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Finding the Brain in the Nose

David H. Brann and Sandeep Robert Datta

Department of Neurobiology, Harvard Medical School, Boston, Massachusetts 02115, USA; email: srdatta@hms.harvard.edu

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Abstract

Olfaction is fundamentally distinct from other sensory modalities. Natural odor stimuli are complex mixtures of volatile chemicals that interact in the nose with a receptor array that, in rodents, is built from more than 1,000 unique receptors. These interactions dictate a peripheral olfactory code, which in the brain is transformed and reformatted as it is broadcast across a set of highly interconnected olfactory regions. Here we discuss the problems of characterizing peripheral population codes for olfactory stimuli, of inferring the specific functions of different higher olfactory areas given their extensive recurrence, and of ultimately understanding how odor representations are linked to perception and action. We argue that, despite the differences between olfaction and other sensory modalities, addressing these specific questions will reveal general principles underlying brain function.

Contents

INTRODUCTION

For most neurobiologists—even for most sensory neurobiologists—there is something different about smell. Olfaction does not seem to follow the common rules that govern the structure and function of other sensory systems. Indeed, our understanding of the functional architecture of the mammalian main olfactory system (**Figure 1**)—the subject of this review—suggests that evolution has engineered a solution to the problem of smell that is fundamentally distinct from that of other sensory systems: Instead of being detected by a handful of sensors, most odors interact with a very large family of odor receptors (ORs) composed of hundreds to thousands of genes (depending upon the species), thereby accommodating the high dimensionality of odor chemical stimulus space (Bear et al. 2016); rather than being routed through the thalamus like, e.g., vision, touch, and audition, peripheral olfactory information enters the cortex directly (Neville & Haberly 2004); unlike the cortical maps that organize information about sound frequency and visual position, olfactory cortex does not topographically represent information about odor chemistry (Roland et al. 2017, Stettler & Axel 2009); and instead of a neat hierarchy of sensory areas that progressively recombine atomized stimulus features into increasingly abstract stimulus representations, olfaction distributes feature information in parallel from the olfactory bulb (OB) to multiple higher brain areas (and multiple layers within the same area), most of which are densely interconnected (Luskin & Price 1983).

Furthermore, from a practical perspective, olfactory processing is hard to study. To characterize visual responses in cortex, today you can make a chronic window over V1 and show rodents a battery of naturalistic images or well-defined synthetic stimuli while recording neural activity in thousands of neurons simultaneously (Stringer et al. 2019). In olfaction, as a general matter, we do not understand the natural statistics of odor stimuli and have not come to a consensus about how to quantify odor similarities and differences (Chae et al. 2019, Haddad et al. 2008). And no chronic cortical windows for us—all of the main higher-order olfactory structures lie at the bottom of the brain (Roland et al. 2017, Stettler & Axel 2009) (**Figure 1**).

And so, if you are interested in the brain, why study the olfactory system? One obvious reason is its long history of yielding general insight into neural function. Experiments on olfaction have unveiled many of the principles that guide our current understanding of the mammalian brain, including (but not limited to) the roles of developmentally specified and activity-dependent molecules in wiring together circuits; of adult neurogenesis in learning; and of dendritic computation, normalization, and spike timing in sensory coding (Adrian 1942, Laurent 2002, Lepousez et al. 2013, Schoppa & Urban 2003, Takeuchi & Sakano 2014, Uchida et al. 2014).

Importantly, there are several reasons to believe that addressing the challenge of olfaction will continue to teach us generalizable lessons about neural function. First, the brain evolved to enable animals to generate ethologically relevant behaviors, and odors arguably represent the most ethologically relevant sensory stimulus for most animals. Consistent with this possibility, ORs are some of the most rapidly evolving genes in the genome, and comparative analysis suggests that

