Olfactory Systems Theory ☆

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Introduction

The most difficult challenges in understanding sensory systems arise in the context of natural scenes. The problems inherent in the sampling, representation, and processing of sensory information within natural environments are substantial; some would even be considered crippling were it not already clear that functioning sensory systems do exist. Hence, understanding these processes as complex systems not only will yield insight into neural processing per se, but also offers the hope of fundamental new insights into stimulus processing for engineering and machine sensation, particularly in areas such as source separation, object construction and identification, and the utility of prior expectations. Given recent insights into the molecular and biochemical events underlying fundamental sensory transduction mechanisms, the complex neural algorithms underlying postacquisition stimulus processing are increasingly the limiting factors in understanding sensory system function. Studying sensory processing mechanisms as complex systems is a critical component of modern neuroscience.

The olfactory modality is particularly amenable to study at the systems level. While many of the difficulties imposed by olfactory natural scenes are analogous to those encountered in other sensory modalities, some of the resulting computational problems are considerably more tractable. For example, there is no clear olfactory analog to the problem in vision that a given visual object does not reliably generate a replicable primary representation—that is, the pattern of activation of retinal photoreceptors in response to a given visual stimulus object differs arbitrarily based upon both eye position and the spatial orientation of the object. In contrast, while the breadths of olfactory primary representations are affected by changes in stimulus intensity and other environmental factors, and occluded by the presence of other odorants, odor-evoked activation patterns among primary olfactory sensory neurons (OSNs) are fundamentally specific to odor quality and hence are reliable as channel-based primary representations, potentially rendering the olfactory binding problem a considerably more tractable goal than its visual counterpart. In contrast, other elements of olfactory stimulus processing are more complex than are their analogs in other modalities. The regulation of receptive field breadth, for example, is classically mediated by lateral inhibitory interactions in modalities such as visual retinotopy or auditory frequency tuning, in which stimulus similarities can be mapped onto physical neighborhood relationships in the brain. In olfaction, however, the similarities among stimuli are mapped high-dimensionally, rendering lateral interactions in functionally two-dimensional cortical networks incapable of mediating this basic sensory filtering process. Different neural mechanisms are required to perform similarity-dependent transformations on high-dimensional sensory information.

While a comprehensive, systems-level analysis of olfactory processing that engages the problems posed by natural scenes becomes considerably more complex than are analyses limited to interpreting the results of highly constrained experimental studies, it also provides vital constraints on functional hypotheses that otherwise would go unrecognized. A robust neural system engages in numerous homeostatic tasks unrelated to stimulus coding per se—for example, pH regulation, energy conservation, prevention of excitotoxicity, maintenance of the appropriate dynamic ranges of individual neurons and networks, and compensatory responses to durable changes in synaptic weights or the incorporation of newly generated neurons that may be necessary for network stability. Such processes may correlate with sensory inputs and hence can easily be interpreted as contributing to "stimulus coding" without casting much light on the dynamics of sensory system operation. Comprehensive, systems-level study of neural circuit operations in complex environments is required in order to come to understand the broader biological networks that underlie robust, functioning sensory systems in vivo.

☆*Change History*: June 2016. TA Cleland made some changes to the text, revised Figure 4 and updated Further Reading section.

Systems Analysis of the Olfactory Modality

In natural environments, airborne chemical stimuli are distributed unpredictably in time and space, and odorants from innumerable sources intermix freely. Furthermore, the mixtures of volatile molecules that define meaningful odors in an animal's environment are inherently variable both in quality and in intensity, depending on numerous external factors, including time of day, season, temperature, weather conditions, and the proximity of the animal to various odorant sources. An effective olfactory system must be able to detect potential signals of interest within these chemically noisy environments, correctly extract these signals from a complex and changing odor background to form stimulus representations, identify these constructed representations with respect to previously experienced odors, differentiate relevant from irrelevant stimuli, and cue an appropriate response. Current theoretical and experimental approaches have tended to break this process down into sets of roughly sequential problems, such as the following sequence: (1) detect and transduce airborne chemical signals, (2) improve the signal-to-noise ratio, (3) modulate selectivity (contrast), (4) translate the representation from a form optimized for stimulus sampling to one compatible with common cortical processing mechanisms (generally considered to be sparse and spike timing sensitive), filter out multiple confusing sources of variance, including (5) differences in intensity (normalization) and (6) unrelated background odorants, and (7) identify relevant stimuli with reference to previous experience. The neural tissues involved in odor detection and recognition processes contain specialized circuitry to perform these essential tasks. Primary OSNs transduce chemical stimuli into electrical signals with high sensitivities and broad dynamic ranges that initially appear to defy mass action law. The axons of all OSNs expressing the same olfactory receptor converge upon one or two common neuropilar regions in the olfactory bulb input layer, termed glomeruli; the resulting high convergence ratios enable substantial improvement in the signal-to-noise ratios of olfactory sensory responses. Local inhibitory circuits within the olfactory bulb filter this primary representation, regulating stimulus selectivity and segregating odor quality information from response differences owing to different stimulus intensities. Other olfactory circuits are thought to utilize short-term synaptic plasticity for odor-background segmentation, whereas long-term plasticity and associative memory networks within the piriform cortex may contribute to the memorization and identification of stimuli sampled from noisy backgrounds. Extensive feedback interactions between the olfactory bulb and deeper olfactory cortices synchronize the activity of related circuits, providing a timebase for the representation and processing of olfactory information on short timescales (loosely termed "temporal coding"). Here, we outline a functional description of olfactory signal processing, emphasizing the functional roles of different neural circuits within olfactory structures (see Fig. 1).
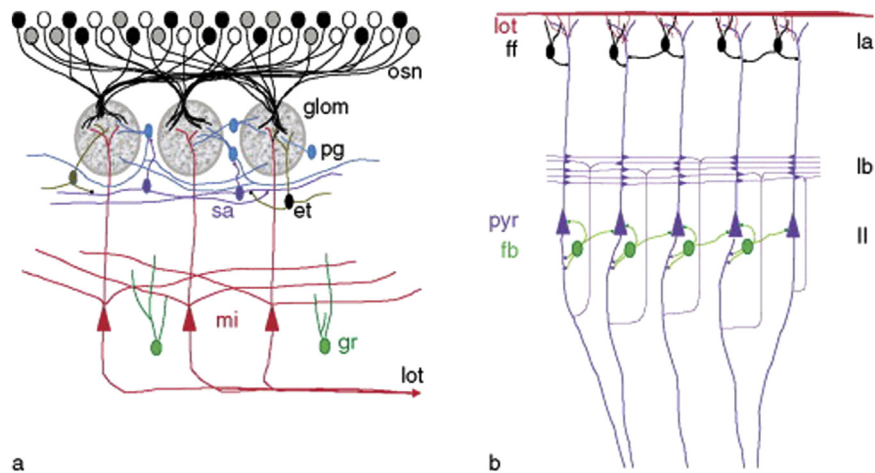

