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SMR: 1343/5

EU ADVANCED COURSE IN COMPUTATIONAL NEUROSCIENCE

An IBRO Neuroscience School

(30 July - 24 August 2001)

"The Olfactory System"

presented by:

Christiane LINSTER

Cornell University
Department of Neurobiology and Behaviour
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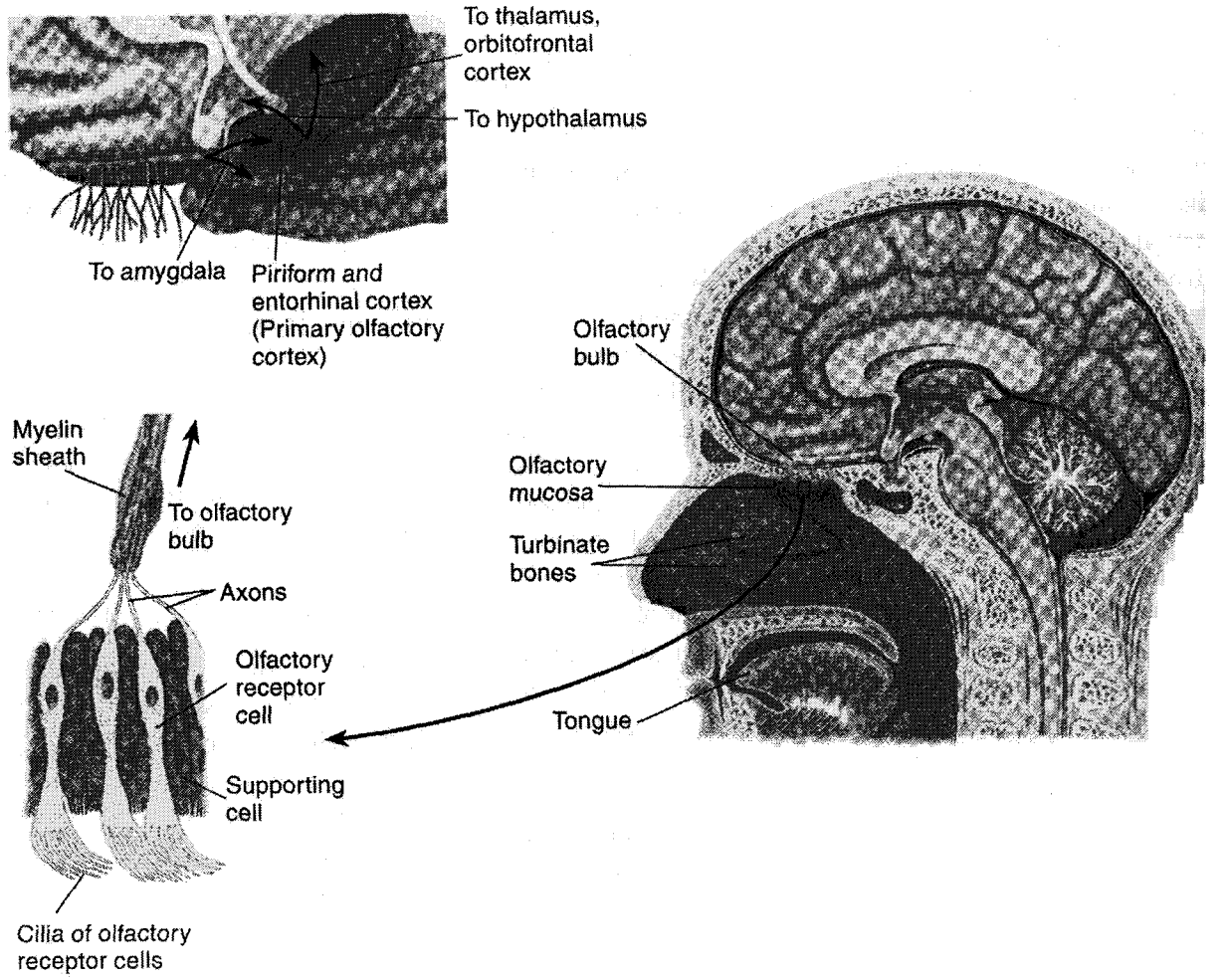
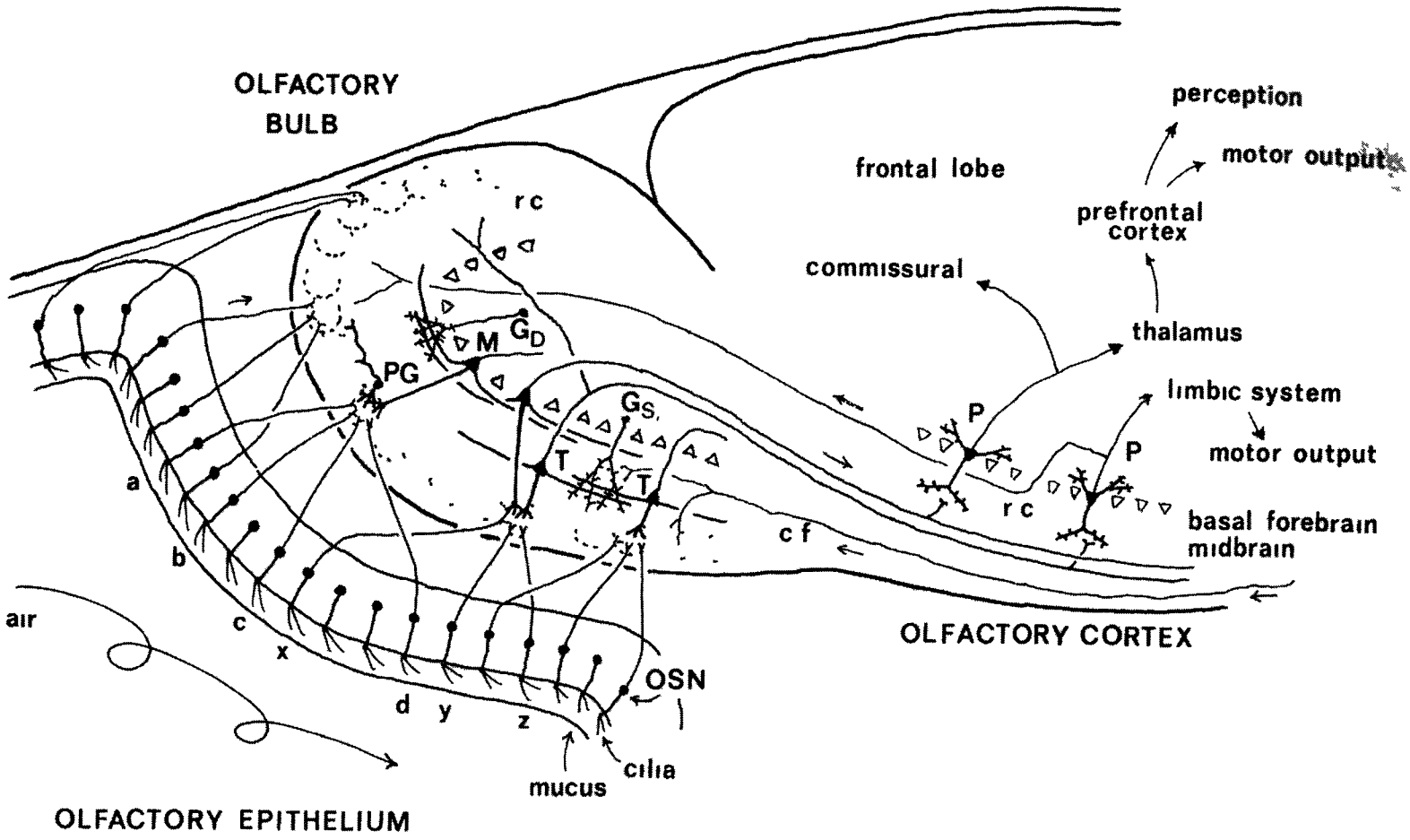
Ithaca, NY 14853
U.S.A.

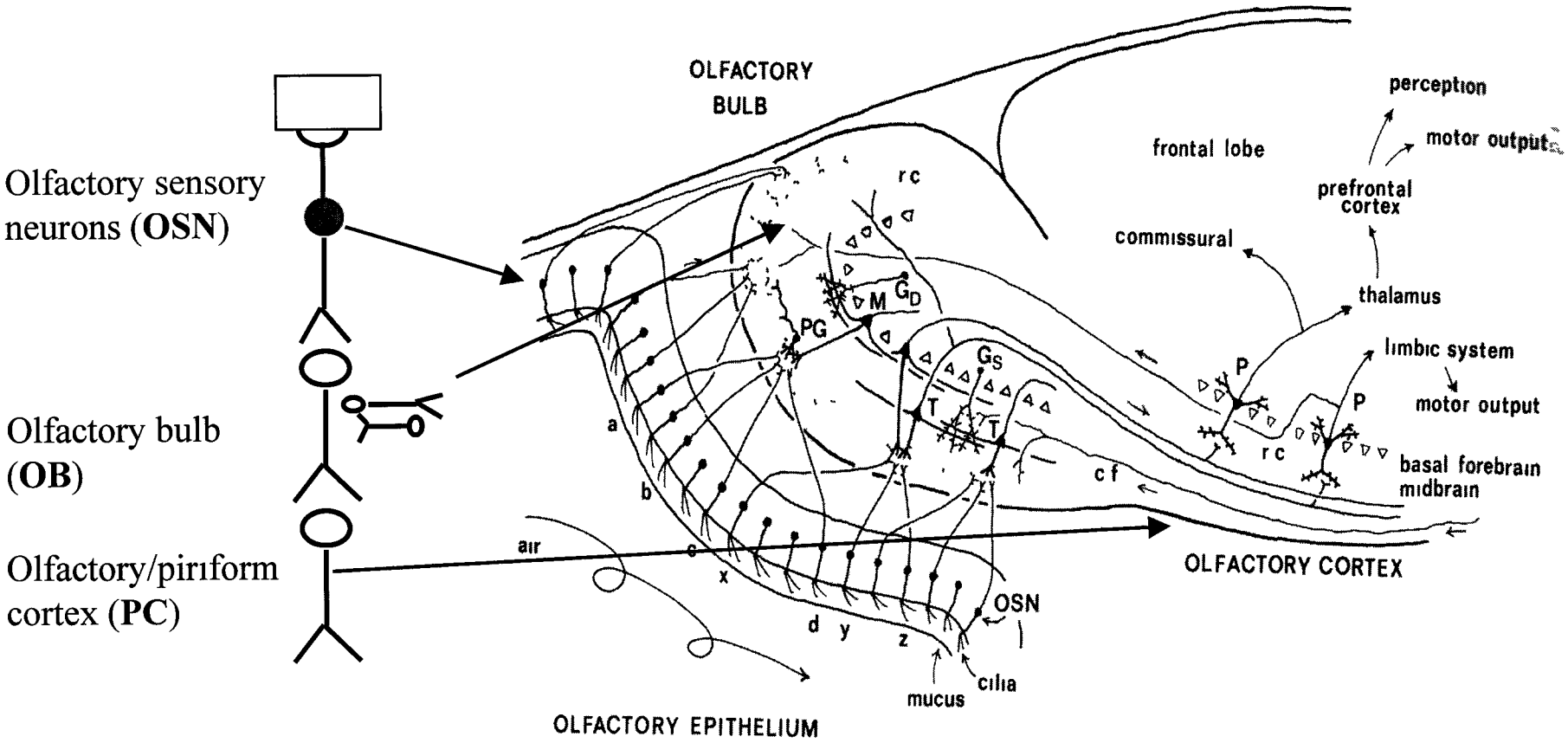
The olfactory system - 1 - where is it?

Figure 7.32
The olfactory system.