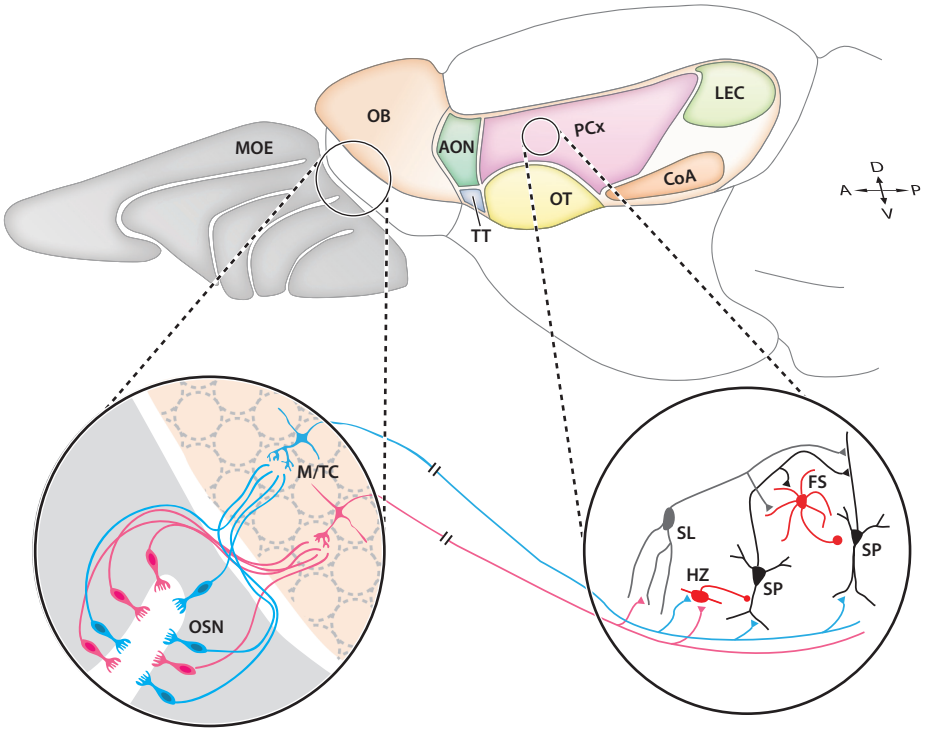

Figure 1

Organization of the mammalian olfactory system. Olfactory sensory neurons (OSNs) reside in the main olfactory epithelium (MOE). Each mature OSN expresses a single odor receptor. The axons of OSNs expressing the same receptor coalesce into structures called glomeruli in the olfactory bulb (OB). Each glomerulus receives projections from a population of OSNs expressing the same receptor, and each receptor is associated with small numbers of glomeruli whose positions are largely invariant across individuals. Mitral/tufted cells (M/TCs) each sample from a single glomerulus and send distributed projections to downstream olfactory regions, including the anterior olfactory nucleus (AON), tenia tecta (TT), olfactory tubercle (OT), piriform cortex (PCx), the cortical amygdala (CoA), and the lateral entorhinal cortex (LEC). In the PCx, excitatory semilunar (SL) cells and spiny pyramidal neurons (SPs) receive direct olfactory inputs from M/TCs as well as feed-forward inhibition from horizontal cells (HZs). The associational fibers from these excitatory principal neurons excite other SPs as well as fast-spiking (FS) multipolar interneurons, which mediate feed-back inhibition.

evolution actively sculpts neural circuits to enable each species to adapt to its particular ecological niche (Bear et al. 2016). The mouse—the most widely used mammalian model system for studying smell—is no exception. Mice in the wild depend upon their noses to forage for food, find mates, and avoid predators, and in the lab, the importance of olfaction is made plain through experiments demonstrating that mice are natural olfactory learners—training a mouse to discriminate closely related odors can be accomplished in as little as a day. In other words, mice (and many other animals) behave as if they were built to smell, suggesting that olfaction offers a clear window into the computational function of the brain as defined by evolution.

Second, genes play an unusually transparent role in defining the functional architecture of the olfactory system. The cloning of ORs a quarter century ago immediately suggested models for how mammalian olfactory circuits organize and process information about smells (Buck & Axel 1991). While most genes-to-function work performed to date has focused on the sensory

periphery, tantalizing hints suggest a molecular logic also underlies the function of central olfactory circuits (Diodato et al. 2016, Handler et al. 2019, Imamura et al. 2011, Inokuchi et al. 2017). The richness of the molecular toolkit in olfaction gives researchers the ability to flexibly manipulate specific information channels and circuit components; this sort of access is critical if we are to falsify theories about neural codes and circuit function.

Third, olfaction solves all the problems addressed by other sensory systems—discrimination, generalization, object invariance, innate behaviors, learning—but it does so in the absence of apparent long-range hierarchies between brain regions. As noted above, olfactory information goes from the nose to the OB to multiple recurrently interconnected allocortical areas; this processed information is then accessed by behaviorally or cognitively relevant brain regions like the orbitofrontal cortex, amygdala, and hippocampus (Diodato et al. 2016, Neville & Haberly 2004). This compact architecture enables researchers to directly explore how olfactory features encoded in the OB are combined with contextual information to create cortical sensory representations that organize information about the olfactory world and to ask how those structured representations are read out to generate actions and percepts (Fournier et al. 2015).

Here we argue that the many differences between olfaction and other sensory systems are not a hindrance but rather an opportunity. Mammalian olfaction per se has been well reviewed elsewhere (Mori & Sakano 2011, Su et al. 2009). Here, we instead describe three key areas in olfactory biology that hold the promise of broadly informing our understanding of brain function. We chose these particular examples to emphasize the importance of continued technical development in opening up new and important questions in olfaction.

FILTERING THE OLFACTORY WORLD

Everything the brain knows about the external olfactory world is a product of filtering performed by the peripheral sensory sheet in the nose. The first stage of this filtering occurs at the level of the OR, whose biophysics define which aspects of odor chemistry are conveyed to the brain. In the main olfactory system, the ORs are G protein–coupled receptors (GPCRs) that are expressed in a one receptor per neuron pattern (Buck & Axel 1991, Monahan & Lomvardas 2015); because there are no lateral connections between olfactory sensory neurons (OSNs), each population of neurons expressing a specific receptor constitutes a distinct information channel that conveys receptor-specific signals to the OB.

Natural odor stimuli are complex mixtures of monomolecular odorants carried in plumes. Although it is possible to use liquid and gas chromatography to identify molecular constituents of complex mixtures (Apfelbach et al. 2015, Ferrero et al. 2011, Lin et al. 2006), the relevant concentrations of mixture constituents as they are delivered to ORs (through the mucus layer that covers the epithelium) are largely unknown (Lucero 2013, Oka et al. 2006). In the context of mixtures, monomolecular odorants can act as agonists, antagonists, and partial agonists (Oka et al. 2004, Rospars et al. 2008, Takeuchi et al. 2009) (**Figure 2*a***). Indeed, most OR-ligand interactions are likely influenced by other monomolecular odors present in natural mixtures (Pfister et al. 2019, Xu et al. 2020). Furthermore, population-level OSN responses to natural stimuli are at least partially normalized in magnitude by competitive interactions between mixture constituents (Reddy et al. 2018).

