gene encodes a guanylyl cyclase isoform similar to the enzyme controlling the cGMP level in vertebrate photoreceptor cells and is required for normal chemotaxis mediated by the ASE and AWC sensory neurons. Because a mutation in the *daf-11* gene causes a similar phenotype as in *C. elegans tax-2/tax-4* mutants defective in the expression of the cyclic nucleotide channel in AWC neurons (*44*), it has been suggested that a guanylyl cyclase–mediated modulation of the cGMP levels might act on the TAX-2/TAX-4 channel.

Conclusions

Cross-phyletic comparisons have revealed striking similarities concerning the organization of olfactory systems as well as the physiological principles and molecular elements underlying the process of chemical sensing. The existence of phylogenetically conserved strategies for detection and discrimination of a vast array of odorants seems to reflect the evolutionary answer to the common challenge imposed by the nature of these chemosensory stimuli. Thus, considering the evolutionary conservation of chemosensitivity, comparative studies using the advantage of invertebrate model organisms should continue to help elucidate fundamental mechanisms of olfaction.

The recent progress in unraveling the molecular machinery mediating the chemo-electrical transduction process in nematodes and arthropods, and in particular the discovery of odor receptors in invertebrates, opens new experimental avenues for deploying the advanced genetic tool kits available in *C. elegans* and *Drosophila melanogaster*. These advances may also initiate studies of olfaction in insect species which damage crops or transmit human diseases. These insects depend heavily on the sense of smell to find food and mates. Detailed knowledge of the relevant receptor types and transduction elements would facilitate the efforts to find compounds that interfere with the insect olfaction and may eventually allow control of insect pests without employing neurotoxic compounds. Thus, research efforts in the field of invertebrate olfaction not only provide greater insight into the fundamental principles of how organisms decipher the world of odors, but also have important ecological and economical potentials.

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REVIEW

A Systems Perspective on Early Olfactory Coding

Gilles Laurent

This review critically examines neuronal coding strategies and how they might apply to olfactory processing. Basic notions such as identity, spatial, temporal, and correlation codes are defined and different perspectives are brought to the study of neural codes. Odors as physical stimuli and their processing by the early olfactory system, one or two synapses away from the receptors, are discussed. Finally, the concept of lateral inhibition, as usually understood and applied to odor coding by mitral (or equivalent) cells, is challenged and extended to a broader context, possibly more appropriate for olfactory processing.

The recent wealth of behavioral (*1–3*), genetic (*4*), molecular (*4–7*), physiological (*8–10*), mapping (*11–16*), and theoretical (*17*) studies on the olfactory system makes olfactory research a most dynamic area in modern neuroscience. This mix of scientific cultures has, however, also produced a sometimes confusing picture of what olfactory coding is about. The relevance for coding of neural placement and neural identity, for example, often is intermixed (*18*), and the methods used to estimate neural responses are so varied that a synthesis of all available data is sometimes difficult. Basic concepts useful to study olfactory coding are thus first briefly reviewed.

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Perspectives on Sensory Coding

Studying a neural code requires asking specific questions, such as the following: What information do the signals carry? What formats are used? Why are such formats used? Although superficially unambiguous, such questions are charged with hidden difficulties and biases. Whereas Shannon and Weaver (*19*) developed information theory to quantify communication through noisy channels, neuroscientists have found that brains do more than just convey information about the world. Sensory circuits evolved to detect selective patterns relevant for survival; they also create qualities that do not exist outside of the brain. Hence, brain codes can be studied from many different perspectives.

A physicist, for example, will look for external features about which neural responses can inform her. In olfaction, these features might be chemical species, chirality, concentration, location, stationariness, or rate of encounter. This approach makes no assumption about the brain. It simply explores the effects of the physical world on neurons.