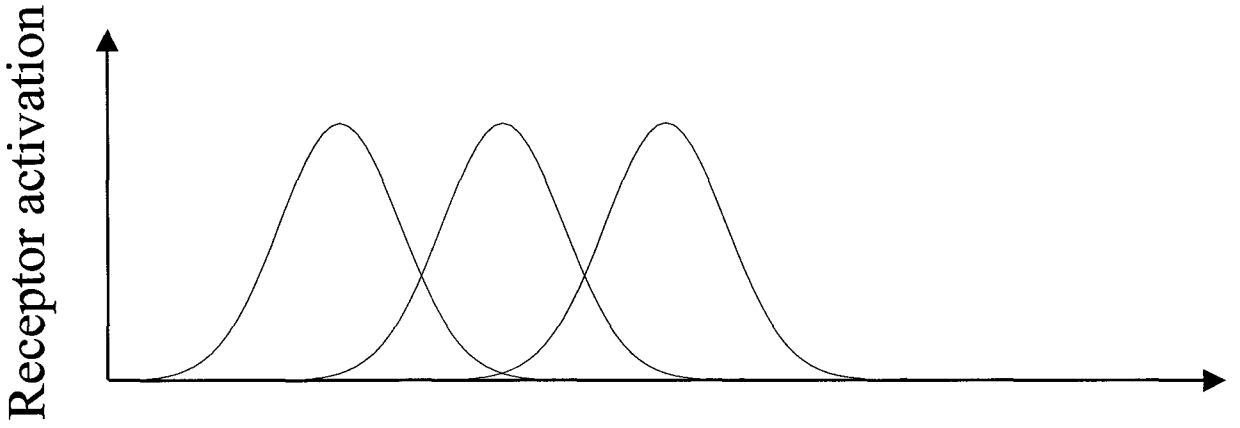


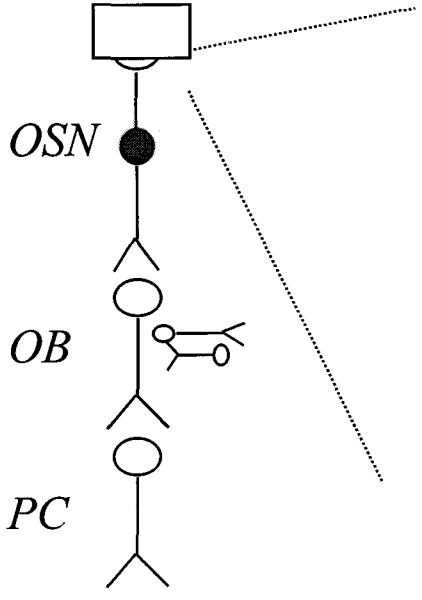
The olfactory system - 2 - Organization

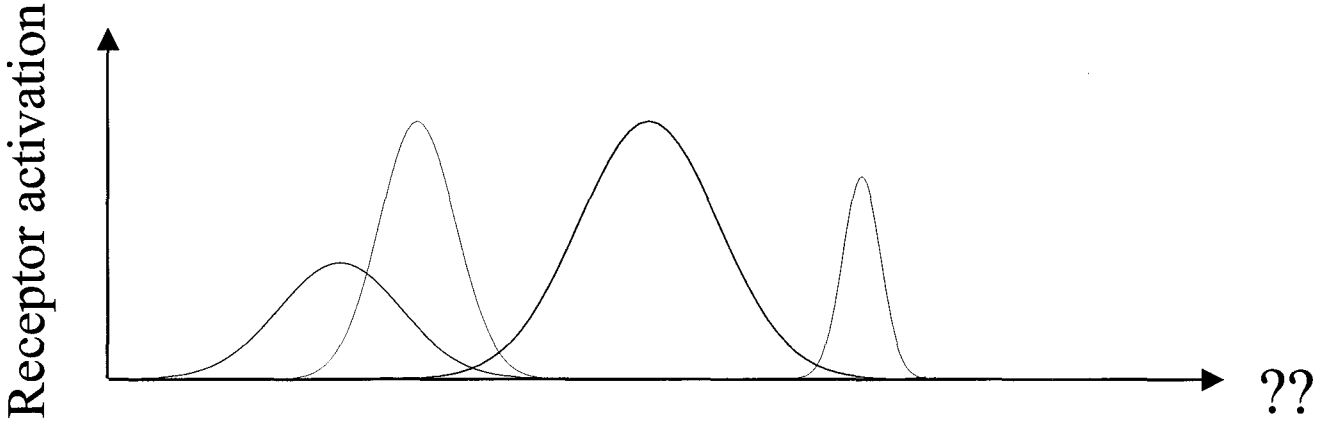



Olfactory sensory neurons (OSN)
Olfactory bulb (OB)
Olfactory/piriform cortex (PC)
OLFACTORY BULB
frontal lobe
perception
motor output
prefrontal cortex
commissural
thalamus
limbic system
motor output
basal forebrain
midbrain
rc
M
GD
PG
GS
T
P
cf
a
b
c
x
d
y
z
air
OSN
cilia
mucus
OLFACTORY CORTEX
OLFACTORY EPITHELIUM

The olfactory system - 3 - Chemical signals

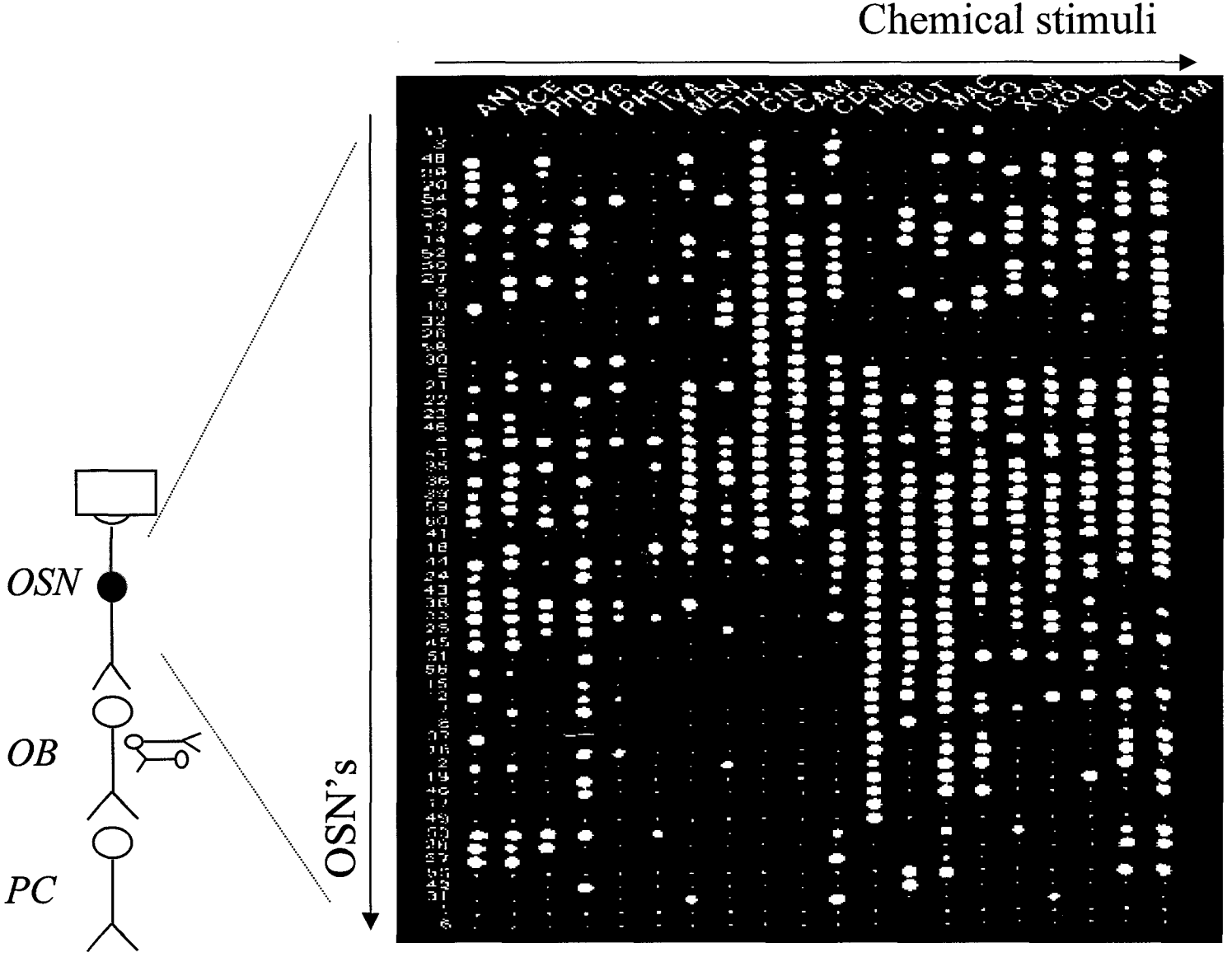




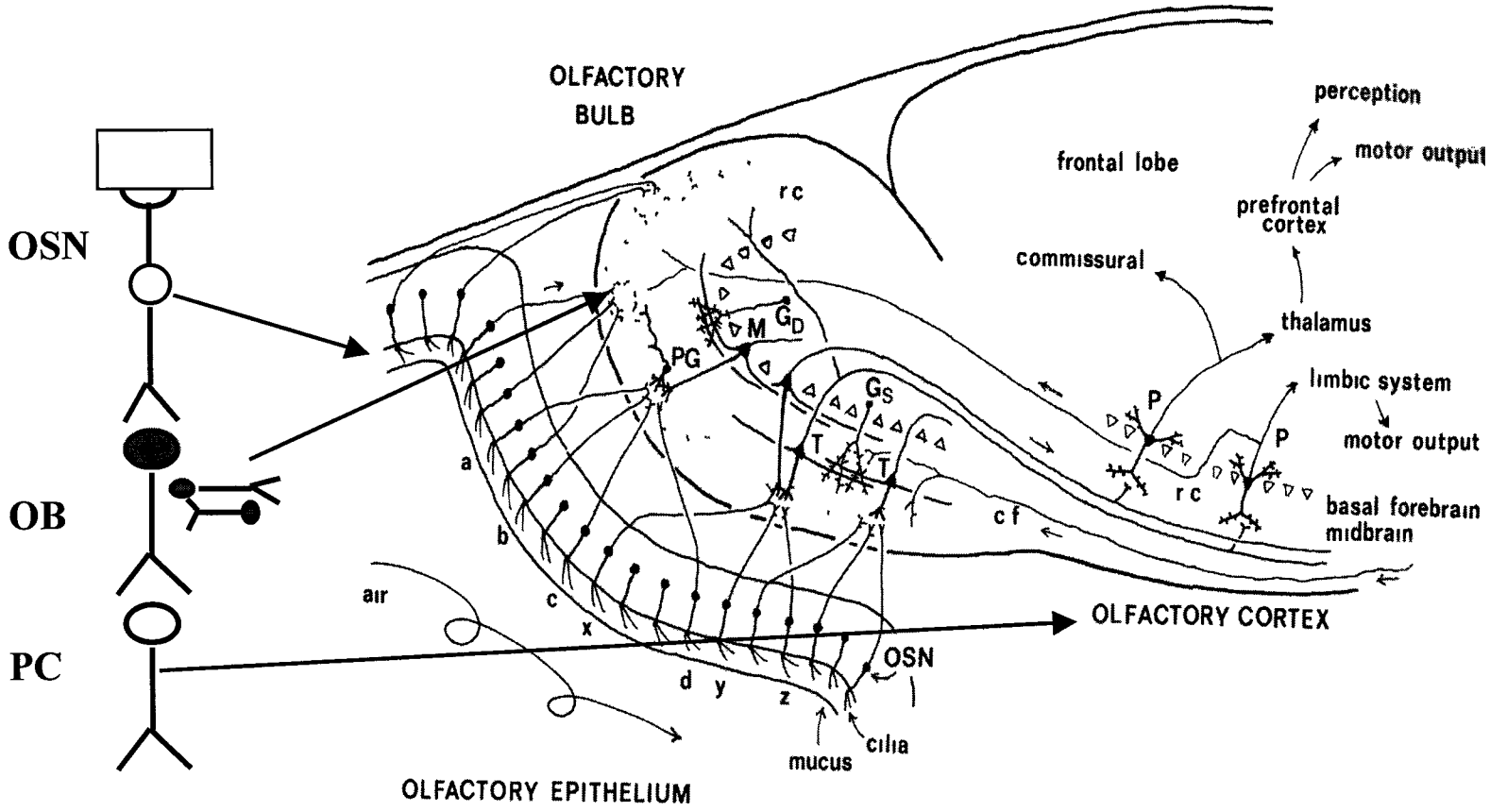


(Number of Carbons, Molecular Weight, Electronegativity?)