Current evidence suggests that individual ORs are broadly tuned toward detectable molecular features of odorants, commonly referred to as odotopes (Araneda et al. 2000, Poivet et al. 2016). Most monomolecular odorants contain multiple chemical features that can be detected by different ORs, and individual ORs generally exhibit broad tuning properties reflecting responses to many molecules (Katada et al. 2005, Nara et al. 2011, Yu et al. 2015). These observations have led

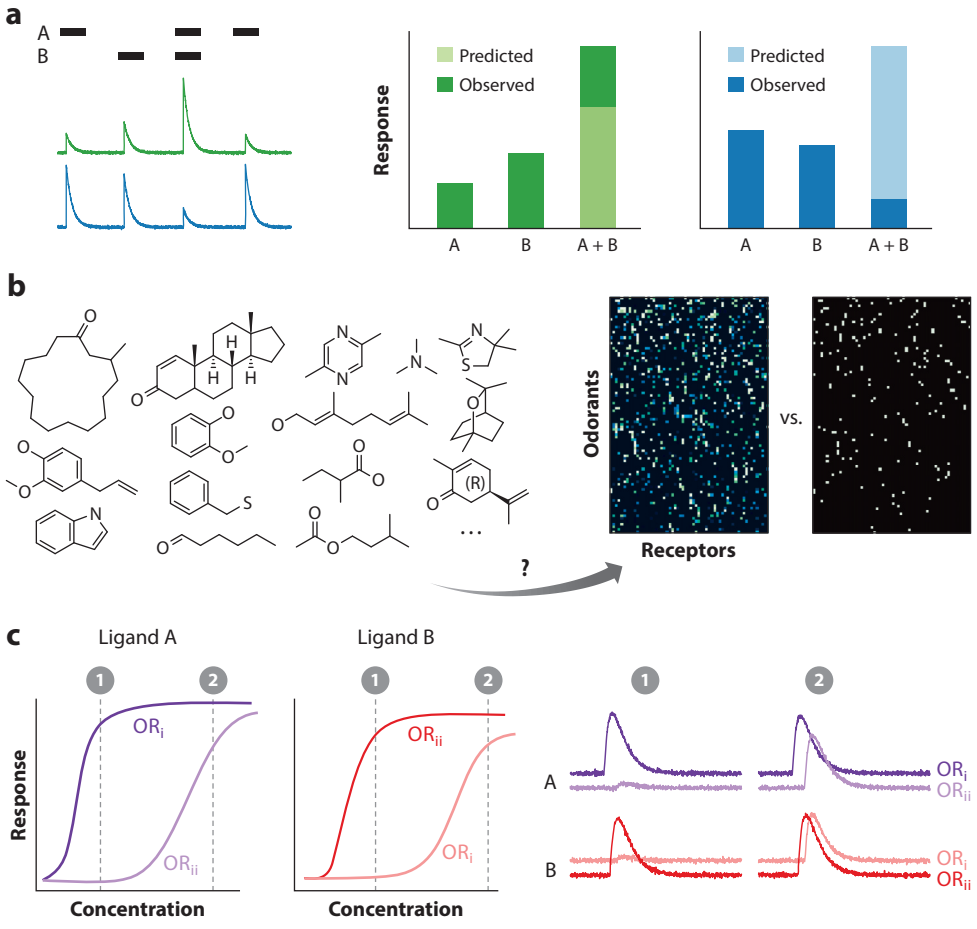

Figure 2

Peripheral coding of odors. (*a*) Receptors often exhibit nonlinearities with enhancement (*green*) or suppression (*blue*) of responses to odor mixtures compared to the predicted linear summation of responses to individual constituents. (*b*) Odorants are detected by olfactory receptors, but given that the majority of receptors have no known ligands, it is unclear how sparse or dense the peripheral odor code is or what chemical features are detected by receptors. (*c*) Ligands may selectively activate high-affinity receptors at low concentrations (①). At the same time, higher concentrations of odorants (②) recruit additional receptors, potentially at delayed timescales. Note that panels *a–c* are schematics meant to emphasize conceptual points.

to a combinatorial coding model in which odors are uniquely represented in the periphery by the specific combination of activated OSNs (Malnic et al. 1999) (**Figure 2*b***). That said, some odors selectively interact with few ORs, and conversely some ORs are highly tuned toward small numbers of ligands (Pacifico et al. 2012, Shirasu et al. 2014). Strikingly, in mice, deletion of single members of the trace amine-associated receptor family (which are expressed in the so-called TAAR system embedded within the main olfactory system) can affect perception and behavior, indicating that single ORs can play nonredundant roles in olfactory system function (Dewan et al. 2013, 2018). These data are consistent with observations demonstrating that allelic variation across human ORs can account for variation in perception (Jaeger et al. 2013, Keller et al. 2007, Mainland et al. 2014).

Interactions between ligands and ORs represent an initial component of the filtering performed by OSNs on chemical odor space. An important additional component—one that plays a key role in determining dose-response curves and temporal response properties—are the downstream signaling pathways that convert OR activation into electrical signals. Although ORs are thought to signal through common secondary messenger pathways (reviewed in DeMaria & Ngai 2010), findings from the vomeronasal olfactory system suggest that internal states can cause hormone-mediated changes in intracellular signaling and stimulus-response relationships (Dey et al. 2015). In *Drosophila*, the coupling of receptor activation to downstream signaling varies across receptors and contexts, suggesting the convergent importance of this regulatory mechanism (Nagel & Wilson 2011, Wilson 2013). Due to differences in spontaneous and odor-evoked activity levels, ORs in the mammalian main olfactory system can influence the expression of axon guidance molecules as well as the expression of histone variants that modulate OSN longevity (Nakashima et al. 2019, Santoro & Dulac 2012). However, whether such differences might also influence downstream components of olfactory signaling pathways remains unexplored.

