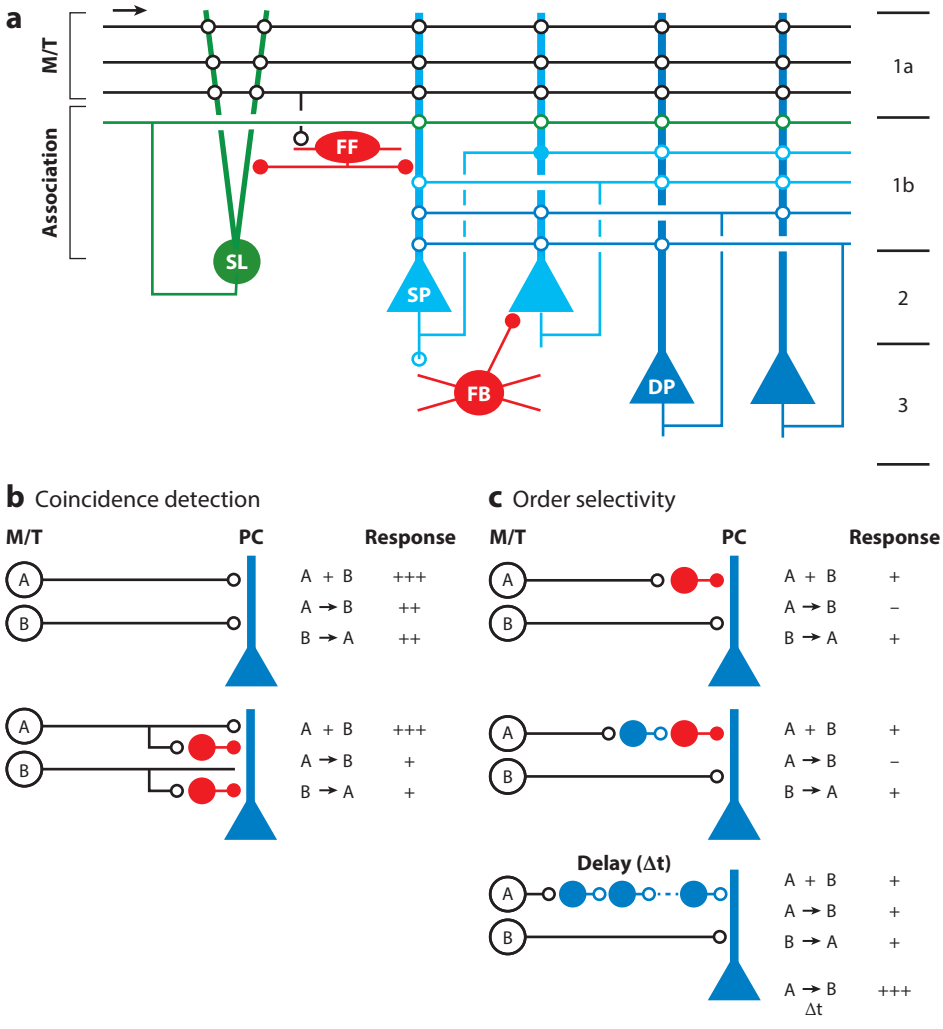


Figure 5

(*a*) Schematic diagram of neural circuits in the piriform cortex. Abbreviations: DP, deep pyramidal neuron; FB, feedback inhibitory interneuron; FF, feedforward inhibitory interneuron; M/T, mitral/tufted; SL, semilunar cell; SP, superficial pyramidal neuron. (*b*) Neural circuits for coincidence detection. Red circles represent inhibitory interneurons providing feedforward inhibition. This piriform cortex (PC) neuron responds strongly when both inputs A and B arrive at the same time (i.e., act as a coincident detector). *Top*: a small lag between stimulus A and B will result in a small decrease in the response due to a relatively large temporal integration window. *Bottom*: Feedforward inhibition narrows the window for temporal integration of the two inputs. (*c*) Neural circuits for order selectivity. *Top*, feedforward inhibition. *Middle*, feedback inhibition; *bottom*, recurrent excitation. Red circles represent inhibitory interneurons, and blue circles represent excitatory neurons.

throughout a train of OB input, whereas feedback inhibition grows as a result of more PC principal neurons being recruited. Recruitment of these two types of inhibition is separated in time, but it is also segregated in space: Feedfoward inhibition targets distal apical dendrites of principal neurons, whereas feedback inhibition is restricted to the soma and basal dendrites. Excitatory OB projections and recurrent input within the PC are also similarly separated in their temporal recruitment and target location. Although the specific manner in which these synaptic properties are engaged in vivo still remains elusive, they provide strong clues about how PC circuits could serve in the discrimination of temporal patterns of OB inputs.