A neuroethologist or psychologist, by contrast, starts with the animal's viewpoint. Through studies of behavior, he determines what the animal cares about. For example, rather than caring about the molecular composition of an odor, an animal may want to identify a mixture as a specific object with particular relevance. If so, odor representation or encoding might emphasize grouping (pattern recognition) rather than analysis (segmentation). The underlying codes should reflect such perceptual biases. The study of perception also reveals qualities, such as color in primate vision, that cannot be predicted from first principles. For example, a red patch can still look red under illumination conditions such that it reflects more short than long wavelengths (*20*). This constancy, the perception of redness, is a retinal and brain construct, not a property of the world. Such knowledge is needed to decipher and understand neural codes. In olfaction, hedonic valence is a concept often discussed; however, its physiological underpinnings are largely unknown. Nothing in the physical world indicates whether an odor is pleasant or not to a given animal. What features of neural activity, if any, are common to good odors? Do bees or pigs have a richer set of such categories, foreign to humans? In short, sensory coding can be studied from the outside (information in a classical sense) or from the inside (meaning). Both approaches are needed.

An engineer has yet a different viewpoint, often focusing on cost and efficiency. These constraints, which are real for a hardware designer, are tricky when one is considering biological codes. The notion, for example, that energetic cost should be minimized (*21*)—a code should favor low total firing (sparseness) because pumps and other homeostatic devices are costly—must be weighed against the animal's ultimate goal, which is to pass on its genes, rather than simply to cut energy losses. Efficiency is relative: It requires the definition of a goal. A code might be efficient from the point of view of bandwidth and speed, but not necessarily for memory storage or recall, because of biological constraints on neurons and synapses. Because olfaction is so closely associated with memory (*22*), some aspects of the early codes for odors (one or two synapses away from the receptors) may result from such later or higher constraints. Neural codes thus owe as much to the animal's needs as to the physics of the external world.

Sources, Channels, and Decoders

To understand coding, the format and information-carrying features of signals transported from a source to a receiver must be examined. Although the approach is clear when applied to traditional communication channels (*19*), it is fuzzier when applied to brain circuits.

Signals. Neurons signal through transmembrane voltage changes—in most cases, action potentials. As far as we know, all information carried by one (spiking) neuron is conveyed by some aspect or aspects of its spike discharge (*23–25*). The study of coding thus requires an estimate of the participating neurons' discharge. In this regard, no technique is perfect. Electrophysiological recordings can provide direct spike times from identified cell types, but simultaneous samples from many neurons are rare. Indirect methods, such as population calcium or voltage imaging, can provide large-scale estimates of activity (*12–16*), but the source of the signal (incoming terminals, intrinsic neurons, outgoing fibers, a complex mix of the above) or the relation between signal and firing rate modulation is often inaccessible. More indirect methods, such as mapping of gene expression (*26*), are even less informative about neuronal activity, although they provide invaluable data on connectivity and its functional implications. Neural coding and decoding are ultimately carried out by neurons: Ideally, the signals collected should thus be converted back into action potentials.

Receiver and decoder. Establishing a code requires showing that the receiver actually decodes the incoming signal. Most studies of neural codes ignore this requirement because it is, at present, very hard to fulfill; the assumption usually is that, if information about x can be decoded by an observer from a family of spike trains, this information must be used similarly by downstream circuits. In addition, because projections between areas are often multiple and reciprocal, the notion of receiver—and thus of code—becomes less well defined the farther the neurons are from the periphery. If a cell population sends projections to several areas, it cannot be deduced that each one of these areas decodes incoming signals in the same way. Cochlear afferents in birds, for example, each bifurcate to two brainstem nuclei with different selective properties. From a spike train, one nucleus extracts information about relative timing, whereas the other selects discharge intensity (*27*). Codes are thus defined by the receivers and can be multiplexed on the same channel. This is relevant for olfactory systems because olfactory perception solves problems whose solutions appear mutually exclusive, such as generalization and fine discrimination. Signals carried by mitral cell axons might contain coexisting codes, processed differently by specialized target circuits or by single targets whose state can be adjusted for one or the other task. Deciphering codes can thus be made easier by studying the decoders rather than the signals. Defining a source is equally important. The deeper the source, the more it is affected by feedback and parallel channels, and the less defined the information channel becomes. It is thus not clear whether the traditional concept of code is useful beyond those well-defined, often peripheral, domains.

Spatiotemporal Codes

Given a defined source and receiver, what forms could codes take? Because the relevant signals are spikes produced by individual neurons over time, any neural code is spatiotemporal. In this context, however, spatial and temporal are commonly (and confusingly) used to carry different ideas: A spatial code is usually really meant to be an identity code and not so much one in which neural position matters; conversely, a temporal code is usually implied to be one in which spike timing does matter. Can these working (and still evolving) definitions be clarified?