Although we have a framework for understanding peripheral odor coding—nonlinear interactions between odors and feature-detecting ORs elicit population-level activity in the sensory sheet, which affords each odor a unique neural representation—key aspects of peripheral odor coding remain unclear. First, and perhaps foremost, we lack a detailed biophysical understanding of any ligand-receptor relationship, as the structure of a mammalian OR has not yet been solved (but see Butterwick et al. 2018). Second, as mentioned above, we do not yet know whether under real-world conditions the receptor array is confronted with ligand mixtures at relatively low concentrations (which would lead to sparse codes carried by high-affinity ORs) or whether effective concentrations are in a range at which denser codes convey information about odor identity (**Figure 2*c***). One possibility is that a few ORs relevant to innate behaviors possess high-affinity ligands, while the remainder of the system encodes information through lower-affinity interactions that lead to dense population activity (Dewan et al. 2018, Horio et al. 2019). For example, in *Drosophila*, where comprehensive odor tuning preferences have been evaluated, most receptors are broadly tuned across a wide range of concentrations, although a handful of receptors (most of which influence innate behaviors) have high-affinity ligands (Hallem & Carlson 2006, Hernandez-Nunez et al. 2015, Mathew et al. 2013). Similarly, mammalian TAAR receptors, which are high-affinity receptors for amines, mediate innate behavioral responses to amines (Dewan et al. 2013, 2018). Finally, we lack information about the diversity of ligand-receptor relationships. Fortunately, a rash of new deorphanization techniques promise to open up mammalian OR tuning for study at the population level. These approaches include reconstituting large receptor arrays in vitro in formats appropriate for high-throughput screening and in vivo methods that use molecular techniques to identify ORs whose gene or protein expression is modified by odor exposure (Jiang et al. 2015, Saito et al. 2009, von der Weid et al. 2015). Recently developed scanning light-sheet methods have also been used to query functional responses to odors in intact olfactory epithelium at the cellular level (Xu et al. 2016, Xu et al. 2020); combined with in situ transcriptomic methods for identifying OR identity, these in vivo approaches could be used to deorphanize ORs at scale.

Answering these questions is critical if we are to ultimately understand how the olfactory system as a whole interacts with odor chemistry. Psychophysics suggests that the olfactory system preserves at least some information about chemical features; these observations have been confirmed by recent work using machine learning to predict perceptual responses to odors on the basis of odor chemistry (Keller et al. 2017, Khan et al. 2007, Snitz et al. 2013). However, in general, the specific chemical features that define relevant odotopes for ORs remain undefined. While machine learning has identified subsets of physicochemical features that can explain responses in either OR populations reconstituted in vitro or the OB in vivo, these methods may not optimally capture the

relevant filtering of chemistry being performed by either ORs in vivo or downstream circuits in the brain (Chae et al. 2019, Haddad et al. 2008, Saito et al. 2009, von der Weid et al. 2015). One promising approach has been to use medicinal chemistry methods to explore how chemical variation influences receptor and neural responses (Poivet et al. 2016). Such an approach may bridge the gap between high-throughput ligand screening and structural methods to identify odotopes relevant for OR binding.

Understanding how the peripheral sensory sheet filters high-dimensional stimulus information arriving in odor plumes will enable us to evaluate strategies used by OSN populations to encode information about the natural statistics of the olfactory world (Lewicki 2002, Lin et al. 2006, Simoncelli & Olshausen 2001, Vincis et al. 2012, Weiss et al. 2012). Exploring peripheral odor codes will also offer general lessons about how large receptor arrays use combinatorial codes to encode information about a high-dimensional chemical space. Importantly, GPCRs and GPCR-interacting proteins are pervasive in the nervous system, and different internal states reflect—and are almost certainly implemented through—GPCR activity (Gainetdinov et al. 2004, Huang & Thathiah 2015). Furthermore, nearly all neuropsychiatric drugs currently deployed in the clinic target multiple neural receptors (Urs et al. 2014). Understanding how odor chemicals ligate the OR array may therefore have important implications for our understanding of neuromodulation and for rationally developing drugs designed to target multiple GPCRs to influence physiology and disease.

HIERARCHY AND RECURRENCE IN OLFACTION

Neocortical sensory systems like audition and vision are characterized by topographic maps that transform feature information (like frequency or position) into a spatial location on the cortical surface. Additionally, these systems are hierarchical—lower areas closer to the sensory periphery encode simple stimulus features, which are then recombined by higher areas to build increasingly abstract sensory representations (DiCarlo et al. 2012, Felleman & Van Essen 1991). Even though neural responses to complex sounds and objects within these long-range hierarchies can be accurately modeled by feed-forward neural networks, there are also recurrent feedback connections within and between areas (Kell et al. 2018, Lamme & Roelfsema 2000, Yamins et al. 2014). Although there are many possible functions for this recurrence, current evidence suggests it augments rather than abolishes the hierarchical processing of sensory information (Gilbert & Li 2013, Kar et al. 2019).