The olfactory system - 4 - Sensory responses



from: Sicard and Holley, 1984. Brain Res. 292:283.


OLFACTORY
BULB
perception
motor output
frontal lobe
prefrontal
cortex
commissural
thalamus
limbic system
motor output
basal forebrain
midbrain
OSN
OB
PC
rc
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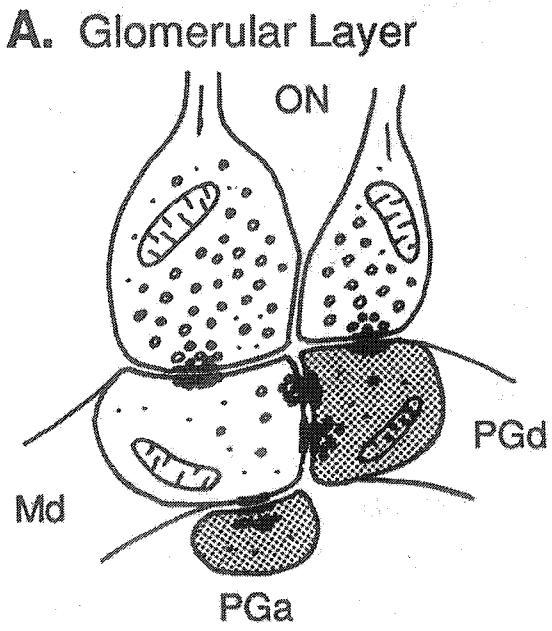
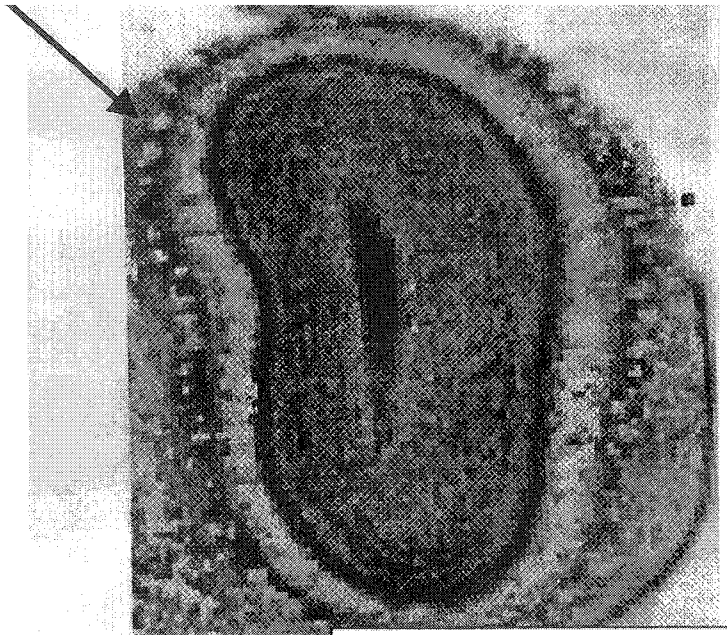
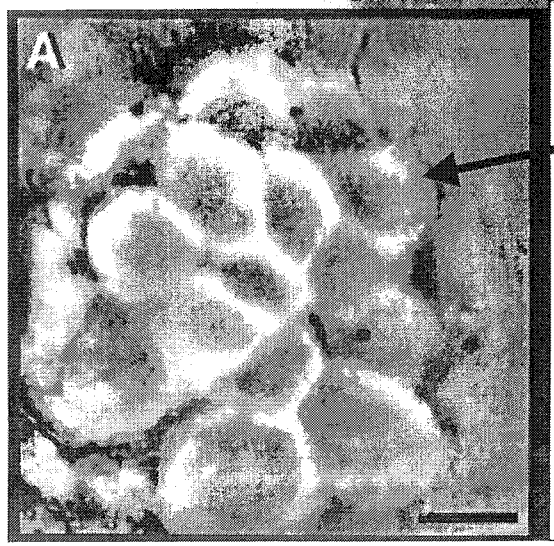
rc
cf
a
b
c
x
d
y
z
air
OLFACTORY CORTEX
OSN
cilia
mucus
OLFACTORY EPITHELIUM