The idea that the OC provides suitable neural circuits that recognize specific spatiotemporal patterns of inputs dates back to the 1980s: Structural features of seemingly random and combinatorial inputs from the OB and recurrent neural circuits in PC resemble those used in theoretical models of autoassociative memory or neural circuits of the hippocampus and entorhinal cortex known to play important roles in learning and memory (Haberly 2001, Lynch et al. 1986). These theories suggested that PC neural circuits may play a role in recognizing not only specific combinations of inputs but also their temporal patterns (Kleinfeld 1986, Sompolinsky & Kanter 1986, Tank & Hopfield 1987). These studies have also suggested that delayed input to PC neurons, which is an essential part of recognizing temporal patterns, can be generated by recurrent excitation and that recurrent inhibitory circuits may provide gain control mechanisms that stabilize and accelerate computations by otherwise-unstable recurrent networks (Chance & Abbott 2000, Jin & Seung 2002). Recent experiments have begun to test the idea that the PC performs odor recognition based on partial inputs (pattern completion) (Barnes et al. 2008, Chapuis & Wilson 2011). Interplay between experiments and theory will be increasingly important to advance our understanding of how the OC recognizes spatiotemporal input patterns and performs its functions at the systems level.

COMPUTATIONAL MERITS: DIFFERENT CODING SCHEMES IN THE OLFACTORY BULB AND THE PIRIFORM CORTEX

As discussed above, accumulating evidence suggests that temporal patterns of activity in the OB play a role in conveying odor information, whereas a firing rate–based code becomes more important in the PC. Why, then, do the OB and the PC use different coding schemes?

Temporal coding might be efficient in terms of firing economy (Gire et al. 2013a). Indeed, temporal coding can provide mechanisms that do not require an increase in firing rates or that require only one spike per neuron (Hopfield 1995). However, according to the efficiency principle, one would not expect to see high spontaneous firing rates as observed in M/T cells. One possible explanation for the high spontaneous firing rate in M/T cells is that cyclic activations of OSNs through airflow facilitate the detection of odorants at low concentrations. When cyclic activations are high enough to cause OSNs to fire spontaneously, the presence of even low concentrations of odorant can be detected as a shift in the timing of spikes in each cycle. This principle is akin to stochastic resonance, a phenomenon whereby a signal that is normally too weak to be detected by a sensor can be boosted by adding white noise to the signal, which contains a wide spectrum of frequencies. Relatively high firing rates and dependency on temporal coding might be, at least in part, explained by this mechanism. Furthermore, the temporal dynamics observed in the OB may reflect the fact that olfaction is a chemical sense utilizing various mechanisms that generate temporally rich neural responses (e.g., interactions between odorants with mucosa and odorant receptors, as discussed above). In addition, although the vast number of inhibitory neurons in the OB may have evolved for different purposes, such as gain control, they have also become a source of temporal responses. The olfactory system may have evolved to exploit these inherent properties

of the system by enabling downstream neurons to read the OB temporal code and convert the temporal code into a rate code.

There are substantial anatomical differences between the OB and the PC: Whereas a relatively small number of neurons (20–50 M cells) transmit odor information that converges through each input channel (glomerulus) in the OB, PC contains at least 2 orders of magnitude more neurons (Shepherd 2003). Whereas efficiency, in terms of the amount of information transmitted per neuron and per unit time, is crucial in the OB, the PC can distribute the information to a large number of neurons. One advantage of a rate-based code over a temporal code is that downstream areas can more readily read out such a code or combine it with other kinds of information encoded in rates. This ability might then facilitate proposed functions of the PC such as the formation of associative memories (Franks et al. 2011, Haberly 2001).

CONCLUDING REMARKS

The challenge of understanding neural coding of sensory information lies in the ability to address comprehensively the key issues of representation, encoding, decoding, and computational merit. In recent years, our understanding of the neural coding in the olfactory system has been advanced by new experimental results and the formulation of theories. In particular, studies that aim to reconcile computational frameworks, constraints of neural circuit dynamics, and neural recording during behavior have played important roles. New techniques such as optogenetics have also allowed researchers to test specific hypotheses regarding neural coding. Here, we review recent evidence for how odor information encoded in the OB is subsequently transformed and read out (decoded) by neurons in PC. One limiting factor of current results is that most of the studies using behavior have focused on the relatively simple task of odor discrimination. As we discussed earlier, specific neural coding may become more critical for computationally challenging and ethologically important tasks such as concentration-invariant recognition (including odor identification at an extremely low concentration) (Uchida & Mainen 2007) and odor segmentation. To address these issues, it will be very important to develop more complex behavioral paradigms both in humans and in experimental animals to elucidate neural coding and computations performed in the olfactory system.

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