The functional architecture of the olfactory system differs sharply from its better-studied siblings, as the OB broadcasts olfactory information to many areas across the olfactory mantle at once (**Figure 1**); these include (but are not limited to) the anterior olfactory nucleus (AON), piriform cortex (PCx), posterolateral cortical amygdala (plCoA), lateral entorhinal cortex (LEC), tenia tecta, and olfactory tubercle (OT). All of these OB-recipient areas (with the exception of OT, which is striatal and not part of cortex) are tightly interlocked through extensive recurrence (Luskin & Price 1983, Millhouse & Heimer 1984). In PCx, for example, the OB is directly connected to primary neurons in both layer 2 (the main OB-recipient layer) and the less understood layer 3; layers 2 and 3 are themselves interconnected via recurrence, and both send projections to other OB-recipient brain areas and back to the OB itself (Bekkers & Suzuki 2013, Diodato et al. 2016, Franks et al. 2011, Giessel & Datta 2014, Haberly 2001, Poo & Isaacson 2011).

Given the shallow and fundamentally recurrent architecture of the olfactory system, how are sensory representations transformed as they pass from the OB to cortex? Although here we do not summarize important work exploring OB odor representations and local circuitry (which is well-reviewed in Burton 2017, Gire et al. 2013, Mori & Sakano 2011, Murthy 2011,

Nagayama et al. 2014, Wachowiak & Shipley 2006), it is clear that presynaptic inputs into glomeruli represent the tuning curves of individual receptors; the OB therefore houses a spatially organized representation of chemical feature space (Johnson & Leon 2007, Ma et al. 2012, Mori et al. 2006, Soucy et al. 2009). The OB is demonstrably not a relay—lateral inhibition and local processing between glomeruli normalize, neuromodulation modifies, and top-down interactions between cortex and the OB reformat OB odor representations in the mitral/tufted cell (*M/TC*) projection neurons that carry odor information forward into the rest of the brain in a state-dependent manner (Boyd et al. 2012, Fletcher & Chen 2010, Kato et al. 2012, Linster & Cleland 2016, Markopoulos et al. 2012). Generally, odor representations are thought to be decorrelated as odor information is processed in the OB, but it is not obvious which odor features are being represented by populations of M/TCs (Chae et al. 2019, Friedrich 2013).

The main recipient of OB inputs—and the best studied—is the PCx. In contrast to the point-to-point connectivity that characterizes other sensory systems, each OB glomerulus sends distributive projections across the entire PCx (Ghosh et al. 2011, Miyamichi et al. 2011, Sosulski et al. 2011). In addition, individual PCx neurons sample inputs from many OB glomeruli (Apicella et al. 2010, Davison & Ehlers 2011). Consistent with these observations, odors activate distributed populations of PCx neurons without any apparent topography (Illig & Haberly 2003, Rennaker et al. 2007, Stettler & Axel 2009). Furthermore, odor-evoked ensembles do not represent individual chemical features but rather encode odor identity in a holistic manner (Gottfried 2010, Wilson & Sullivan 2011, Yeshurun & Sobel 2009). These holistic representations reflect the collective influence of excitatory afferents (which encode information about the set of odotopes detected by the nose) and recurrent excitation that originates in the PCx and actively reshapes odor representations both directly within PCx and through centrifugal projections in the OB (Bolding & Franks 2018, Boyd et al. 2012, Franks et al. 2011, Haddad et al. 2013, Markopoulos et al. 2012, Otazu et al. 2015, Poo & Isaacson 2011, Suzuki & Bekkers 2012).

To date, four main functions have been assigned to the PCx recurrent network. First, centrifugal projections from PCx to the OB appear to recruit local inhibition to decorrelate peripheral odor representations (Bolding & Franks 2018, Boyd et al. 2012, Otazu et al. 2015). Second, the recurrent network amplifies the earliest signals from the OB while filtering slower signals that reflect odor concentration (Bolding & Franks 2017, 2018; Roland et al. 2017; Stern et al. 2018), as genetically blocking PCx recurrent connections abolishes concentration-invariant responses in PCx without changing the temporal dynamics of responses in the OB (Bolding & Franks 2018). The recurrent network is therefore essential for building concentration-invariant representations of odorants. Third, recurrence likely instantiates at least some aspects of odor experience, as olfactory learning requires acetylcholine, which preferentially influences and modifies the recurrent network (Chapuis & Wilson 2013, Linster & Hasselmo 2001). Finally, the recurrent network has been proposed to underlie the ability of PCx to act as an auto-associational network capable of pattern completion (Haberly 2001, Hasselmo et al. 1990, Wilson & Sullivan 2011). Task-dependent pattern completion has been observed in the PCx, but mechanistic insight linking specific network properties and representational stability in the face of noise has thus far been lacking (Bao et al. 2016, Chapuis & Wilson 2012, Qu et al. 2016).

These findings support a model in which different odors evoke activity in distinct cortical ensembles; these odor-specific ensembles are the products of afferent inputs and recurrence and are modulated in an experience- and task-dependent manner. Given this model, it remains unclear how odor-evoked cortical ensembles encode information about odor chemistry to support perception (which, as mentioned above, depends at least in part upon odor chemical features). While most quantitative evidence suggests that odor-evoked ensembles are highly decorrelated with each other, in some cases chemically related odors have been observed to activate overlapping

populations of neurons (Roland et al. 2017, Stettler & Axel 2009). Indeed, feed-forward computational models of the PCx and related structures, based upon the premise that PCx neurons randomly sample glomerular inputs, suggest that odors that evoke overlapping patterns of OR activation should, to some degree, recruit overlapping populations of cortical neurons (Babadi & Sompolinsky 2014, Fusi et al. 2016, Litwin-Kumar et al. 2017, Peron et al. 2020, Schaffer et al. 2018). However, the degree to which cortical ensembles actually represent chemical relationships is not known. Given that few experiments have recorded cortical odor responses across training or during distinct tasks, it also remains unclear how bottom-up odor codes capturing chemical features are shaped by top-down circuits reflecting task demands or experience (Chu et al. 2016, Koldaeva et al. 2019, Yamada et al. 2017).