Figure 1 Simplified schematic illustration of olfactory circuitry. (A) Olfactory sensory neurons and olfactory bulb circuitry. Olfactory sensory neurons (osn) expressing the same olfactory receptor project to a given glomerulus (glom) in the olfactory bulb, within which they make synaptic contacts with mitral cells (mi), periglomerular and superficial short-axon cells (pg, sa; in reality probably part of the same heterogeneous class of interneurons), and external tufted cells (et). Periglomerular and mitral cells make reciprocal dendrodendritic synaptic contacts with each other within the glomerular neuropil: periglomerular cells inhibit mitral cells while mitral cells excite periglomerular cells. External tufted cellsexcite mitral cells, whereas the (unfortunately misnamed) superficial short-axon cells convey long-distance, nonspecific lateral inhibition onto distant mitral and external tufted cells, effecting feedback normalization. Deeper within the bulb, within the external plexiform layer, mitral cell secondary dendrites extend broadly and laterally, forming reciprocal dendrodendritic synapses with inhibitory granule cells (gr). Spike trains from mitral cells, the principal neurons of the olfactory bulb, are delivered to multiple secondary olfactory structures via the lateral olfactory tract (lot). (B) Circuitry of the piriform (olfactory) cortex. Within cortical layer Ia, mitral cell axons of the lateral olfactory tract (lot) excite both the primary apical dendrites of pyramidal cells (pyr) and the dendrites of feed-forward inhibitory interneurons (ff), which in turn locally inhibit the pyramidal cell dendrites. In layer Ib, the pyramidal cell dendrites also receive excitatory inputs from other pyramidal cells. These dense excitatory feedback connections are called association fibers and are known to undergo long-term potentiation. Pyramidal cells also excite a second class of inhibitory local interneurons called feedback interneurons (fb), which in turn inhibit a small number of nearby pyramidal cells. The cell bodies of pyramidal cells and feedback interneurons comprise layer II of piriform cortex.

Stimulus Transduction and Signal-to-Noise Enhancement

Primary OSNs number in the millions in rodents. Specialized cellular properties within individual OSNs have been hypothesized to improve their sensitivities to odor ligands well beyond their ligand–receptor dissociation constants, while their large, redundant populations and correspondingly high convergence ratios onto the glomeruli of the olfactory bulb have been proposed to yield advantages such as improved signal-to-noise ratios and broader dynamic ranges. The molecular receptive ranges, or chemical receptive fields, of different odorant receptors overlap substantially, such that the identity of odorants is not associated with the activation of a specific receptor, but rather is represented by a distributed, combinatorial representation. From a theoretical point of view, this type of representation has several advantages: first, the number of unique odor representations is not limited to the number of different receptor types, but can be estimated as m^n, where n denotes the number of receptor types and m denotes the number of recognizable states that each sensor can assume, ultimately limited by the signal-to-noise ratio of the system. Second, the fact that structurally and perceptually similar odorant molecules activate correspondingly overlapping sets of olfactory receptors establishes a basis for the recognition of stimulus similarity in the olfactory system. A reliable metric for stimulus similarity facilitates a tolerance for variance among repeated stimulus samples and also is prerequisite for basic postsensory cognitive processes such as generalization. Combinatorial representations not only exhibit greater coding capacities than do labeled-line systems, but also are more robust to degradation, noise, and natural variation in stimulus parameters. Fig. 2 illustrates the characteristics and advantages of combinatorial stimulus representation in the olfactory system.