Space. Only if position plays an intrinsic coding function should a code truly be called spatial. Short of this, it is an identity code, in which information depends on which neurons are active rather than where they lie. A code can be truly spatial because of intrinsic features pertaining either to the encoding or the decoding of the message. In the retina or the skin, for example, receptor position is an intrinsic component of the encoding of external space. More interesting is the encoding of sound frequency in vertebrate hearing. This code is spatial for cochlear hair cells because each hair cell's frequency tuning depends on its mechanical resonance, which depends on its position along the basilar membrane. Neural position can be important also for decoding, as in sound localization circuits (*27*). There, input coincidence depends on physical delay lines (axons), such that a neuron's

depth in a brain nucleus determines the lengths of incoming axons and thus, the distribution of delays that it is selective for. In these examples, modifying neuron position while keeping connections intact would misinform the receivers. Few such spatial codes are known. Most known brain codes appear to rely on neuronal identity. Do ordered olfactory receptor projection "maps" in the olfactory bulb (OB) (*4, 26*) then play an intrinsic role in olfactory codes or do they reflect, for example, optimized developmental instructions or cabling solutions? As yet, no convincing hypothesis or data suggest an intrinsic role for position in odor coding (whether for identity, concentration, or position in space) in the OB. Although the characterization of projection maps will undoubtedly help us decipher odor representation, codes at this level of the olfactory system, as far as is known, seem to rely on information contained in both neural identity and interneuronal timing. Position may play a role in the periphery, that is, in the encoding of short-range odor location using gradients along receptor arrays. The partial disorientation of ants on a trail after their antennae have been crossed, for example, strongly suggests that ants carry out bilateral comparisons (*28*). The underlying mechanisms are as yet unknown.

Time. If coding is considered one neuron at a time, coding variables accessible to this neuron are spike time (relative to an event), interspike intervals, or higher-order features such as sequences of interspike intervals. Each variable could, on its own, encode something about the stimulus: A downstream decoder, depending on its properties or those of the circuit in which it lies, might detect from the incoming axon the occurrence of a spike, an instantaneous or sustained firing rate change, or a given interspike interval. Traditional views of neural coding generally oppose mean rate codes to temporal codes. Mean rate interpretations, however, are often simply a consequence of experimental conditions in which a constant stimulus is sustained for a long time. Rate codes can in fact take many shades, depending on the length of the integration window chosen to compute firing rate. Ideally, such an integration window should match the duration over which the stimulus remains constant. If a stimulus changes rapidly, the computed rate may change rapidly also. Hence, what really matters to identify the temporal nature of a code is the determination of the reliability and temporal resolution of the encoding and decoding elements, as well as the conditions under which these features can be adapted. If coding is now considered over many neurons at a time (downstream decoders generally use signals from many upstream sources), the coding variables expand to include relational features between incoming spikes (*23, 24*). Those relational features can be synchrony or more complex temporal correlations, such as delays (*29, 30*), coherent periodic activity (*8, 30, 31*), or coherent waves of activation (*15*). These may be described as correlation codes. Here also, the real task is to define the temporal resolution of the elements, the higher-order features necessary to reconstruct or identify the stimulus (for example, a sequence of spikes across a neural ensemble), and ultimately to show that those features are required for the animal's behavioral performance.

Encoding of time and temporal encoding. Temporal codes can be viewed in different contexts (*24*): In one, temporal neural discharges simply follow the temporal variations of the stimulus, and spike timing thus provides information about the occurrence of a change in the stimulus with a certain accuracy (*24, 25*). In olfaction, this type of coding of a time-varying signal is relevant to tasks such as tracking pheromone plumes (*32*). Specialized neurons in the macroglomerular complex of moths—the analog of the vertebrate accessory olfactory bulb—can follow 100-ms-long odor pulse delivery at rates of a few hertz (*33*) and could thus inform the animal of its course in and out of a plume. A different, more subtle, context is one in which temporal firing patterns do not result directly from the time-varying features of the stimulus. Rather, such patterns are a product of brain circuit dynamics. If they are reliable, these temporal patterns can then encode nontemporal features of a stimulus. In olfaction, such temporal encoding has long been suggested (*8–10, 34*) and recently has been shown to be relevant (*30, 35, 36*): In the insect antennal lobe (AL)—the analog of the vertebrate OB—stimulus identity can be deciphered from the identity of the neurons that fire together within a ±5-ms window and from the temporal evolution of this synchronized assembly at each cycle of a 20-Hz synchronized and distributed oscillatory pattern (*30*). The relevance of synchronization for decoding by downstream neurons and for fine behavioral odor discrimination was demonstrated directly (*35, 36*).