The olfactory system - 5 - Glomeruli

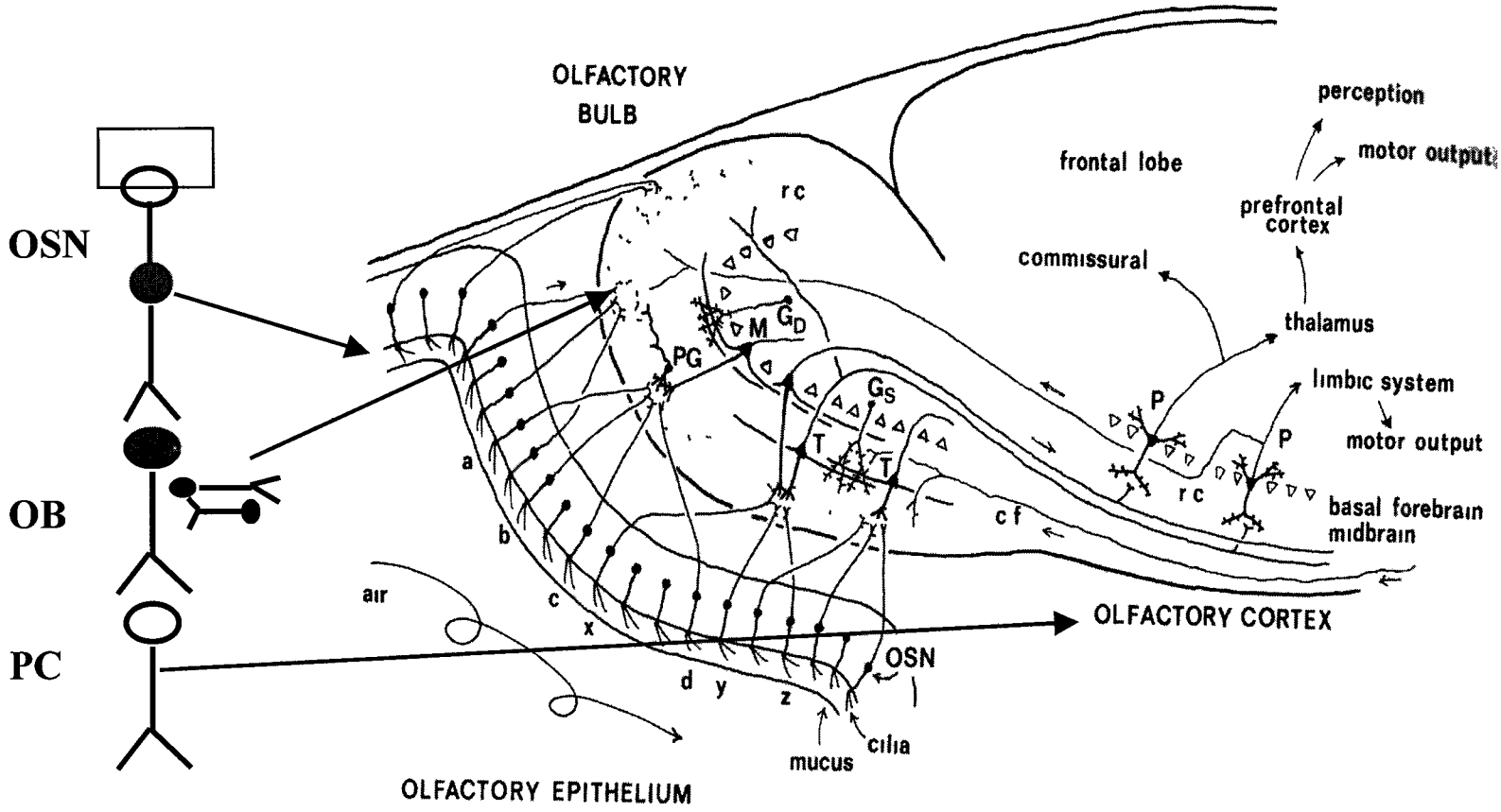
Rat olfactory bulb: ~2000 glomeruli



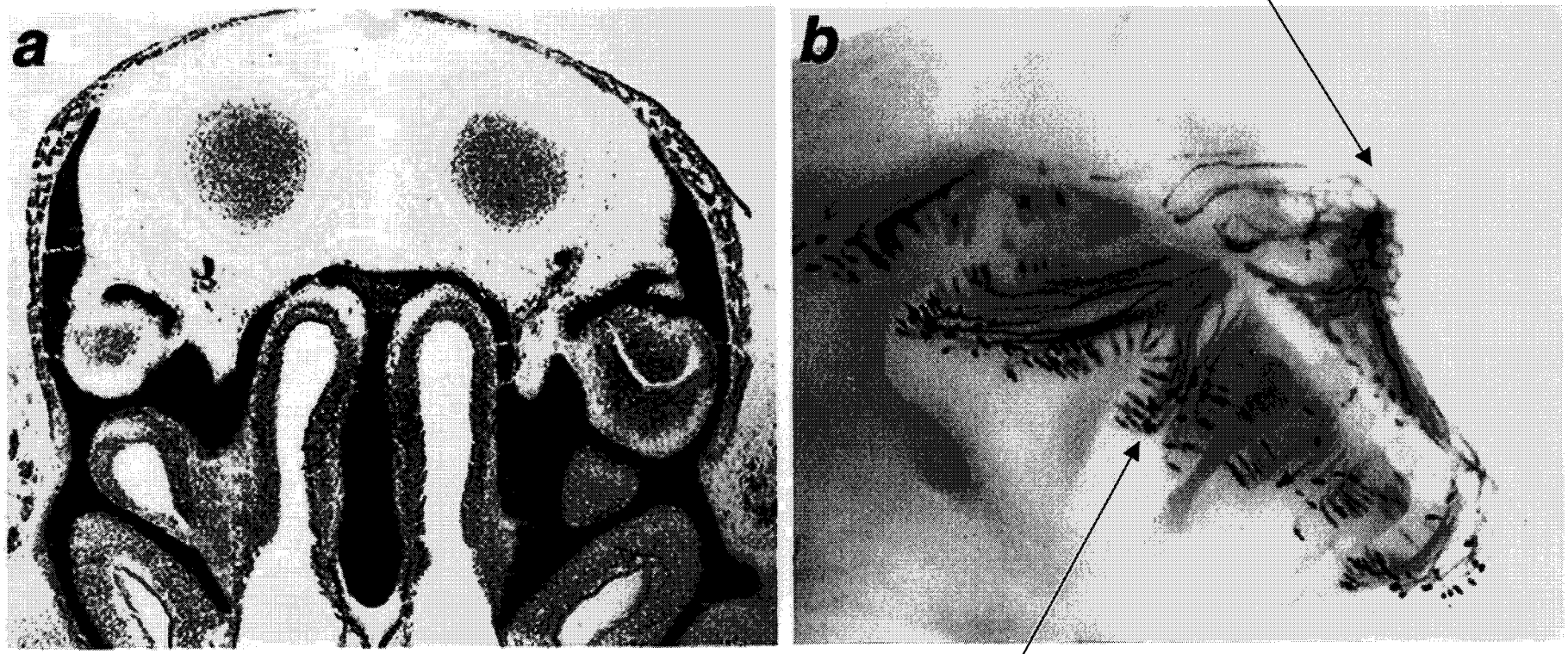




Honeybee antennal lobe:
65 identifiable glomeruli

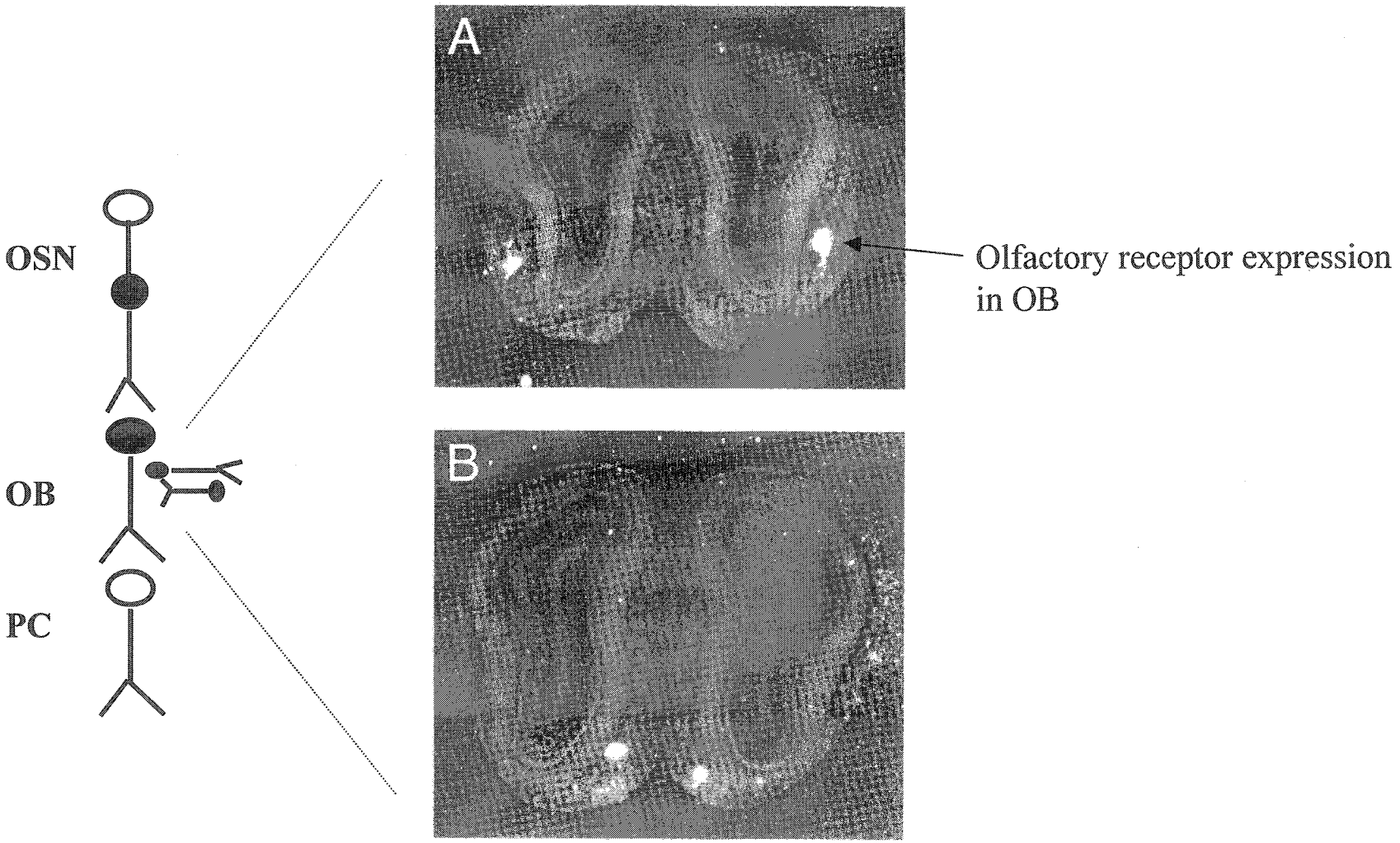

OSN
OB
PC
OLFACTORY
BULB
frontal lobe
perception
motor output
prefrontal
cortex
commissural
thalamus
limbic system
motor output
basal forebrain
midbrain
rc
M
G_D
PG
G_S
P
T
a
b
c
x
d
y
z
air
cf
OLFACTORY CORTEX
OSN
cilia
mucus
OLFACTORY EPITHELIUM

The olfactory system - 6 - OSN projection pattern



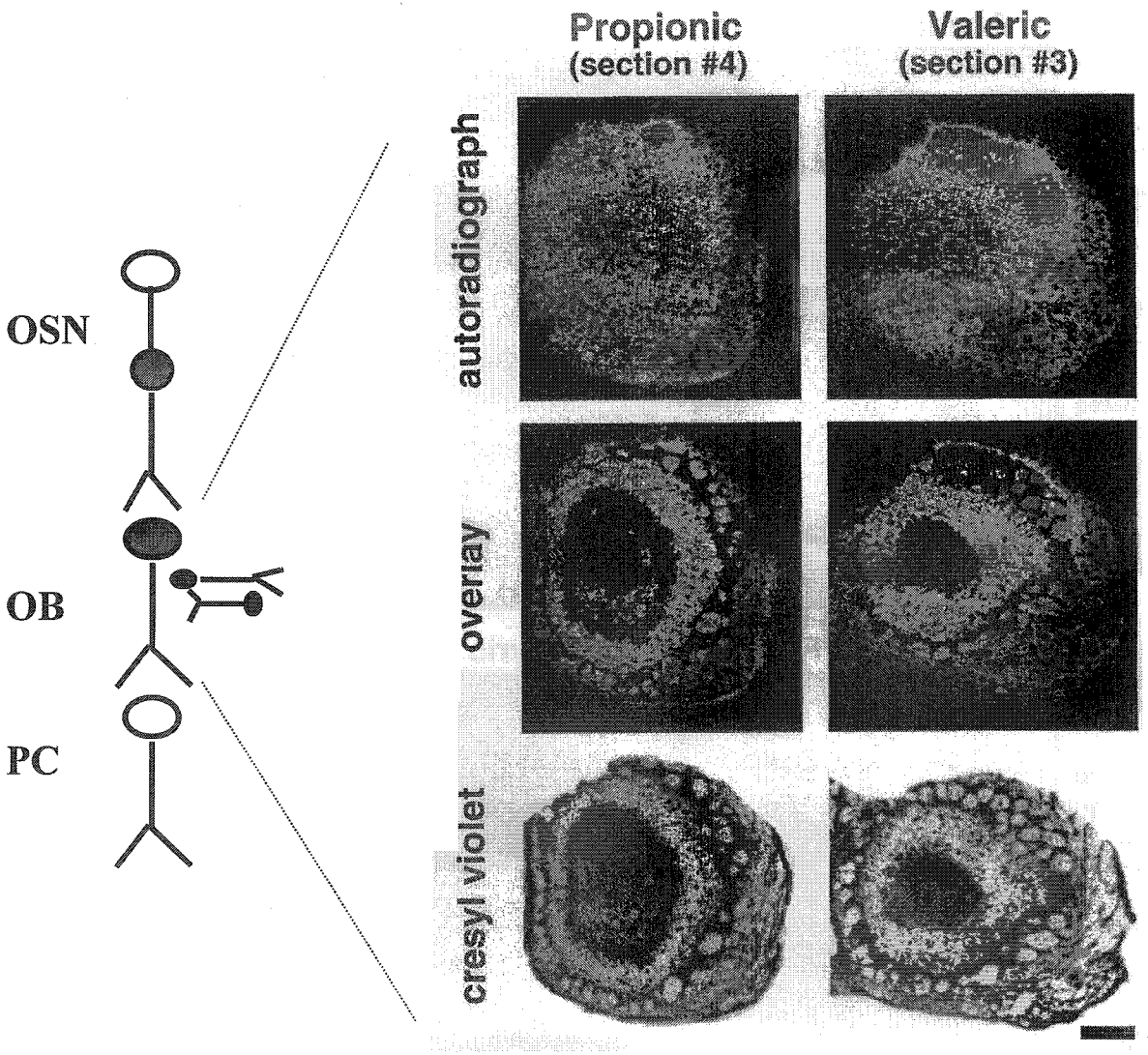
Mombaerts et al. 1996 Cell 87: 675

The olfactory system - 7 - OSN projection pattern



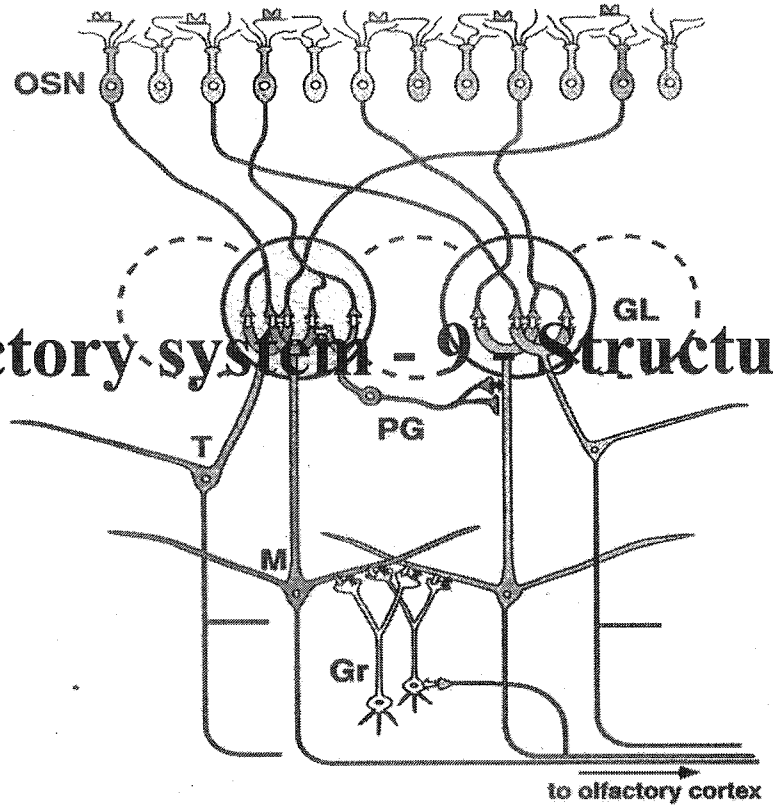
Mombaerts et al. 1996 Cell 87: 675

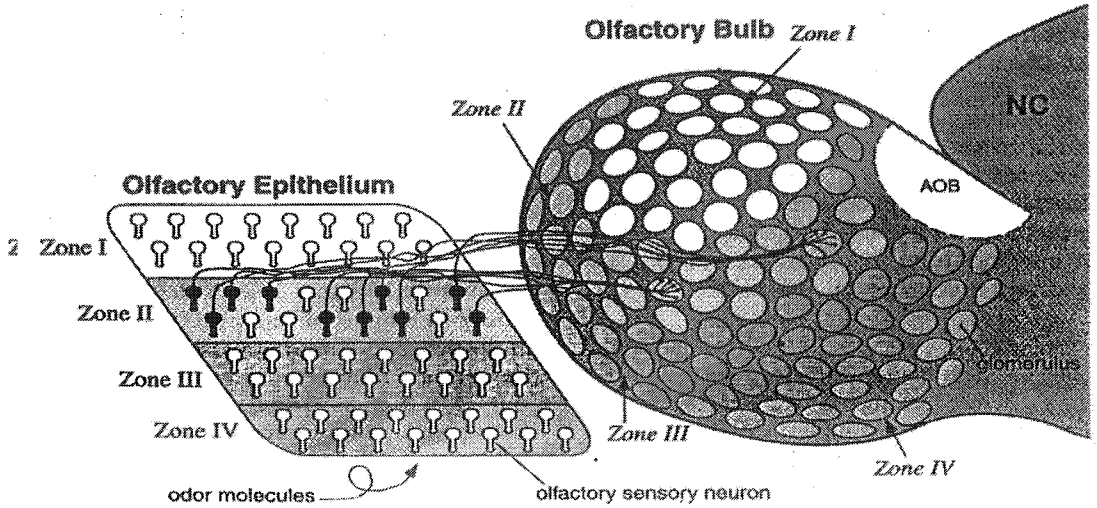
The olfactory system - 8 - Glomerular activation patterns