Contrast Modulation and Normalization

Distributed patterns of activity in response to chemical stimuli are transmitted to the olfactory bulb via OSN axons that terminate in the glomeruli of its input layer. The olfactory bulb is believed to filter and transform these incoming sensory data, performing normalization, contrast enhancement, and similar operations before conveying the processed olfactory information to several different secondary olfactory structures via mitral cell axon collaterals. Because of the patchy and nontopographically organized representation of olfactory stimulus similarity across the olfactory bulb, contrast enhancement operations in this system cannot rely on physical proximity-based mechanisms such as center-surround lateral inhibition. (Indeed, olfactory stimulus similarity is not a static property; maps of olfactory similarity space depend on the statistics of the odor environment as well as on the structures of olfactory receptors expressed in the nose.) Instead, the bulb appears to mediate an analogous operation relying solely on local feed-forward inhibition coupled with global, nonselective feedback inhibition. In addition to enabling contrast enhancement in
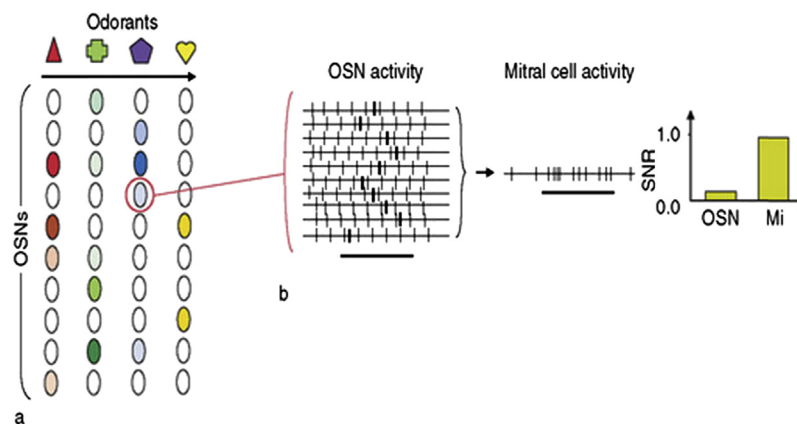

Figure 2 Combinatorial stimulus representation and signal-to-noise improvement. (A) Every odorant chemical binds to several types of olfactory receptors with different characteristic affinities, hence activating several different classes of olfactory sensory neurons (OSNs) to differing degrees (depicted by color saturation). Furthermore, the same OSN may be activated by many different odorants. Consequently, each chemical activates a unique combination of receptors with a characteristic pattern of activation levels. With only 10 OSNs, assuming only four discrete activation levels for each OSN (as depicted), 4^{10}, or 1,048,576, odors can be uniquely represented by the ensemble. Furthermore, combinatorial representations degrade gracefully; substantial information about odorant quality is preserved even if subpopulations of OSNs are destroyed or inactive. (B) OSN convergence improves the olfactory signal-to-noise ratio (SNR). In the present context, the signal-to-noise ratio can be defined as the number (or density) of spikes evoked by the signal of interest (odor presentation) divided by the total number (density) of spikes produced during the time of observation. Spikes specifically evoked in OSNs by odorant presentation are depicted by thicker vertical lines; thinner lines denote background spiking activity. Hundreds or thousands of OSNs with similar selectivity for odorants converge upon each mitral cell in the olfactory bulb. Even if the signal-to-noise ratio is extremely low in individual OSNs (i.e., if the stimulus-evoked increase in activity is nearly undetectable with respect to the OSN's baseline activity, as depicted), the convergence of many such neurons will evoke a substantial increase in the density of incoming spikes impacting a single mitral cell (Mi), reliably affecting its level of activation. This corresponds to a higher SNR in mitral cells when compared with any of its cognate OSNs.

a high-dimensional modality such as olfaction, this nontopographical mechanism does not require a built-in foreknowledge of the similarities in molecular receptive ranges expressed by different olfactory bulb glomeruli in order to distribute inhibition correctly, and is entirely independent of the physical location of glomeruli within the olfactory bulb. Briefly, OSN axonal arbors in each glomerulus deliver glutamatergic excitation upon mitral cell and external tufted cell dendrites as well as the dendritic spines of local inhibitory neurons known as periglomerular cells. These periglomerular cell spines directly deliver γ-aminobutyric acid (GABA)$_A$ergic shunt inhibition onto mitral cell dendrites in parallel to the excitatory inputs that the latter receive directly from OSNs (Fig. 3A) and indirectly via external tufted cells. Theoretical models indicate that this configuration enables nontopographical contrast enhancement in a similarity space naturally inherited from the current chemosensory environment; mitral cells associated with a given odorant receptor are activated only by the highest affinity odor ligands, responding to lesser degrees of cognate OSN activation with a net inhibitory response (Fig. 3B). Odor-evoked activity patterns across mitral cell ensembles (secondary representations) are consequently sparser and less overlapping than are the corresponding primary representations observed among OSNs, as visualized in imaging studies of glomerular activation patterns (Fig. 3C). Furthermore, the stringency of this transformation appears to be regulated by centrifugal neuromodulatory inputs, specifically including inputs mediated by nicotinic cholinergic receptors in the glomerular layer.
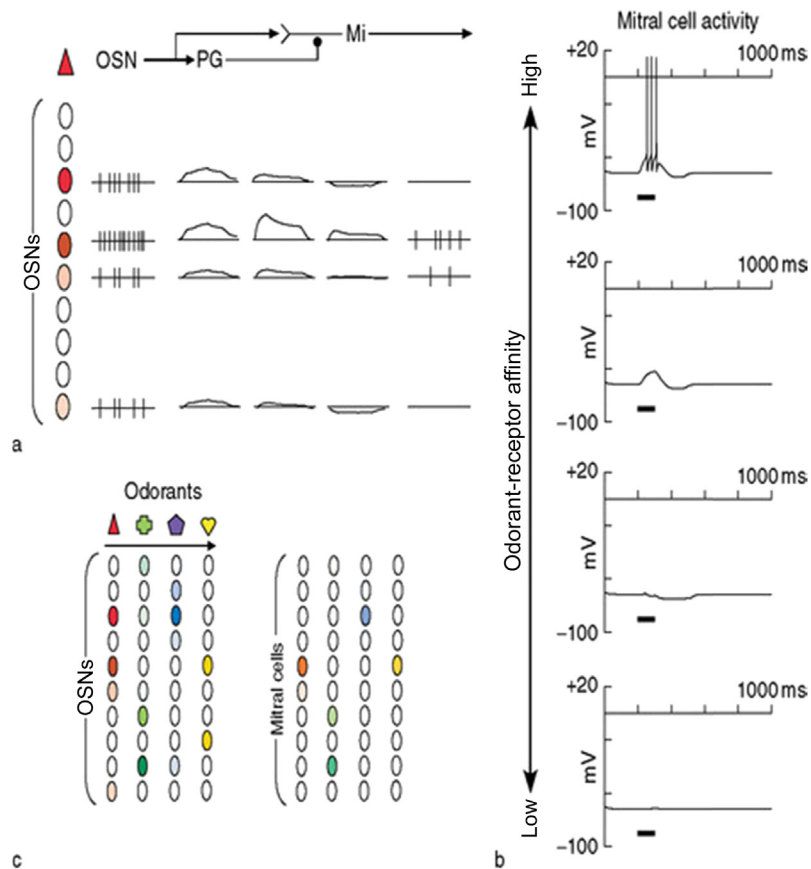