The Nature of Odors

Odor space. Natural odors, such as flower fragrances, are often mixtures of many molecules in relatively specific ratios. Because many thousands of volatile chemicals exist, the number of possible mixtures is staggeringly large. Are all possible odors meaningful? Natural scenes in vision may be used as an analogy (*37*); imagine an image of n by n pixels that can each independently vary in intensity. The state space (all attainable states of the system) of possible images has n^2 dimensions, and each dimension represents the intensity of one pixel. The vast majority of possible random images (noisy canvases) in that space, however, will have no meaning for the higher visual system (*38*), which suggests that vision evolved to process a very small subset of all possible visual stimuli. This must be reflected, many believe, in the structure and operations of the visual system, including the retina. Is olfaction similar? Although the number of natural odors surely is smaller than that of all possible odors, little seems to prevent randomly synthesized odors from being perceived as distinct or meaningful. The perfume industry makes its living from this fact. In other words, although the higher visual system in most cases will treat two random dot images as two indistinguishable objects, the olfactory system appears able to assign a specific identity, or value, to any (or a great number of) random component mixtures. This synthetic (*39*) property makes olfaction very special and suggests that its codes may differ from those in vision: The olfactory system seems designed to accommodate the unpredictability of the olfactory world. However, the statistics of natural odors have, to my knowledge, not yet been explored as have those of natural visual scenes (*40*). Such studies appear very important, but how should one, for instance, calculate the redundancy of a natural odor? This might be possible by studying the extent of overlap between receptor responses, as is done with color vision. Note that this synthetic property of olfaction does not exclude the existence of very specialized receptors or pathways adapted to each animal's ecological niche, such as for the detection of conspecifics or food for specialists (*41*). I focus rather on the broader, nonspecialist systems, across which coding strategies may be transferable.

The physics of odor signals, integration windows, and bandwidth. Whereas the visual and auditory systems process signals whose propagation in the world is predictable, olfaction must deal with turbulent flow of the medium (*32, 42*). A passive detector placed away from a source experiences intermittent odor pulses lasting from a few milliseconds to more than a second, with interpulse intervals between several 100 ms and minutes. Information about source size, location, and distance can thus be found in the statistics of pulse and interpulse durations sampled over moderately short periods and in the variance of concentration fluctuations (*42*). Mean concentrations are not necessarily the most informative measurements. Many odor-driven behaviors, such as the search for a mate in moths, depend on the analysis of chemically predictable (genetically programmed) but physically complex signals that must often be intermittent to allow detection and orientation (*32*). In these systems, odor identity is decoded by highly specialized and sensitive neurons, and the temporal structure of odor fila-

ments can be followed quite accurately (*33*).

Many odor identification tasks, however, will take place in headspace, that is, very close to the source—inside a flower for a bee or against a fire hydrant for a city dog—and thus provide different sampling opportunities. In addition, odor sampling is usually not passive. Many vertebrates sniff, and many arthropods, in which olfaction is not coupled to breathing, flick their olfactory appendages on detecting an odor. These behaviors dictate the duration (hundreds of milliseconds to seconds), number, and frequency of odor samplings. Moreover, the elements of the perireceptor milieu (external sensory structures, mucus, odorant binding proteins, and so on) probably act as temporal filters on quickly varying signals (*43*). The integration window for odor processing must therefore take into account the physics and chemistry of the stimulus and the sampling environment, as well as the sampling behavior of the animal. Olfactory codes may thus differ greatly for the many olfactory tasks an animal must solve.