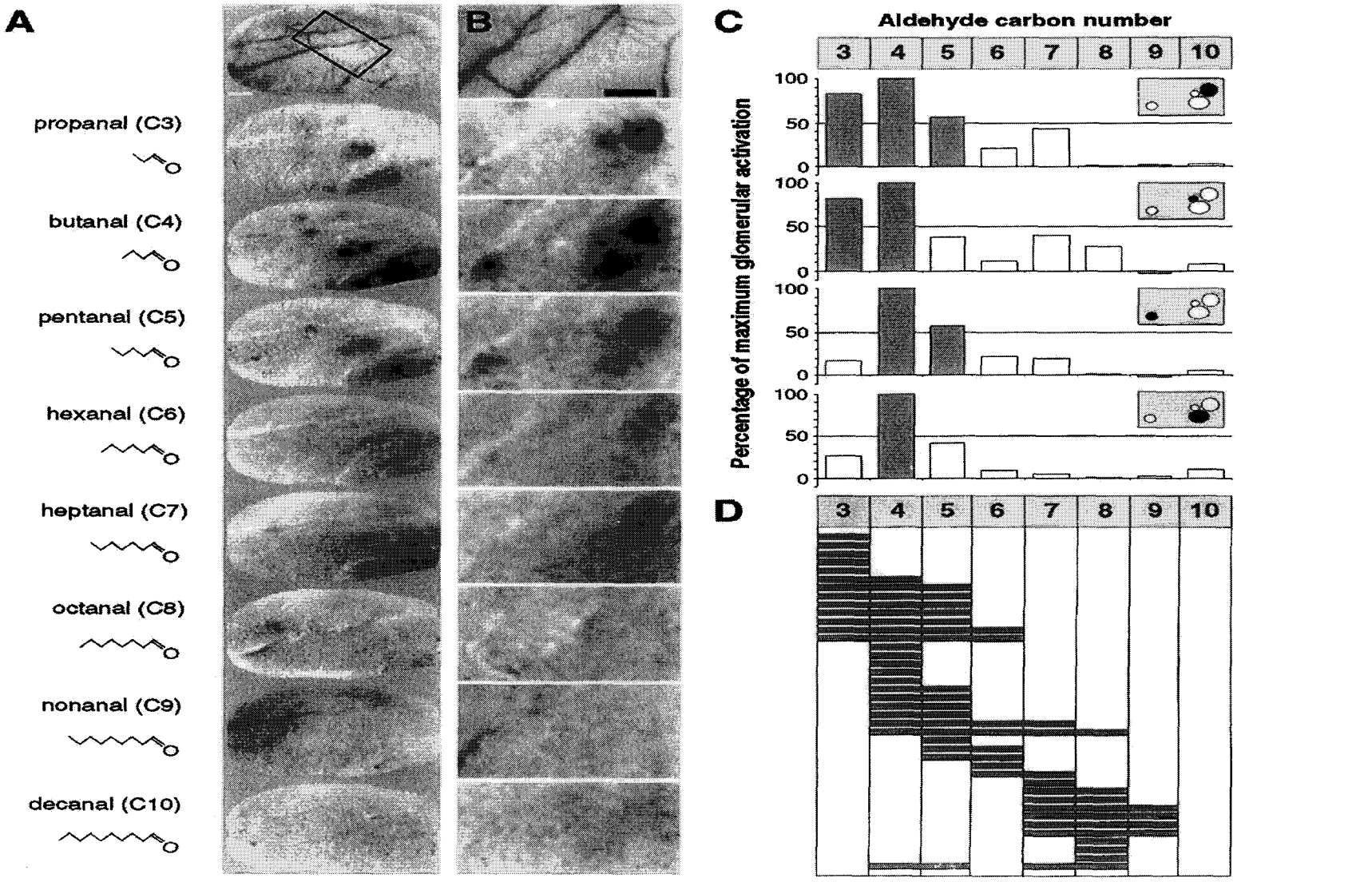
Johnson, Woo, Hingco , Pham and Leon (1999)
J. Comp. Neurol. 409:529

The olfactory system - 9 - Structure





Optical imaging in rat olfactory bulb - response patterns to aliphatic aldehydes

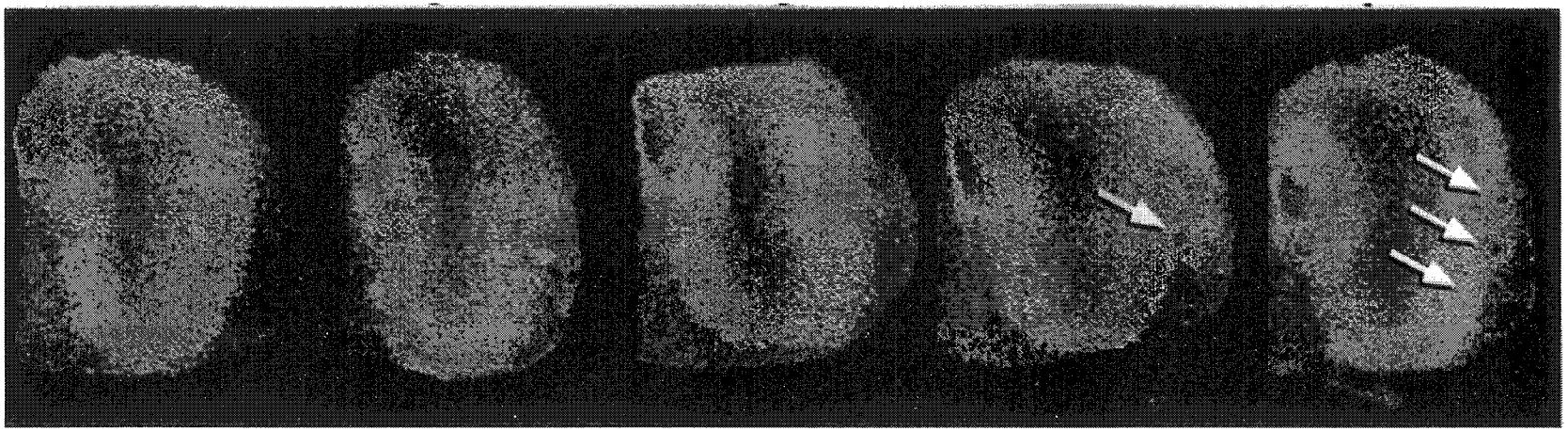


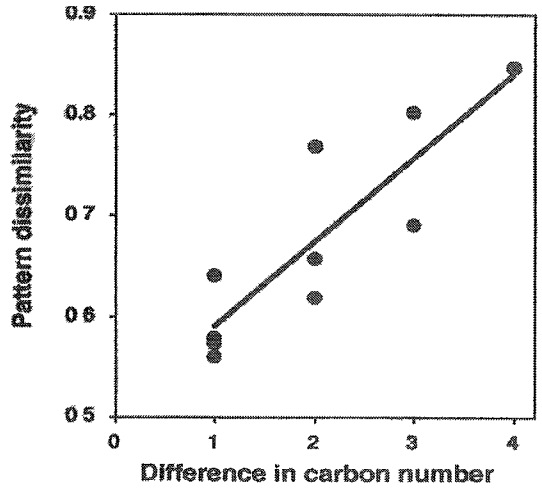
Rubin and Katz LC (1999) Neuron 23: 499

Bulbar activity patterns in response to *n*-fatty acids

2-deoxyglucose imaging in rat olfactory bulb - response patterns to fatty acids

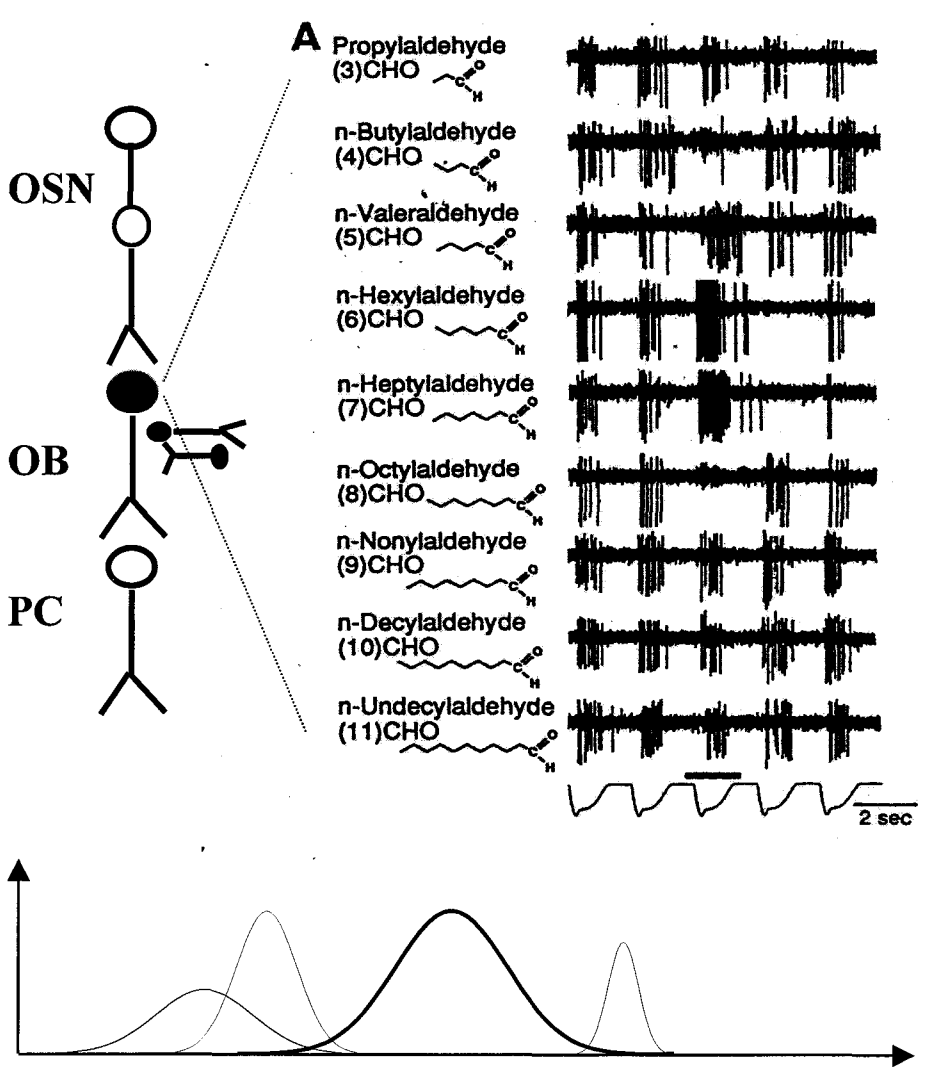
CHOH(2) CHOH(3) CHOH(4) CHOH(6) CHOH(5)