As mentioned above, the OB projects to many brain regions in addition to the PCx, and many of those brain regions send projections back to PCx. In general, the main observations made for odor responses in the PCx hold in other OB target regions like the AON, plCoA, and OT: Individual neurons respond to multiple chemically distinct odorants, and odors evoke activity in ensembles of neurons (Iurilli & Datta 2017, Kikuta et al. 2010, Wesson & Wilson 2010). One study directly compared neural responses in PCx and plCoA and found no substantial representational differences across a large panel of monomolecular and natural odors, suggesting that the main computations that govern cortical odor representations are shared across regions (Iurilli & Datta 2017). Similarly, the OT has been proposed to harbor piriform-like representations for odors (Payton et al. 2012).

The lack of long-range hierarchies, extensive recurrence, and apparent similarities in representational strategies among OB recipient areas in the olfactory mantle suggest that the ability of the olfactory system to support odor perception and behavior is the consequence of the coordinated action of the entire network. Indeed, predictive coding models stipulate that the purpose of such interlocking networks is to make comparisons between expected and observed stimuli (Grabska-Barwińska et al. 2016, Keller & Mrsic-Flogel 2018, Zelano et al. 2011). However, there are also indications that individual higher olfactory regions are specialized for different functions. The plCoA, for example, receives topographically stereotyped and localized patterns of inputs from individual OB glomeruli whose parallel outputs to PCx are uniform and distributive (Miyamichi et al. 2011, Sosulski et al. 2011). Consistent with these observations, ectopic activation of PCx ensembles is sufficient to generate new odor-behavior associations, suggesting a primary role for PCx in learning, whereas the plCoA is thought to mediate innate odor-triggered behaviors (Choi et al. 2011, Root et al. 2014). Similarly, recordings from OT suggest it is primarily involved in linking odors to outcomes after reward-based learning, and recordings for AON suggest it is involved in orienting toward salient odor sources (Gadziola et al. 2015, Kikuta et al. 2010, Millman & Murthy 2020, Rabell et al. 2017).

We propose a model in which the superficial similarity of odor representations across different higher olfactory brain regions belies significant diversity that affords each area a unique perceptual function. Thus far, codes across different brain regions have mostly been qualitatively compared after testing with different (and arbitrarily chosen) odor sets (but see Iurilli & Datta 2017). The systemization of odor stimuli will be helpful for identifying coding differences across olfactory brain areas. Odor codes in OT, for example, are almost certain to be distinct from those in PCx and plCoA, due to the lack of recurrent excitation in the striatal OT (Giessel & Datta 2014, Millman & Murthy 2020, Wesson & Wilson 2011). Additional diversity will likely be revealed through careful cataloging of cell types and their projection patterns. While nearly all in vivo recordings of PCx, plCoA, and OT odor responses have been made without regard to cellular identity, there is significant cellular heterogeneity across all olfactory brain regions, and it is clear that these cell types differ in terms of their connectivity (Chen et al. 2014, Diodato et al. 2016,

Large et al. 2018, Murata et al. 2015). Finally, new technologies are beginning to enable simultaneous recordings of multiple olfactory brain regions; such experiments are necessary to decipher sensory transformations across interconnected olfactory brain regions (see, for example, Bolding & Franks 2018, Wang et al. 2019). These approaches will help to pinpoint the loci where sensory representations are modified by experience to support behavior and to reveal how representations are interrelated across olfactory regions (Semedo et al. 2019).

The neural ensembles that respond to odors in cortex encode odor identity holistically, in a manner analogous to the construction of higher-order representations for visual objects in inferotemporal cortex (DiCarlo et al. 2012, Wilson & Sullivan 2011). However, only a fraction of the total neural variance observed in olfactory cortex can be attributed to odor stimuli (Bolding & Franks 2017, Iurilli & Datta 2017). This observation is consistent with the notion that PCx and perhaps other higher olfactory areas are associational and therefore deeply task and state dependent (Haberly 2001). The olfactory system therefore offers an important opportunity to ask mechanistic questions about how synthetic object representations are created, how these representations are molded by task demands, and how information is selectively routed through highly recurrent circuits (Qu et al. 2016). Understanding neural circuit function has traditionally been hampered by recurrence, whose existence undermines efforts to assign functions to specific neural stations within interconnected circuits. Emerging techniques to specifically manipulate recurrent connectivity, which as noted above have been deployed in the olfactory system to study concentration invariance, hold the promise of untangling the web of interactions between brain areas (Bao et al. 2016, Bolding & Franks 2018, Peron et al. 2020); such experiments should yield general lessons about the ability of recurrence to shape sensory representations and to possibly enable forms of predictive coding.