Imagine reading this article with your nose. Although possible in principle (one might learn to assign odors or concentrations to words or letters), the rate at which information could be conveyed would likely be low. Olfaction is poor at following many or rapidly varying signals. It is a low-bandwidth sense. Whereas a fly's or a primate's retina must update its signals every few tens of milliseconds, thus imposing very specific temporal constraints on the retinal codes (*23–25*), odor sampling usually occurs on a much slower time scale. This feature enables the use of time as a dimension for odor identity codes.

Peripheral Odor Coding

Convergence. Recent studies in mammals established that olfactory receptor neurons (ORNs) that express the same odorant receptor protein all converge precisely to the same two glomeruli in the OB (*4, 26*). The convergence ratio from generalist receptors to the OB or AL principal neurons is about 1000:1 in rodents (*26, 44, 45*) and 100:1 in many insects (*46*). What could convergence mean for odor codes? A first role is perhaps to heighten the sensitivity of their targets so as to ensure detection. A second might be to increase signal-to-noise ratios by averaging out of uncorrelated noise. Because ORNs of the same type are distributed randomly over wide zones of the nasal cavity (*5*), local odor fluctuations may be uncorrelated over space and thus, in principle, exploited to reduce input noise by postsynaptic summation. Field potential recordings from the nasal epithelium of some vertebrates, however, reveal synchronized oscillatory activity (*8*), whose origin appears to be local (*47*). The function of such peripheral synchronization, which does not exist in all noses, remains unknown, and its potential influence on noise processing needs to be determined.

Specificity. Molecular studies also suggest that ORNs each express only one type (or a small number) of OR genes (*4, 5, 26*). This suggests that the odorant specificity of an ORN might be determined by that of its OR proteins. Given the known specificity of other heterotrimeric GTP-binding protein (G protein)–coupled receptors in the brain, ORN responses also might be specific. Before considering the data, several important issues must be noted: Binding specificity depends on concentration. To be functionally relevant, tests of ORN specificity should be in odor concentration ranges as defined by behavioral performance (neither too close to threshold nor too high) and in physiological conditions of odor access to the receptor (normal perireceptor milieu). From a coding perspective, interesting concentrations are the highest ones in which behavioral performance remains specific, because one may observe a mismatch between receptor and behavioral specificity, implying nontrivial population decoding. Second, because odor sampling by an animal is usually repetitive, receptor specificity should probably be measured both in the sensitized and adapted states. Third, specificity of odor or binding (or both) is very hard to define precisely, for no one knows yet what odorant receptors recognize. Operational definitions are presently based on chemical categories, which may turn out to be inappropriate. Fourth, what ultimately counts from a coding perspective is the spike output of an ORN. To quantify ORN specificity, one thus really needs to know how ORN spike trains are decoded by the brain. With these caveats, what do the data say? A recent in vivo overexpression study suggests that one olfactory receptor gene might, under these conditions, confer relative specificity, as assessed by nasal epithelium electrical measurements (*7*). Calcium imaging in vitro (*6, 13*) and electrophysiological recordings in vivo (*48*), however, indicate that individual ORNs usually respond to many odors, including ones that belong to different chemical classes. These results are consistent with population imaging studies showing that odors (including monomolecular ones) usually activate broad areas of the OB or AL (*12, 14, 16*). In honeybees, the tested concentrations were shown to enable behaviorally specific responses (*49*). These results are also consistent with rat studies showing that odor discrimination remained possible after massive OB lesions (*1, 3*). Odor codes across receptors thus appear to be distributed and combinatorial, and the extent of receptor activation seems to increase with concentration (*12, 14, 16*). Precise odor identification can occur in concentration ranges in which receptor activation is not highly specific. These results do not exclude the coexistence of very specific ORN types, with specific adaptive roles (*41*).