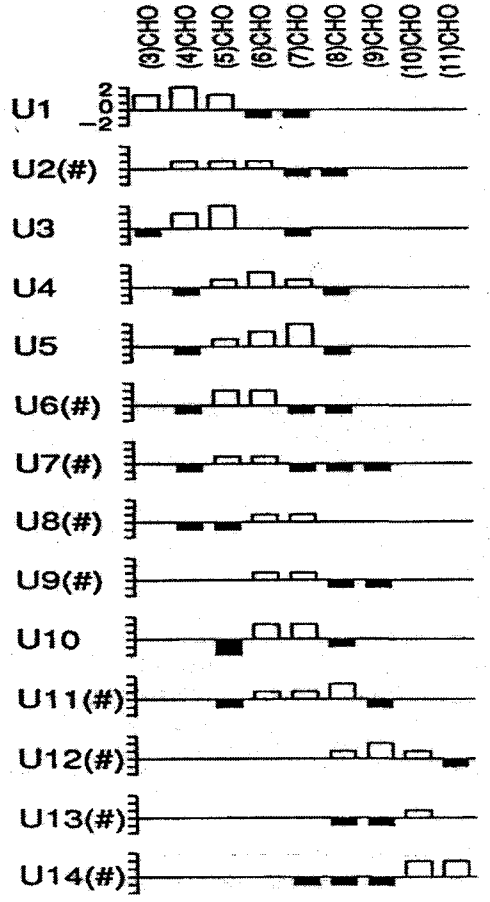




Johnson, Woo, Hingco, Pham and Leon (1999)
J. Comp.Neurol 409:529

The olfactory system - 11 - Mitral cells

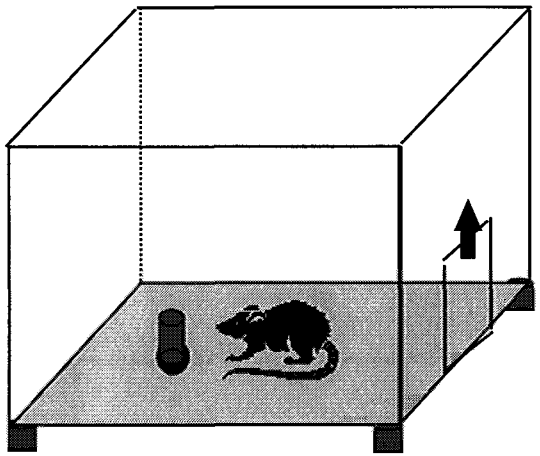


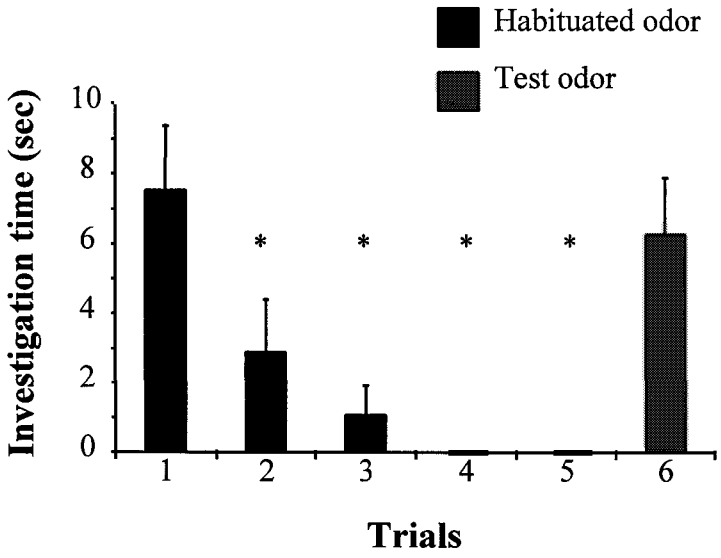


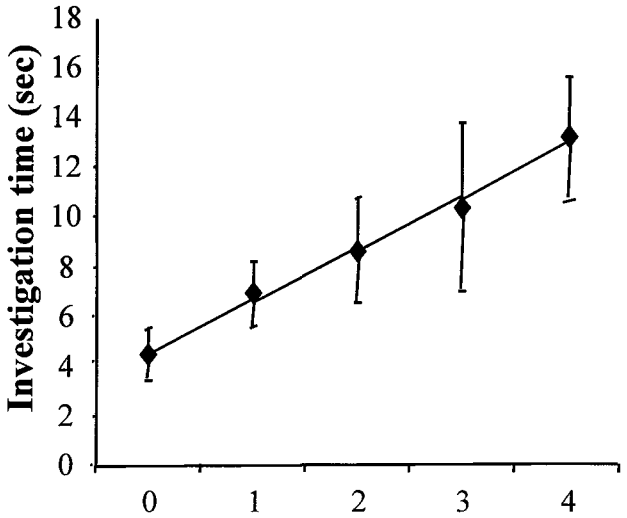
*(**Number of Carbons**, Molecular Weight, Electronegativity?)*

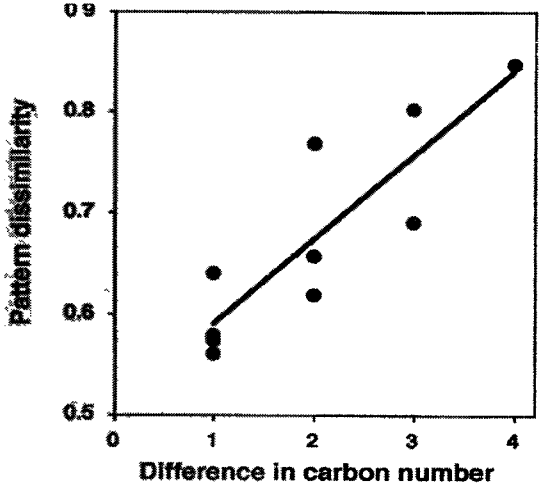
Yokoi et al., 1995. Proc. Natl. Acad. Sc. 92:3371

The olfactory system - 12 - Neural responses and perception







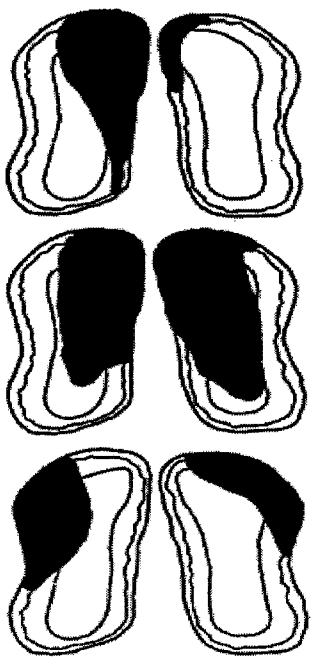


Linster et al. 2001 Behavioral Neuroscience

The olfactory system - 14 - Lesioning of the "spatial" representation does not impair odor processing

* Several experiments have shown that lesioning of "hot spots" of neural activation in response to previously learned odors does not impair the recognition of these odors

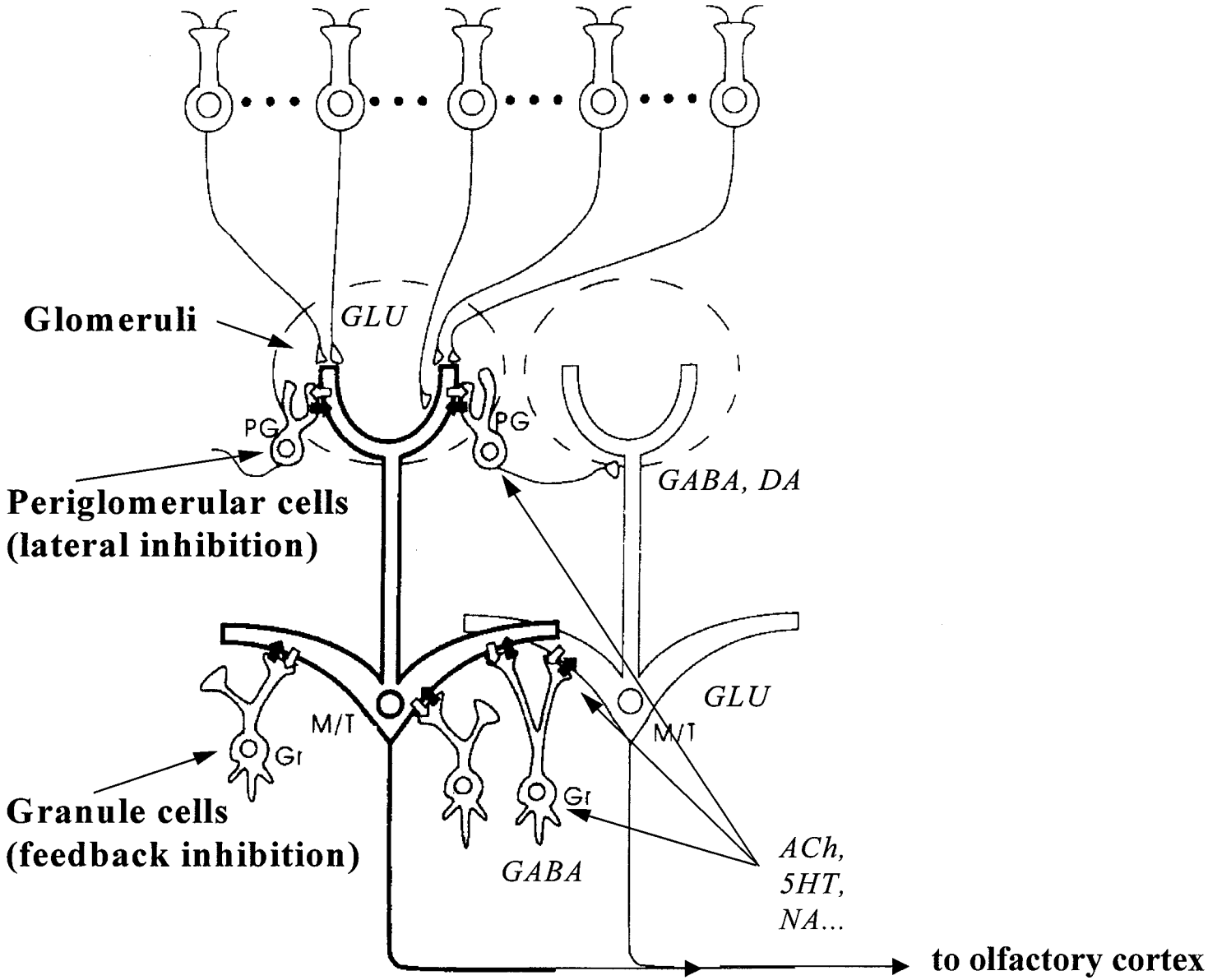
* Experiments have also shown that lesions of up to 80% of the OB do not impair odor learning in neo-natal rats



Slotnick et al. showed that after lesioning the olfactory bulb in those areas that are mainly activated in response to propionic acid, rats have no impairment when asked to remember a previously learned response to that odor; in addition they show no impairment when asked to learn a novel odor task involving propionic acid.

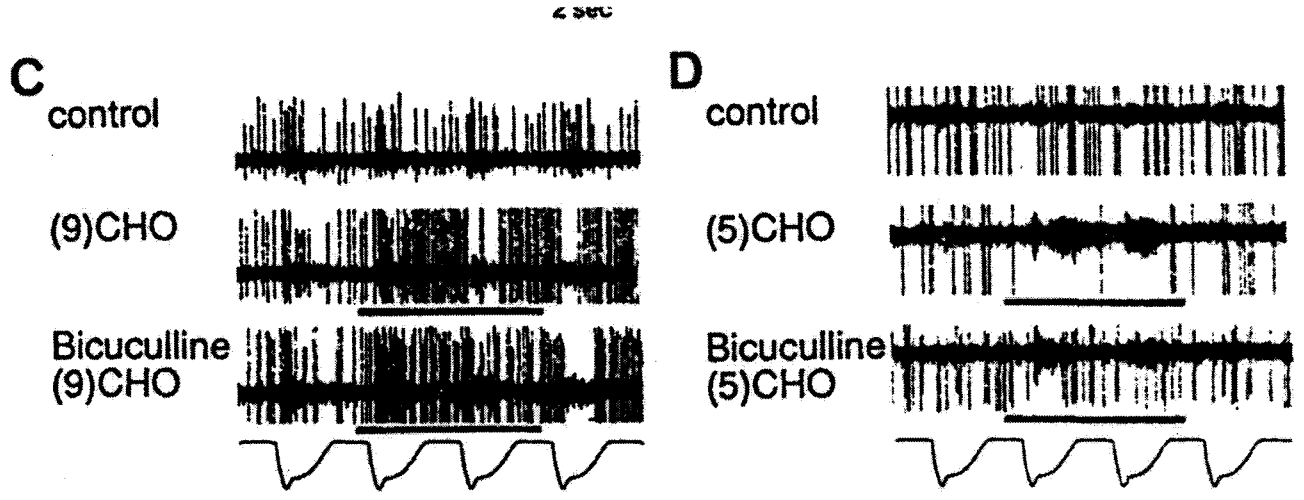
Slotnick et al. 1997. Brain Research 762: 89

The olfactory system - 15 - Beyond the glomerulus



The olfactory system - 16 - Role of inhibitory neurons

* Decrease of (lateral) inhibition changes "molecular receptive field" of individual mitral cells