IT ALL COMES BACK TO BEHAVIOR

As mentioned above, both the OB and higher olfactory brain regions encode information about odor identity through patterned neural activity. In principle, there are many ways in which neural firing can signify that an animal is smelling one thing and not another. Indeed, olfactory structures have been suggested to use a variety of neural codes, including dynamical, temporal, spatial, and ensemble codes (Gire et al. 2013, Laurent 2002, Murthy 2011, Uchida et al. 2014, Wilson & Mainen 2006) (**Figure 3**). In addition, a recently developed theory—called primacy coding—has been proposed as a mechanism to enable cortex to efficiently parse the large number of glomeruli activated after odor exposure (Wilson et al. 2017). Primacy coding asserts that the brain identifies odors by foveating on the first few ORs activated after inhalation; thus, the most relevant ORs for any given odor mixture are those that have the highest affinity for its monomolecular constituents, and which therefore recruit neural activity early during sampling (**Figure 3*f***). This possibility has been supported by perceptual experiments demonstrating that optogenetic masking has a greater impact early in a sniff (Wilson et al. 2017). Recent analysis of temporal odor responses in PCx revealed that odor coding has distinct fast (<50 ms after odor sampling) and slow phases, suggesting that the cortex may be able to take advantage of temporal windowing to facilitate odor identification (Bathellier et al. 2008, Bolding & Franks 2018).

Importantly, however, these many possible olfactory codes are not mutually exclusive; for example, in the OB, an ideal observer can decode odor identities and concentrations by observing the spatial patterns of glomerular activation, the temporal patterns of glomerular and M/TC activation, and the dynamical trajectories traced out by projection neurons (Bathellier et al. 2008, Cury & Uchida 2010, Fukunaga et al. 2012). How, then, shall we arbitrate from among different possible olfactory codes? One might argue that the best code is the most informative code, but

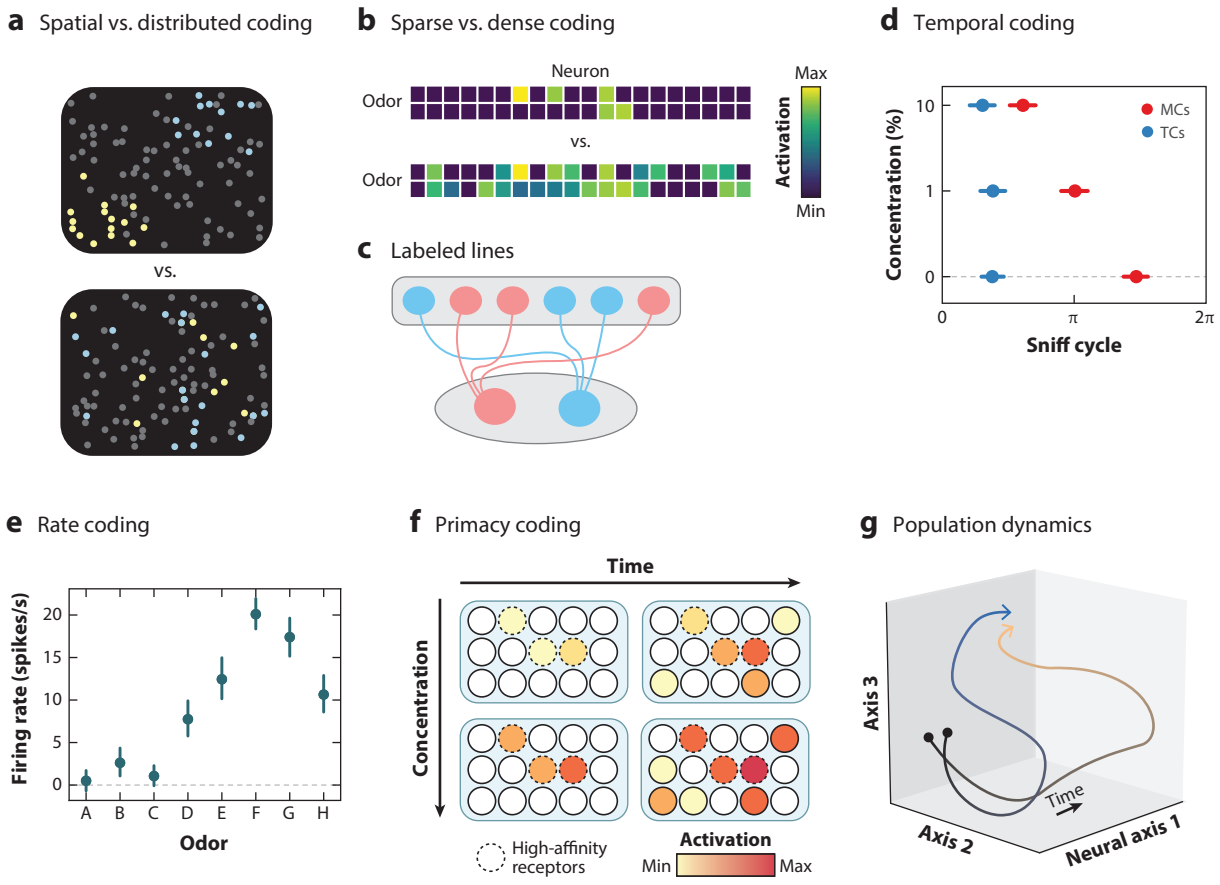

Figure 3

Olfactory neural codes. (*a*) In some sensory systems, stimuli activate spatially clustered groups of neurons (*yellow* and *blue*); however, in regions like PCx, odors activate distributed ensembles, indicating that chemical information is not mapped topographically. (*b*) Odors may sparsely or densely activate (*brighter colors*) sets of neurons. Such response densities and overlaps impact the ability of downstream decoders to discriminate between odors. (*c*) In neural codes that rely on labeled lines, information about separate odors (*red* and *blue*) remains segregated across olfactory regions, allowing for hardwired links between receptor activation and downstream behavior. (*d*) In temporal coding models, spiking is restricted to specific phases of cyclic temporal patterns, such as oscillations or sniffing. Ongoing odor dynamics can modify the links between these temporal features and spiking, as observed in OB mitral cells (*red*) shifting to firing earlier in the sniff cycle at higher concentrations. Panel *d* adapted with permission from Fukunaga et al. (2012). (*e*) Odors can also be encoded with rate codes, in which a given neuron responds to different odors (A–H) with different firing rates. (*f*) In the primacy coding model, decoding odors is facilitated by only considering low latency responses, which likely correspond to high-affinity receptors. To assign odor identities, the primacy coding model ignores the broad array of receptors that can respond at later time points, especially with high odorant concentrations. Panel *f* adapted from Wilson et al. (2017) under the Creative Commons Attribution (CC BY 4.0) International license. (*g*) Odors (*blue* and *yellow*) can also be discriminated by analyzing the population activity dynamics they elicit, such as their separate trajectories through neural space.