Lateral Inhibition: A Systems Perspective

Signals from ORNs are sent directly to the OB or AL, where they are further processed (*45, 46, 50–52*). OB and AL circuits contain two broad classes of neurons (excitatory projection cells and, for the most part, inhibitory axonless local neurons) (*44, 45*). Because the principal neurons [mitral and tufted (M-T) cells in mammals] have one primary dendrite within one glomerulus or a few glomeruli and because inhibitory neurons (granule cells) contact nearby M-T cells through their secondary dendrites, this connectivity is often interpreted as underlying a form of lateral inhibition to sharpen M-T cell tuning (*50, 52*). This view combining anatomy and function is strongly influenced by what we know about retinal processing (*53, 54*). The spatial receptive field of many retinal neurons can be characterized by a tuning curve shaped as a difference of Gaussian function. The operation enhances edges, that is, amplifies local differences relative to local similarities. This seems useful—the visual world is full of relevant edges (*40*)—and underlies many visual illusions (*54*). A simple transfer of this concept to olfaction is, I argue, unwarranted. First, it is not strongly supported by available data (*51, 52, 55*). Second, it relies on many assumptions that may not apply to olfactory codes. (Many inhibitory cell types and neurotransmitter receptors coexist in OB and AL circuits, so that inhibitory connections can underlie a variety of parallel processes. This section focuses only on fast inhibitory feedback by granule cells or their functional analog in insects.)

The case for. The first argument in favor of lateral inhibition in early olfaction is anatomical. M-T cells do indeed contact granule cells, which in turn contact other M-T cells (*53, 56–58*). One caveat, however, is that M-T cells also inhibit themselves via granule cells (*45, 57*). The relative importance of self- and lateral inhibition is rarely discussed, and the two types of connectivity are sometimes lumped together (*55*), without clear functional justification. The second result, possibly consistent with lateral inhibition, comes from paired mitral or projection cell recordings showing precisely antagonistic responses (*31, 50, 59*). The third comes from work in rabbit OB, indicating that M-T cells' responses can sometimes be described by tuning curves with inhibitory surround (*51, 55, 60*). In these tuning curves, the intensity of a mitral cell response is plotted against one tested chemical feature of the stimulus family (for example, carbon chain length). The local

mechanisms responsible for this inhibitory surround were recently examined (*55*). These results, however, are hard to interpret, for responses were obtained in conditions not ideal for quantification [hand-held odor stimuli, one or two trials (which precluded statistics), undefined response boundaries]. Finally, these experiments did not show detuning after inhibition blockade.

The case against. This tuning curve view of lateral inhibition rests on two unspoken but key assumptions: that information lies in single neuron firing rates, and that a sharp tuning curve is desirable. Both assumptions need to be examined. The first assumption says that information is carried independently by neuron firing rates. Imagine, however, that the decoder of a mitral cell output is tuned to detect higher-order features in the incoming spikes, such as coincidence across many cells, periodicity, delays, or sequences. Olfactory neurons are known to display complex response profiles (*10, 34*) and to synchronize (*8, 9*). Correlation codes have indeed been identified in which information, absent from firing rate measures, can be retrieved from temporal relationships between the spikes of coactivated neurons (*30*). It was also shown that when an odor is presented several times in succession to a locust, principal neuron response intensity decreases as temporal precision increases over the first few trials (*61*). This response evolution is in fact accompanied by an improvement in odor discrimination based on the information contained in the discharge patterns. In other words, strong or naïve responses can be less informative if decoding does not simply rely on rates (*61*).

The second assumption says that sharp tuning curves are better than broad ones. Several computational studies challenge this view for population codes. Without making any assumption about decoding schemes and by simply aiming to maximize mutual information between a stimulus and the response of a neural population that encodes it, it can be shown that optimal tuning curve widths depend critically on the stimulus dimension (*62*). Only for one-dimensional stimuli do narrower tuning curves improve coding by each neuron (*63*). In addition, this conclusion depends critically on the covariance of the noise. If tuning curve sharpening is done by common lateral connections, correlated noise is introduced, counteracting the information gain caused by sharpening (*64*). Sharper curves are thus better only if they are shaped independently.

The second caveat is that the logic of a lateral inhibitory network, if present, is hard to comprehend in odor space. Because mitral cells usually respond to many odors including ones that belong to different chemical groups (*50, 65*), how is proximity along the various odor dimensions determined by the network? More precise predictions need to be made and tested. In the same vein, consider OB anatomy. Although rodent mitral cells send a primary dendrite in a single glomerulus (tufted cells often visit several), their secondary dendrites cover a large area. Indeed, the 20 to 40 mitral cells sharing the same glomerulus send a circular carpet of lateral secondary dendrites that can extend 1 to 2 mm around this glomerulus, that is, directly below tens to hundreds of other glomeruli (*45*). Because of the density and extent of intermixed granule cell projections, mitral cell primary responses are thus exposed to massive numbers of possible influences from what can hardly be called a local neighborhood.