Figure 3 Local computation of contrast enhancement. (A) Odor presentation evokes a distributed pattern of activation among olfactory sensory neurons (OSNs), communicated to the olfactory bulb via convergent axonal projections. OSN activation excites mitral (Mi), external tufted (ET), and periglomerular (PG) cells in the olfactory bulb input layer, while periglomerular cell dendritic spines concurrently inhibit mitral cell primary dendrites, resulting in a final activation pattern among mitral cells that is narrower and more precise than that originally evoked among OSNs. Corresponding to the schematic at the top are the five columns depicting neuronal activity (from left to right): spike trains in sensitive OSNs, synaptic activation of periglomerular cells by OSNs, synaptic activation of mitral cells by OSNs, net synaptic activation of mitral cells after factoring in periglomerular shunt inhibition, and evoked spiking activity in mitral cells. The indirect excitation pathway of mitral cells (via ET cells) is omitted for clarity. (B) Computational modeling of glomerular circuitry, demonstrating nontopographical contrast enhancement. Odorants with low affinity for the depicted mitral cell's cognate odorant receptor evoke no response in the mitral cell depicted, while odorants with moderate affinity activate OSNs but evoke a net inhibitory response in the corresponding mitral cell. Only the highest affinity odorants evoke action potentials in mitral cells. (C) These local computations result in distributed, odor-specific activity patterns at the level of mitral cells that are considerably sparser than those conveyed by the OSNs, thereby establishing greater contrast (less overlap) between the representations of structurally similar odorants. (B) Adapted from Cleland, T.A., Sethupathy, P., 2006. Non-topographical contrast enhancement in the olfactory bulb. BMC Neurosci. 7, 7, with permission.

In general, higher stimulus intensities both increase the activity of sensitive primary sensory neurons and broaden the neural response by recruiting additional, more weakly tuned primary sensory neurons into the activated ensemble. In the olfactory system, this corresponds to increased probabilities of ligand–receptor binding as ligand concentration rises, eventually binding significantly even to receptors for which the ligand in question has very low affinities. Hence, as odor concentrations rise, an increasingly broad range of OSNs become activated, substantially broadening the primary representation. In contrast, mitral cell activity in response to increasing odorant concentrations is variable; individual mitral cells may increase or reduce their response levels (to greater or lesser degrees), may exhibit shorter spike latencies, or may transition from a net excitation to inhibition, or vice versa. They do not, however, exhibit reliably monotonic increases in activation levels comparable to those observed in individual OSNs or populations of convergent OSNs (the latter observed via glomerular activity imaging). That is, some form of normalization process is clearly active between the primary representation across the OSN population and the secondary representation composed of mitral cell spiking activity patterns.

Normalization processes in sensory systems are essential for segregating quality from concentration effects and for constructing intensity-independent representations of stimulus quality. Indeed, identifying methods of forming intensity-independent representations is a major research concern in many sensory modalities. In principle, intensity normalization processes require global feedback inhibition, in which uniform inhibition is delivered to all units in proportion to the mean activity level of all sensory inputs. In the olfactory system, this normalization was originally proposed to rely upon a functionally excitatory "small world" network formed by glomerular layer interneurons within the olfactory bulb. More recent experimental work has demonstrated that this computation is instead mediated by dense, long-distance, direct projections among glomeruli by inhibitory interneurons. Briefly, a heterogeneous network of GABAergic and dopaminergic interneurons (drawn from populations traditionally characterized both as periglomerular and superficial short-axon cells) is excited by afferent input and projects broadly across the OB glomerular layer, inhibiting mitral and external tufted cells in distal glomeruli. The result of this computation is a preservation of relative activity levels among glomerular outputs across a wide range of absolute stimulus intensities (Fig. 4).