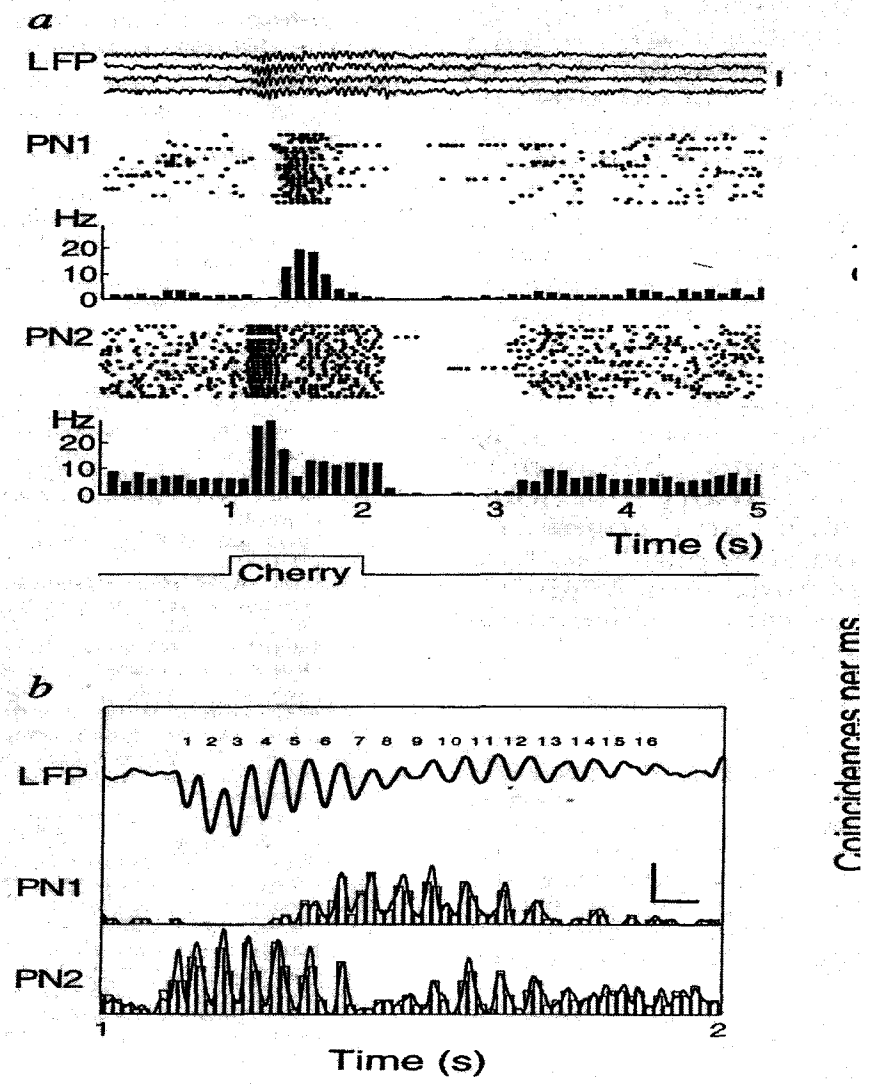


Yokoi et al., 1995. Proc. Natl. Acad. Sc. 92:3371

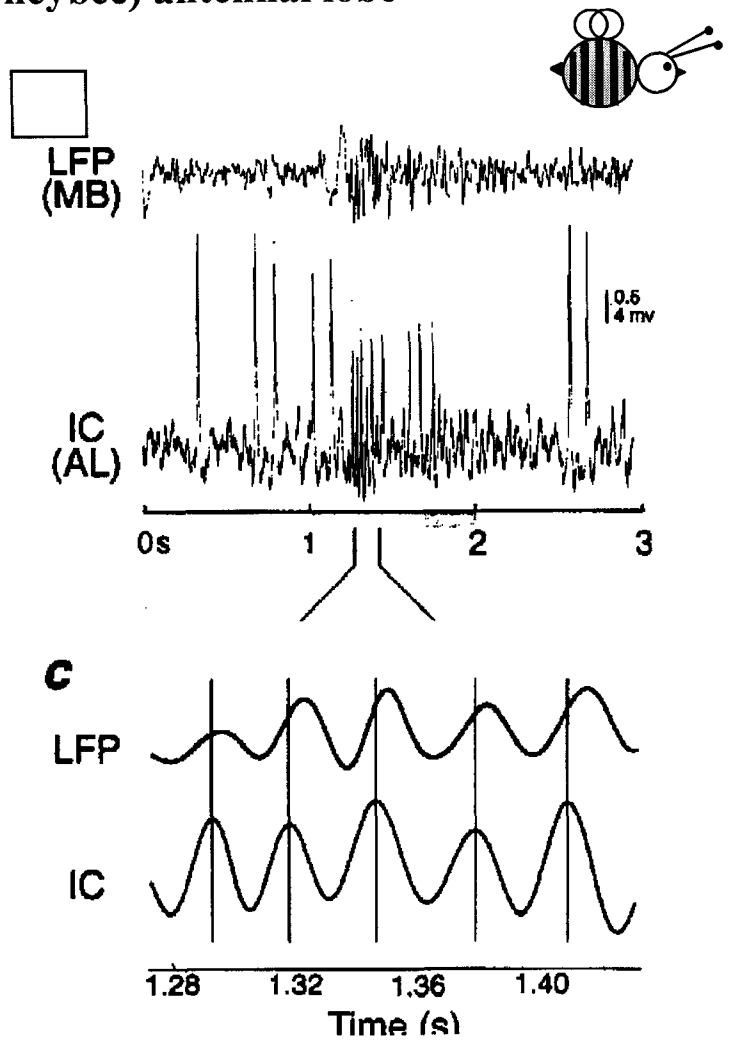
*Decrease of (feedback) inhibition changes threshold and gain of odor responses

Duchamp-Viret and Duchamp 1993 Neurosc. 56(4): 905.

Odor evoked oscillatory responses in insect (locust and honeybee) antennal lobe

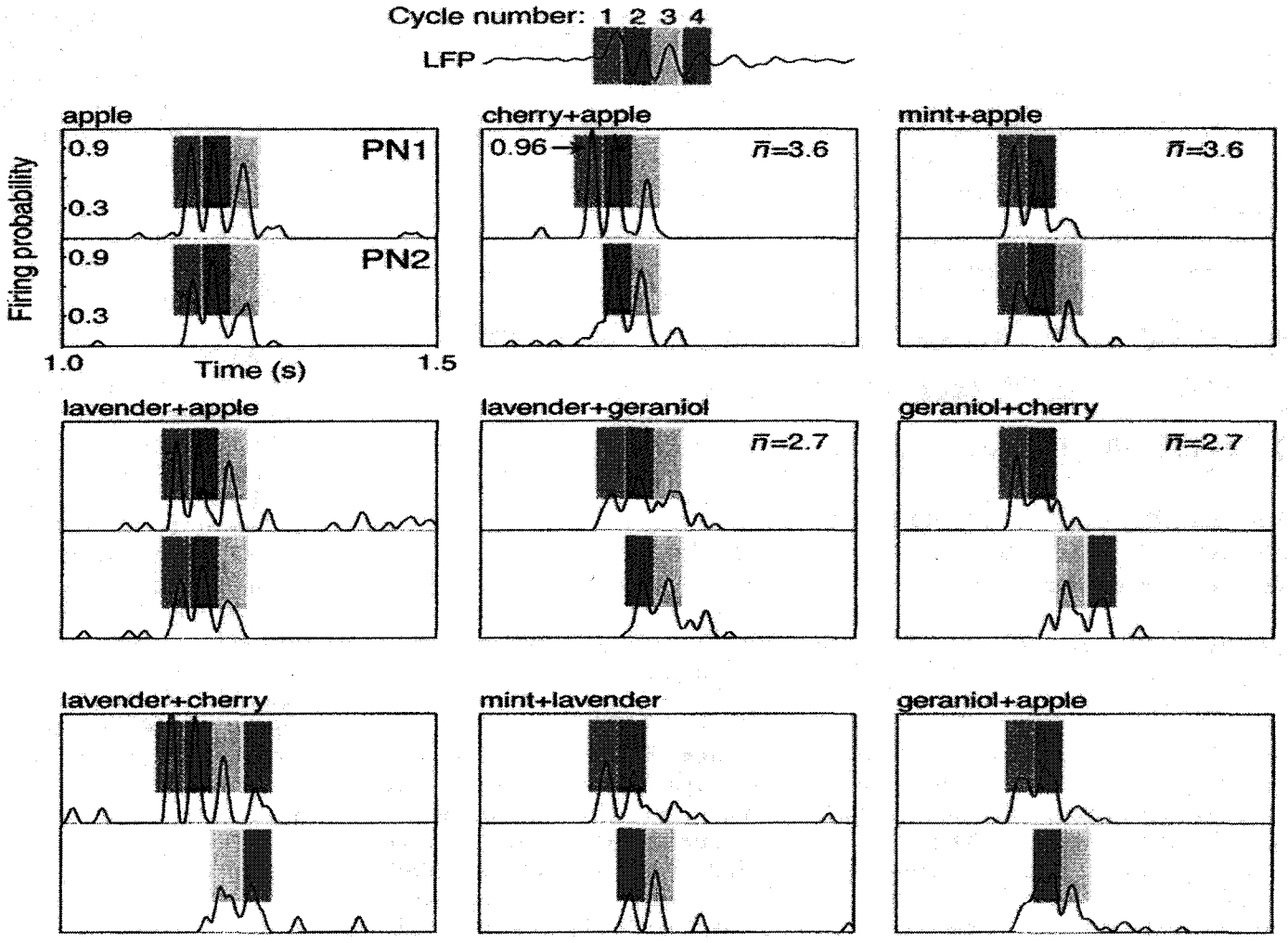


Wehr and Laurent 1996 Nature, 384: 162



Stopfer et al., Nature 390, 1997.

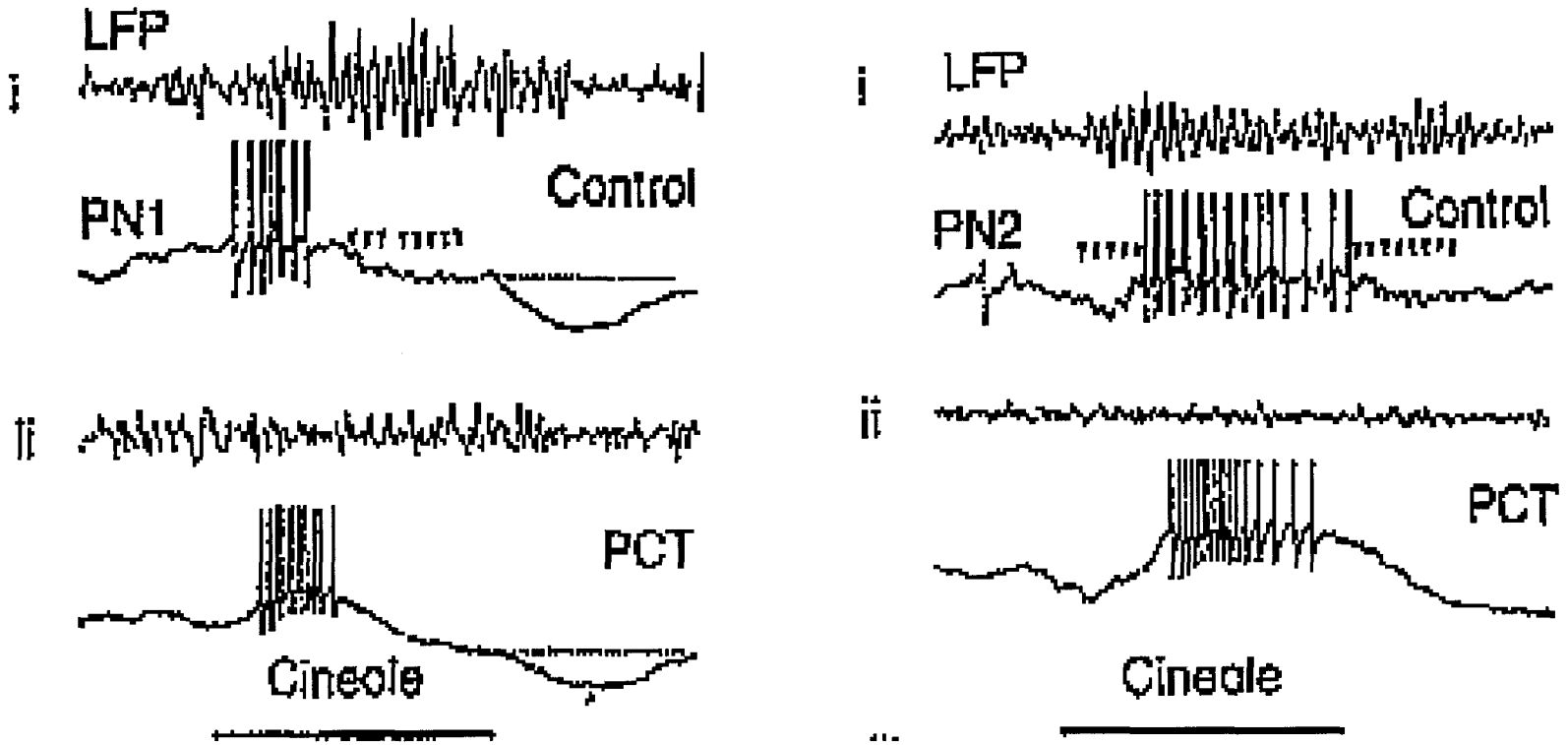
The olfactory system - 18 - Is there a "temporal" code ?