Third, lateral inhibition in vision is interpreted as useful to increase local contrast. For a local contrast to exist, there needs to be proximity and simultaneity (dark pixels close to light ones) or rapid temporal succession (dark pixels rapidly replacing light ones) of different inputs (dark and light pixels). What are the equivalent stimulus features for odors? Moreover, is the olfactory system designed to enhance the separation of two competing stimuli or to fuse them as a third odor? Behavioral data from mammals and honeybees show that complete segmentation of even binary mixtures is difficult. In particular, the detection of one learned odor in a binary mixture is harder if the two odors are similar (*2, 3, 39*) and models built to recreate this effect make explicit use of conventional lateral inhibition (*66*). In these models, lateral inhibition helps rather than hinders generalization from a learned odor to a similar one with the same biological relevance. Hence, although such type of lateral inhibition may indeed be useful for olfactory coding, a convincing naturalistic, behavioral, or computational case remains to be made for its existence.

Finally, experiments by our group on odor responses in insect principal neurons showed that blockade of fast inhibitory feedback via local neurons never evoked a detectable broadening of odor tuning—that is, the unmasking of new odor responses or the strengthening of certain existing responses (*35, 36*). Rather, odor discrimination using the information contained in principal neuron spike trains before and after fast inhibitory feedback blockade was unchanged (*36*). Inhibitory blockade, however, desynchronized activated principal neurons (*58*), causing an impairment of fine behavioral odor discrimination (*35*) and a decrease in information about odor identity recoverable from downstream neurons (*36*). Hence, downstream neurons detect relational aspects of their input. Olfactory coding cannot be studied one neuron at a time or by using rates alone: Information is contained across neuron assemblies that cannot be extracted by simple averaging. Inhibition is therefore important indeed for olfactory coding, but within a framework that differs from conventional lateral inhibitory rules. Rather, inhibition is proposed to be, partly, a mechanism that regulates the complex dynamics of olfactory network responses. We proposed that odor encoding and decoding make explicit use of these dynamics (*30, 35, 36*).

An alternative framework. From a functional point of view, early sensory circuits must, in some way, optimize data formatting (*37, 38, 54*). The existence of bottlenecks (the optic nerve, the lateral olfactory tract, for example) imply the elimination of redundant information. Although odor redundancy is hard to define, inhibition should nevertheless be seen as a potential actor in this optimization process. How should this role be studied in olfaction? First, contrary to their visual and auditory counterparts, olfactory systems are structurally shallow: Cortical and memory systems are only two synapses away from the receptors, and there is no clear evidence for separate functional streams, other than the pheromonal and generalist pathways. Psychophysics reveals that olfaction is a low-bandwidth, synthetic sense, generally favoring global perception rather than segmentation. It seems, therefore, that odor codes might not require the multitude of local processing modules necessary in vision or hearing for details to pop out. Second, when studying early olfactory codes, we must consider the possibility that downstream receivers build their own odor representations from information pooled across sources via operations different from linear averaging. Because correlation codes cannot be deciphered by focusing only on single neurons, response specificity should be seen from the system's, not a single cell's, perspective. In this framework, we view inhibition as a mechanism that builds global specificity not by sharpening individual neurons' tuning curves—the system is not apparently built to decompose—but by shaping population dynamics so as to make global representations specific (*30*) and concise (*61*). In this framework, some single neuron responses to a select set of odors might well look as if they could define a conventional tuning curve. But a great many will not, although lateral inhibitory influences onto them are just as important for global specificity. In short, I believe that lateral inhibition so defined is important and that its contribution to sharpening should be revealed globally rather than locally. In this framework, tuning curves may not be the best way to understand odor codes.

In conclusion, the study of olfactory coding sits at the intersection of several established and evolving areas of modern neuroscience. My goal was not to update many excellent reviews (*26, 44, 65*) but rather to

challenge some conventional views and place this perspective in a broad functional context. In short, traditional concepts transferred literally from the study of other senses may not always be appropriate for olfactory codes. The time seems ripe for combining theories that emphasize global dynamics with experimental approaches that provide cellular and spike time resolution (*9, 30, 36, 67*), as well as behavior.

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