Synchronization and Binding

After the excitatory and inhibitory inputs converging on mitral cell primary dendrites have been integrated, olfactory stimuli are represented in broadly distributed levels of mitral cell activation across the olfactory bulb that largely determine whether any given
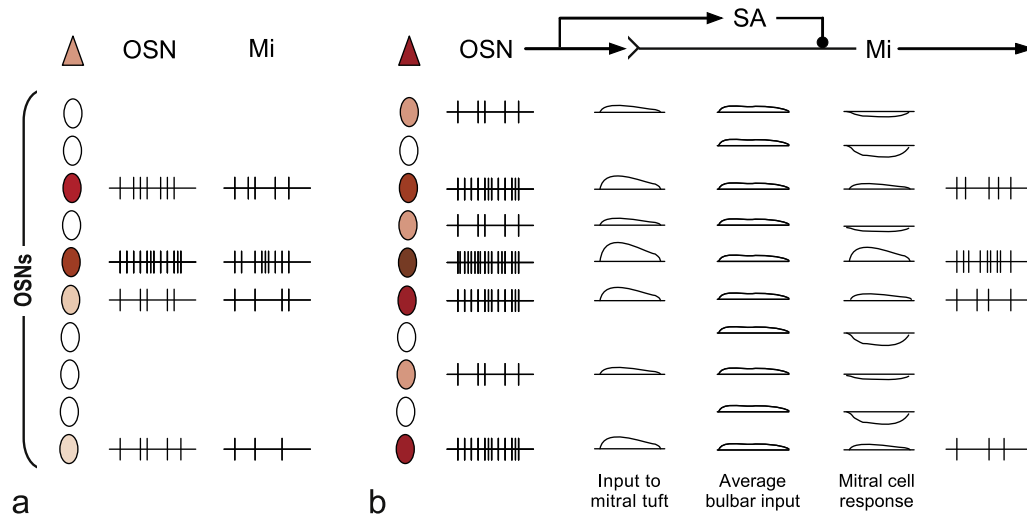

Figure 4 Normalization of odorant concentrations by glomerular-layer processing. (A) At the lowest odor concentrations, for sake of argument, the spatial pattern of activity among mitral cells (Mi) may largely reflect the pattern of activated glomeruli, in turn reflecting presynaptic olfactory sensory neuron (OSN) activity (activation profiles of bulbar interneurons not shown). (B) When higher concentrations of the same odor are presented, increased ligand–receptor binding evokes both stronger activation of sensitive OSNs and the recruitment of additional OSNs expressing lower affinity receptors into the activated ensemble, broadening the primary representation (column 1, OSN). This intensified and broadened OSN activity evokes correspondingly broader and more intense excitatory synaptic input to mitral cell dendritic tufts (directly and also indirectly via ET cells; column 2) as well as to periglomerular cells (not depicted here; see Fig. 3) and superficial short axon cells (SA). Short-axon cells project broadly (laterally) and nonspecifically across the glomerular layer, such that the SA population as a whole delivers a rough average of total bulbar activation (column 3) as inhibition onto all ET and mitral cells. The functional outcome of this computation is to normalize the afferent activation at each glomerulus to the mean bulbar activity level, resulting in a relational mitral cell representation that is tolerant of concentration changes (column 4, Mi). This normalization generates relatively concentration-independent representations of odor quality at the level of mitral cell output, presumably facilitating the recognition of odors irrespective of intensity (column 5; compare with A).
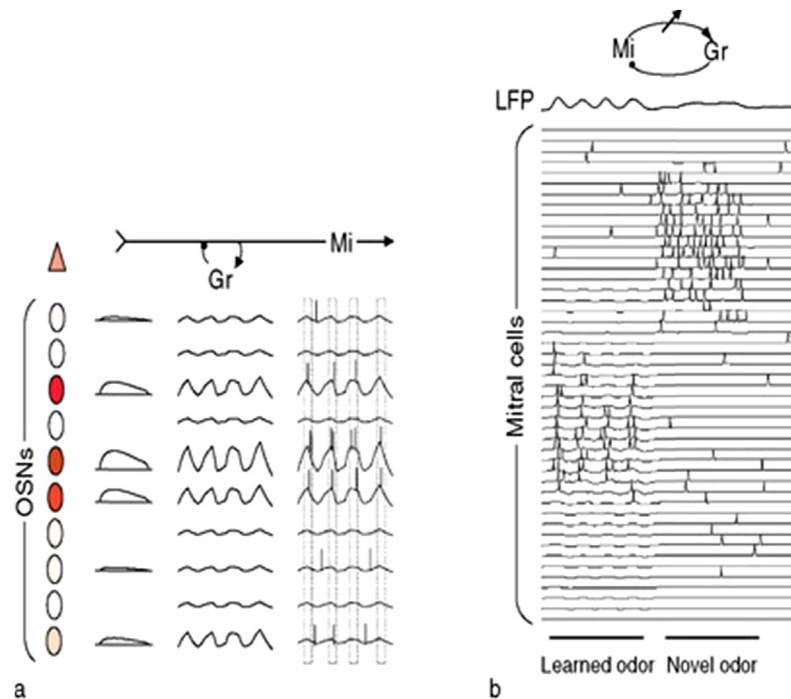
Figure 5 Synchronization of mitral cell firing. (A) The timing of mitral cell (Mi) action potentials is shaped by bulbar computations. Intrinsic subthreshold oscillations within mitral cells as well as recurrent synaptic interactions among mitral and granule cells (Gr) can regulate spike timing so as to regulate the synchronization of spiking activity among mitral cells. Mitral cells receive odor-specific patterns of afferent input excitation from olfactory sensory neurons (OSNs; column 1); activated mitral cells in turn activate granule cells. Due to the excitatory–inhibitory feedback interactions among mitral and granule cells, as well as between the olfactory bulb and higher olfactory cortices, rapid field potential oscillations in the olfactory bulb (column 2) are evoked by olfactory input as well as by the process of active sampling. The regular, synchronized delivery of inhibitory synaptic inputs onto mitral cell lateral dendrites interacts with the differing levels of input activity among mitral cells to shape the timing of evoked action potentials in mitral cells (column 3). Groups of activated mitral cells thereby form synchronized assemblies representing the odor stimulus presented. (B) Due to activity-dependent synaptic plasticity between mitral and granule cells, bulbar oscillatory dynamics in response to learned or behaviorally relevant odorants can be enhanced with respect to those evoked by novel odorants. Here, computational modeling output showing mitral cell response profiles to two different odorants (activating different subsets of mitral cells) is depicted. Owing to the pattern of altered synaptic weights between mitral and granule cells induced by prior learning, the odorant previously learned by the model olfactory system exhibits coherent oscillations in mitral cell membrane potentials and in the local field potential (LFP), as well as in more sharply synchronized mitral cell spikes. The novel odorant evokes comparable levels of mitral cell spiking, but this activity is less able to induce coherent oscillations and synchronize spike timing among mitral cells.