given the vagaries of evolution, there is no guarantee that the most theoretically informative coding strategies are the ones used by the brain to address real-world problems. Since sensory codes are useful only insofar as they can be read out to support perception—and since lab animals report perception via behavior—behavioral analysis is a key tool for exploring the meaning of sensory codes in the brain (Jazayeri & Afraz 2017, Panzeri et al. 2017). Indeed, behavior has long been useful for exploring the neurobiological basis of olfaction in many contexts, e.g., for defining

speed-accuracy tradeoffs and perceptual thresholds, for establishing the ability of the olfactory system to identify subtle differences in stimulus timing, for relating neural to perceptual similarity, and for relating psychophysical performance to the information content of neural codes (Abraham et al. 2004, Bhattacharjee et al. 2019, Chu et al. 2016, Cury & Uchida 2010, Erskine et al. 2019, Mathis et al. 2016, Miura et al. 2012, Resulaj & Rinberg 2015, Rinberg et al. 2006, Smear et al. 2013, Uchida & Mainen 2003, Wesson et al. 2008, Wilson et al. 2017, Wojcik & Sirotin 2014).

We argue that dissecting out the unique function of each olfactory brain region will require identifying those aspects of each area's neural code that are actually decoded, and that in turn requires studying odor-driven behavior. One important approach will be to combine highly precise behavioral measures with targeted neural manipulations, such as those enabled by patterned stimulation and multiphoton holography (Lerman et al. 2018, Peron et al. 2020, Russell et al. 2019); these methods will allow the spatial, temporal, and dynamical aspects of a given neural code, all of which are naturally intermingled, to be rationally teased apart. This type of experiment could be used to test primacy theory, for example, or to establish the distinct roles of early versus late post-sniff neural activity in PCx (Bathellier et al. 2008, Bolding & Franks 2018, Wilson et al. 2017).

Although the current focus on studying olfactory behaviors with reward-based perceptual discrimination paradigms has, as noted above, taught us much about olfactory psychophysics, behavioral strategies, and their relationships to neural codes, it is possible that at least some findings reflect contextual and task idiosyncrasies that will not generalize to more naturalistic circumstances (Jordan et al. 2018, Koldaeva et al. 2019, Mendonça et al. 2018, Zariwala et al. 2013). It is therefore important to also develop more ethological tasks in which freely moving animals continuously decide how and where they will sample olfactory information by actively sniffing and navigating among naturalistic turbulent odor plumes (Baker et al. 2018, Gire et al. 2016, Vickers 2000, Wachowiak 2011). It is possible that much of the neural variability in higher olfactory areas will only be understood when lab animals are engaged naturalistically in odor seeking and related ethologically relevant challenges like using olfaction to engage a mate or avoid a predator. In this context, it is worth noting that there have been few recordings of neural activity in OB or PCx as animals freely behave and interact with odor plumes in an arena; although neural activity has been recorded in the context of two-alternative forced-choice tasks, during such experiments subjects obligately shove their noses into a port while being confronted with square wave stimuli (but see Burton et al. 2019, Erskine et al. 2019). Furthermore, we know very little about unrestrained odor sampling behavior (at both the sniffing and pose dynamics levels), as the machine learning–based technologies required to understand complex patterns of action during free movement are only now being developed and gaining adoption (Datta et al. 2019, Mathis et al. 2018, Wiltschko et al. 2015). Given the state of the field, it therefore remains unclear how odor sampling intersects with the natural statistics of odor stimuli to generate representations as animals freely behave, or how other OB recipient regions like the AON and LEC support olfactory navigation behaviors (Kikuta et al. 2010, Leitner et al. 2016, Rabell et al. 2017).

It is worth noting that these two general approaches to exploring odor codes—careful manipulations and ethological tasks—stand in tension with each other; causal optogenetic manipulations are most easily performed in the context of simple overtrained tasks with defined structure, while more ethological tasks require free behavior that poses challenges for stimulus control, neural recordings, and behavioral characterization. Fortunately, technologies to measure neural activity and behavior during unrestrained tasks are rapidly developing. Furthermore, the conceptual framework for how we think about the relationship between neural activity and naturalistic behavior—and the ways in which we can most usefully interpret optogenetic experiments—is continuing to mature (Datta et al. 2019, Gomez-Marin & Ghazanfar 2019, Jazayeri & Afraz 2017, Krakauer et al. 2017, Panzeri et al. 2017). Given that the brain evolved to generate behavior,

it is likely that much of what is learned conceptually and practically from these lines of olfactory research will teach us general lessons about how neural codes are decoded into perception and behavior in the brain. Moreover, since PCx is ontogenetically and functionally related to critical brain areas like the hippocampus, gaining this insight should shed light on how activity in distributed neural circuits is linked with behavior and modified via learning (Fournier et al. 2015, Haberly 2001).

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