mitral cell will evoke action potentials in response to a given odorant presentation. The timing of mitral cell spikes, however, is influenced by the intrinsic dynamics of the olfactory bulb as well as by the dynamics of feedback from other brain areas. Both intrinsic mitral cell membrane properties and network dynamics between mitral and granule cells are believed to influence mitral cell spike timing; indeed, synchronization of the spikes produced by those mitral cells most responsive to a given stimulus can further refine the representation of this stimulus and alter its capacity to drive activity in postsynaptic neurons (Fig. 5A). Furthermore, due to activity-dependent synaptic plasticity between inhibitory granule cells and mitral cell lateral dendrites, the degree of synchronization as well as the identities of the neurons most tightly synchronized with one other can be regulated dynamically (Fig. 5B). Indeed, mitral cell synchronization properties depend strongly on ascending cortical and neuromodulatory inputs, suggesting additional mechanisms by which odor representations can be modified by centrifugal factors.

Odor–Background Segmentation and Mixture Interactions

Olfactory segmentation problems arise when two or more odors from different sources are present at the same time. The basis of the problem is that there is no a priori reason why the multitude of odorous molecules that together comprise one natural odor, such as the scent of oranges, should be processed as a single complex stimulus, while other odorous molecules, present at the same time, do not contribute to the perceived scent of the stimulus. The outcome is that an orange can be identified by scent largely irrespective of whether it is being smelled while standing on a beach, in a perfumer's shop, or on a factory floor. The core mechanistic problem is
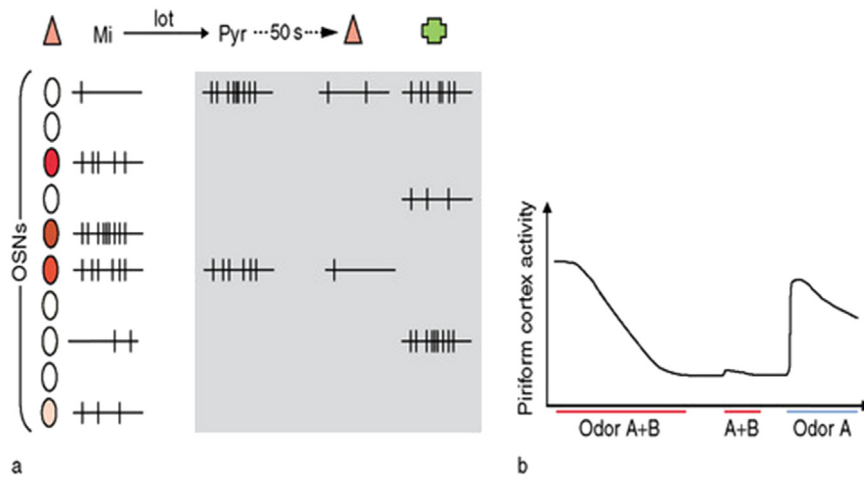
Figure 6 Odor–background segmentation in the piriform cortex. (A) Mitral cell (Mi) axons project from the olfactory bulb via the lateral olfactory tract (lot) to synapse with pyramidal cells (Pyr) in the piriform cortex. Piriform pyramidal cells and olfactory bulb mitral cells have receptive fields for odorants that are comparably broad. The excitatory synapse between mitral cells and piriform pyramidal cells undergoes short-term synaptic plasticity when an odorant is continuously presented for roughly 50 s, suppressing the pyramidal cell activity previously evoked by that odorant. Due to internal computations within the piriform cortex, this adaptation to prolonged odor stimulation is relatively specific to the broad, complex activity patterns evoked by configural odors rather than to each elemental chemical feature (odotope). Hence, even pyramidal cells that are fully adapted in response to a background odor still remain responsive to novel odors. No topological specificity is retained between mitral cells and piriform pyramidal cells; the alignments of pyramidal cell spike trains in shaded regions do not correspond to the rows illustrating connectivity between olfactory sensory neurons (OSNs) and their cognate mitral cells. (B) Prolonged presentation of a binary odorant mixture (A + B) leads to adaptation of evoked activity in piriform cortex due to suppression of mitral cell synaptic inputs. Subsequent presentations of that mixture elicit minimal responses. However, presentation of a single component (A) of this binary mixture again evokes increased activity, demonstrating that pyramidal cell adaptation is specific to complex, configural odors.

how the broad profile of activated receptors can be correctly deconstructed into groups or patterns associated with given stimulus sources, even when the arrays of odorant receptors sensitive to each stimulus source overlap substantially.

Odor segmentation problems can be classified into two categories: odor–background segmentation, in which a novel odor is detected and identified in the presence of a preexisting odorous background, and mixture segmentation, in which multiple odor stimuli are detected at roughly the same time. Recent electrophysiological studies have shown that odor–background segmentation can be achieved at the level of second-order sensory synapses. Synaptic interactions between olfactory bulb mitral cells and pyramidal cells in the piriform cortex undergo a form of short-term plasticity which results in the suppression of information transmission between these two structures after approximately 50 s when an odorant is continuously present. Consequently, piriform pyramidal cells rapidly suppress their responses to background odorants, but remain excitable in response to novel odorants (Fig. 6A). Interestingly, this adaptation of pyramidal cell responses is specific to configural odors, rather than to odor elements, such that responses to the individual elements of a fully adapted odor mixture, if presented separately, are not suppressed to the same degree as is the response to the mixture (Fig. 6B). This clearly suggests a regulation of synaptic suppression that is more complex than simple feed-forward desensitization, and that is deployed with reference to a preestablished configural odor representation, or odor template. This, of course, begs the question of how such configural odor representations are constructed and retained at this level.

Simultaneous-onset mixture interactions pose a substantially more complex computational problem. While mixture processing has been studied at the perceptual level using intramodal blocking, overshadowing, and comparable behavioral paradigms, to date there is no satisfactory model of how simultaneously presented odor mixtures can be segmented and identified. Computational efforts toward addressing this problem have relied upon built-in cues specifying the odor source to which a given response element belongs, avoiding the heart of the problem. Indeed, current theories suggest that this problem may not be solvable by feed-forward properties alone, but rather may rely critically on learned, preexisting odor templates. If correct, this suggests an essential role for associative memory and network attractor dynamics, not only in olfactory learning as traditionally construed, but also in the very process of odor identification.

Odor Binding and Associative Memory

Binding among the multiple features of any given odor stimulus has been proposed to occur in the piriform cortex. Briefly, the ensemble of activated mitral cells that fire quasi-synchronously in response to a given odor stimulus activates a corresponding population of pyramidal cells. Whereas, at the level of the olfactory bulb, individual mitral cell responses predominantly reflect the

elemental chemical features of odorant molecules, the combined representations of these features are integrated at the level of piriform cortex and are durably associated with one another via long-term synaptic plasticity across the pyramidal cell network. The feedback excitatory "associative fibers" that mediate these patterns of association are prominent features of piriform cortex, along with feed-forward and feedback inhibitory pathways. Indeed, the piriform cortex has long been modeled as an autoassociative memory network capable of learning odor representations and later reconstructing these learned representations from partial or degraded inputs, while also excluding unexpected or spurious additional inputs, a property known as pattern completion (Fig. 7A–C). While considerable work remains to be done in this area, it is likely that the circuitry of piriform cortex is essential to the construction of potentially meaningful, configural odor representations.

Forming discrete, identified sensory objects is traditionally considered necessary before such objects can be associated with a contingency such as reward or punishment. In the orbitofrontal cortex (a multimodal sensory cortex which receives direct input from the piriform cortex as well as from structures associated with other sensory modalities), neurons can be activated by odor presentation, but their response properties depend substantially less on physical stimulus attributes and more on the learned,
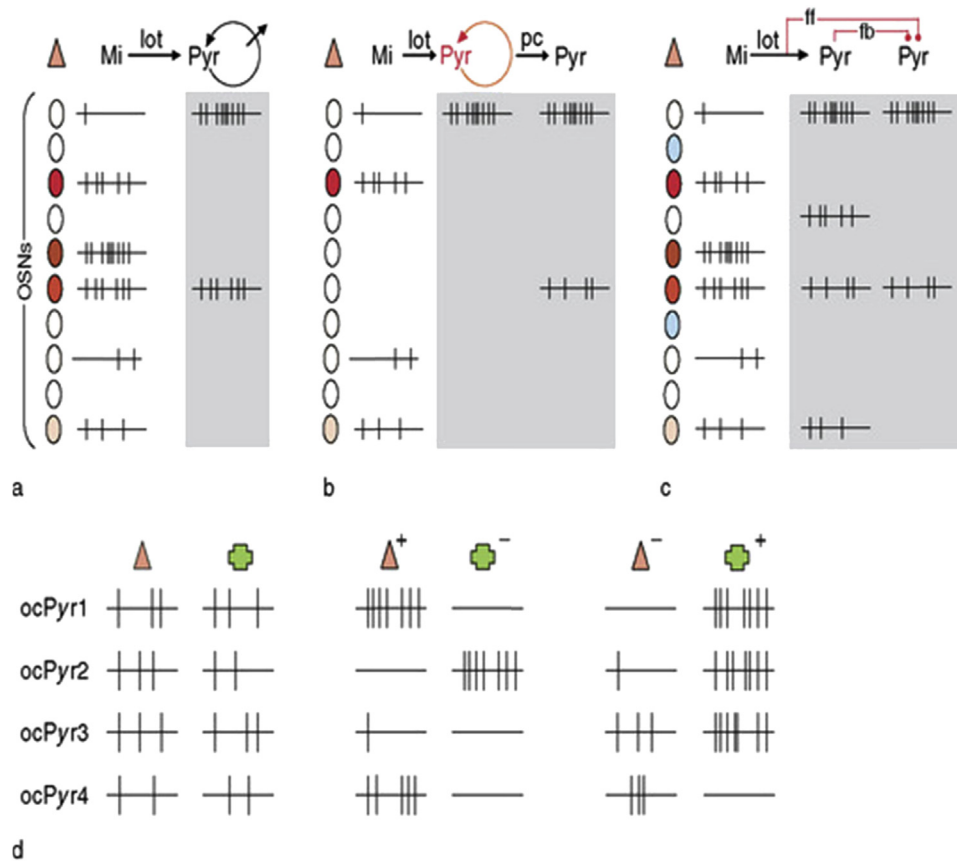

Figure 7 Associative memory and reward associations. (A) The highly interconnected association fiber network of the piriform cortex is thought to underlie learned associations between the elements of odor stimuli, generating and imprinting the patterned representations of complex odors. During the presentation of a rewarded odor stimulus, excitatory associative synapses from mitral cells (Mi), arriving via the lateral olfactory tract (lot), are strengthened among those piriform pyramidal cells (Pyr) responsive to that stimulus. No topological specificity is retained between mitral cells and piriform pyramidal cells; the alignments of pyramidal cell spike trains in shaded regions do not correspond to the rows illustrating connectivity between olfactory sensory neurons (OSNs) and their cognate mitral cells. (B) Upon subsequent presentation of the same odor, even if a subset of the normally activated pyramidal cells is not activated by the afferent inputs, associative circuitry within piriform cortex can perform pattern completion (pc), recreating the complete odor-specific activity pattern in pyramidal cells. (C) Other piriform circuitry incorporating feedback (fb) and feed-forward (ff) inhibitory interneurons can perform the complementary operation, reducing noise in the representation by suppressing pyramidal cell activity extraneous to the learned activity pattern. Both pattern completion and noise reduction are important for the robust comparison of noisy and variable stimulus representations with the memorized patterns of previously encountered stimuli. (D) Pyramidal neurons in orbitofrontal cortex (ocPyr) can be responsive to olfactory stimuli, but their responses are primarily dependent on learned associations and context. Most orbitofrontal pyramidal neurons change their responses to an odor stimulus depending on its predictive properties (e.g., for a reward, or even for the absence of a reward in a context where reward is associated with other odor cues). Weak responses are depicted in response to two novel odors (left-hand pair of columns). After both odorants are used in rewarded odor discrimination training, with one predicting reward (+) and the other predicting no reward (−), the responses of orbitofrontal pyramidal cells to either odorant are durably altered (middle pair of columns). After reversal training, in which each odorant is associated with the opposite contingency, orbitofrontal responses to these odors are again modified (right-hand pair of columns).

expected contingency of the odor (Fig. 7D). Hence, orbitofrontal odor responses may be better described as representing expectation, or the acquired meaning of an odor stimulus, rather than as coding for odor identity in the physicochemical sense. Reciprocal orbitofrontal projections to anterior piriform cortex further suggest that these learned, configural representations may be used dynamically to shape cortical responses to odors.

Learning, Experience, and Neuromodulation

The neural activity elicited by odorant stimulation depends increasingly on experience, behavioral relevance, and the motivational state of the animal as the representation progresses centrally from the primary sensory epithelium, factors that are thought to be mediated by centrifugal projections into these olfactory structures. Indeed, most olfactory areas interact with one another and with deeper, multimodal cortices via feed-forward and feedback connections, and also receive neuromodulatory inputs from the horizontal limb of the diagonal band of Broca (cholinergic), the locus coeruleus (noradrenergic), and the raphe nucleus (serotonergic). These cortical and neuromodulatory inputs dramatically influence neural activity patterns and the dynamics of olfactory processing within the olfactory cascade, and presumably mediate these experience- and state-dependent contributions to sensory representations.

Conclusion

The promise of the olfactory system as a model for understanding sensory processing as a complex system—from physical stimulus properties to cognitive object—is becoming increasingly clear. The peripheral processing of odorant stimuli in the olfactory epithelium and olfactory bulb is predominantly oriented toward adequately sampling the volatile chemical environment. Olfactory neuronal properties and bulbar circuit architecture are adapted to the physical and statistical properties of chemical stimuli and serve to mitigate the ambiguities and limitations inherent in the sensory transduction of stimuli in this modality. Impressively, orbitofrontal cortical representations of the acquired meaning of odors are only three synapses removed from the primary sensory representation, suggesting a singularly compact and tractable cascade of neural representations that may provide unique opportunities to understand how afferent sensory inputs are integrated with the neural representations of memories and behavioral state in order to create meaningful percepts. While the problem must not be oversimplified—for example, mitral cells also project to the cortical amygdala, the subcortical olfactory tubercle, and a series of medial cortices, and piriform and entorhinal cortical circuitry is considerably more intricate than discussed herein—the olfactory system remains a particularly attractive target for research in neural systems.

Further Reading

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