Wehr and Laurent 1996 Nature, 384: 162

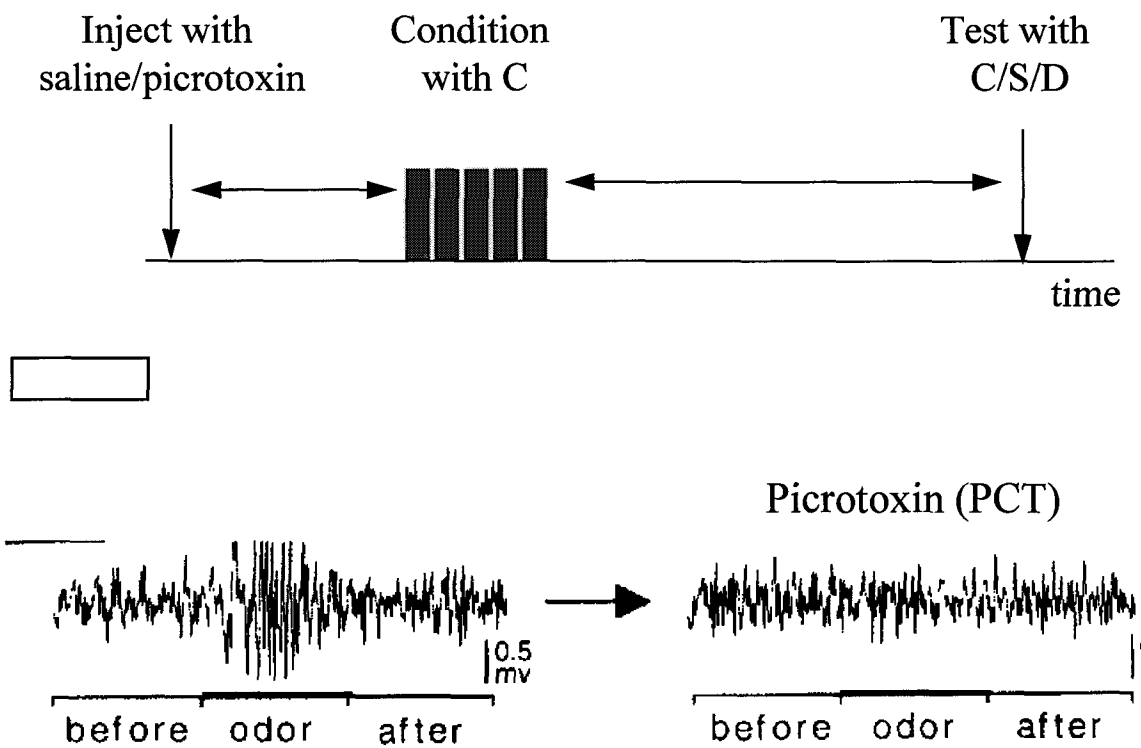
The olfactory system - 19 - Role of inhibition

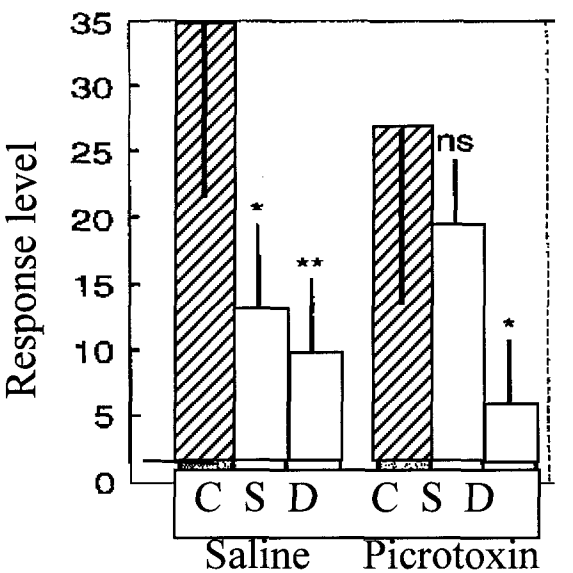
Suppression of GABA-ergic Inhibition Decreases LFP Oscillation but preserves spike pattern



MacLeod and Laurent, Science 274, 1996.

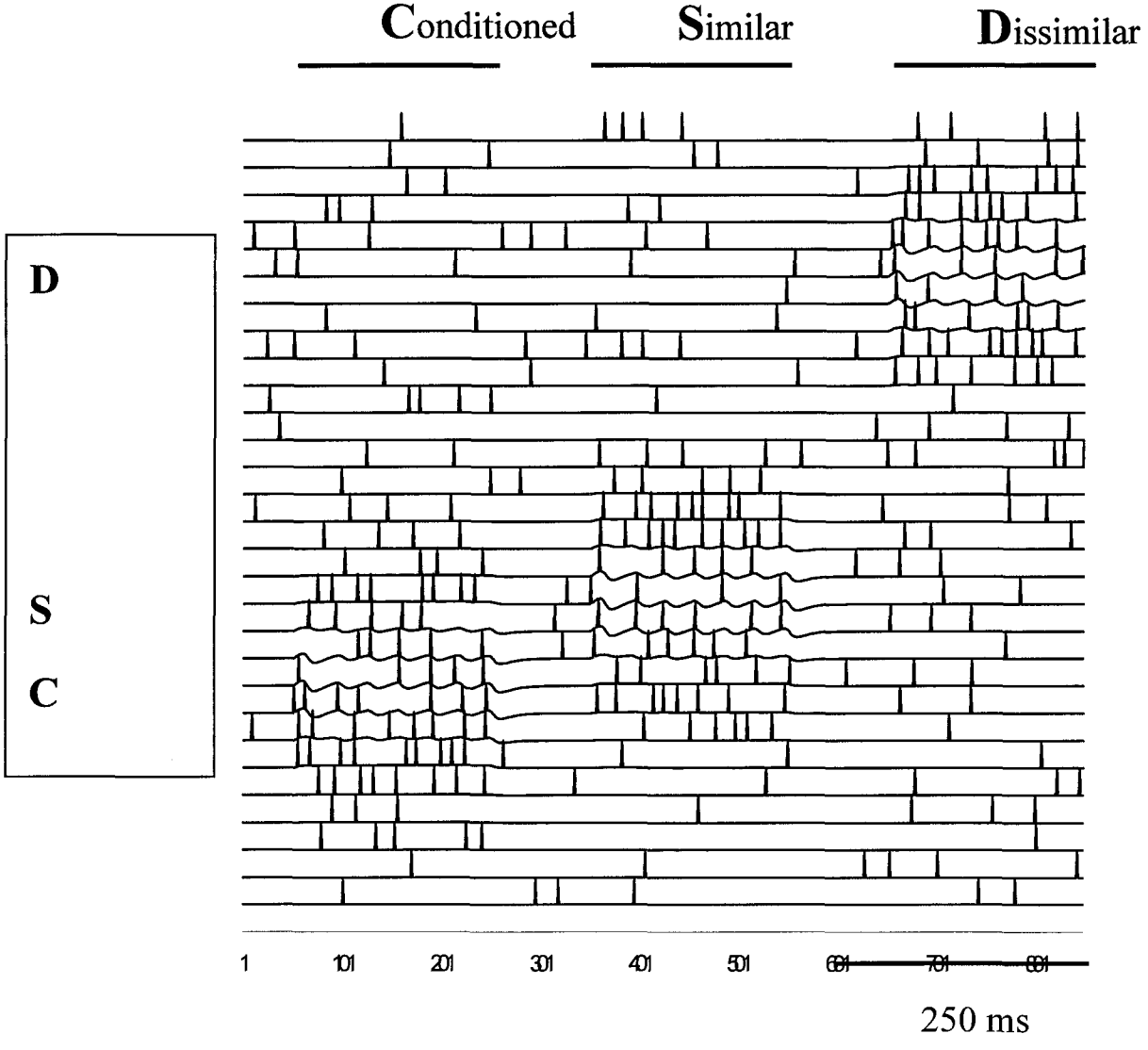
The olfactory system - 20 -
Decrease of synchronization impairs some, but not all odor processing



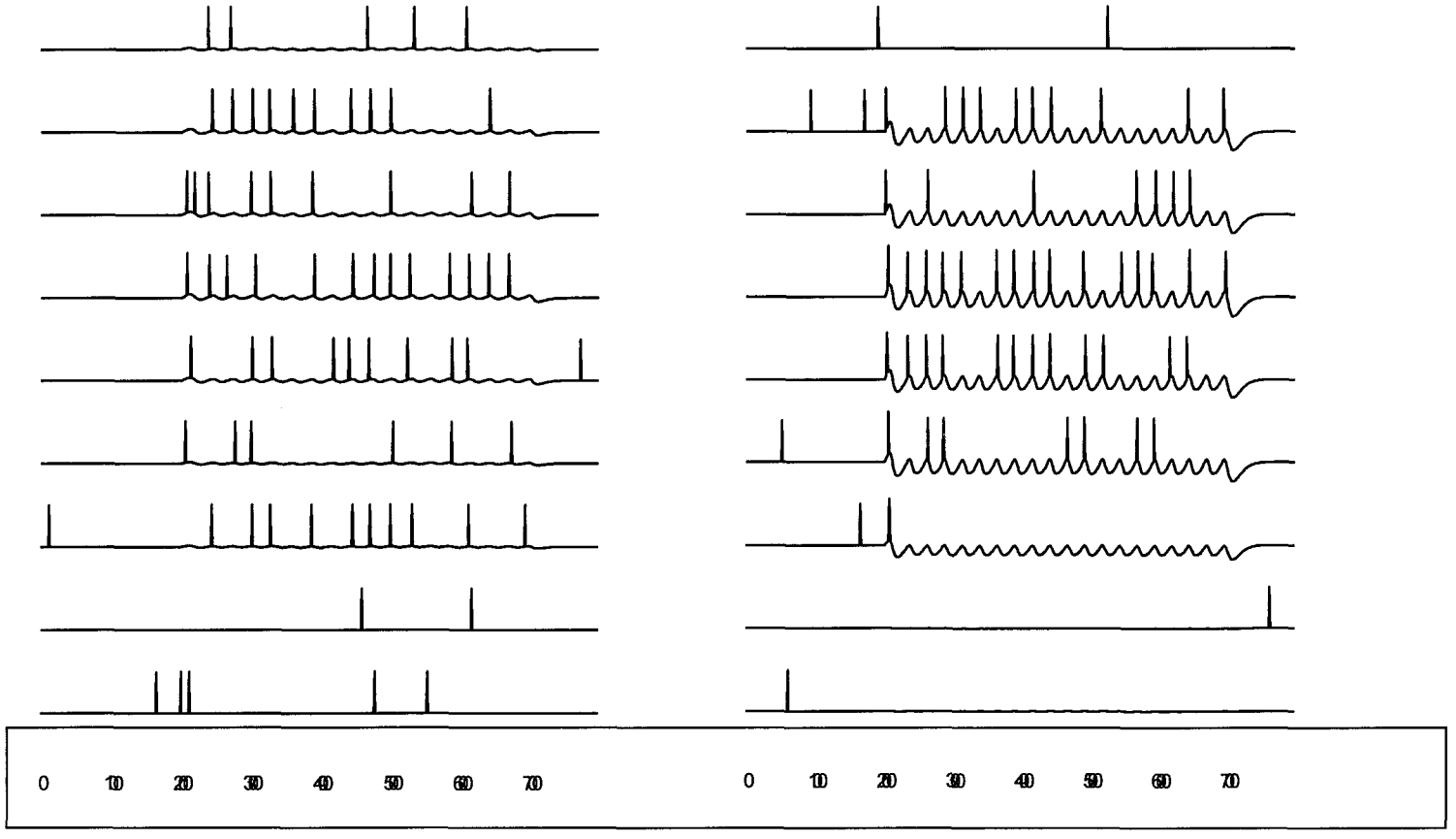


from: Stopfer et al., Nature 390, 1997.

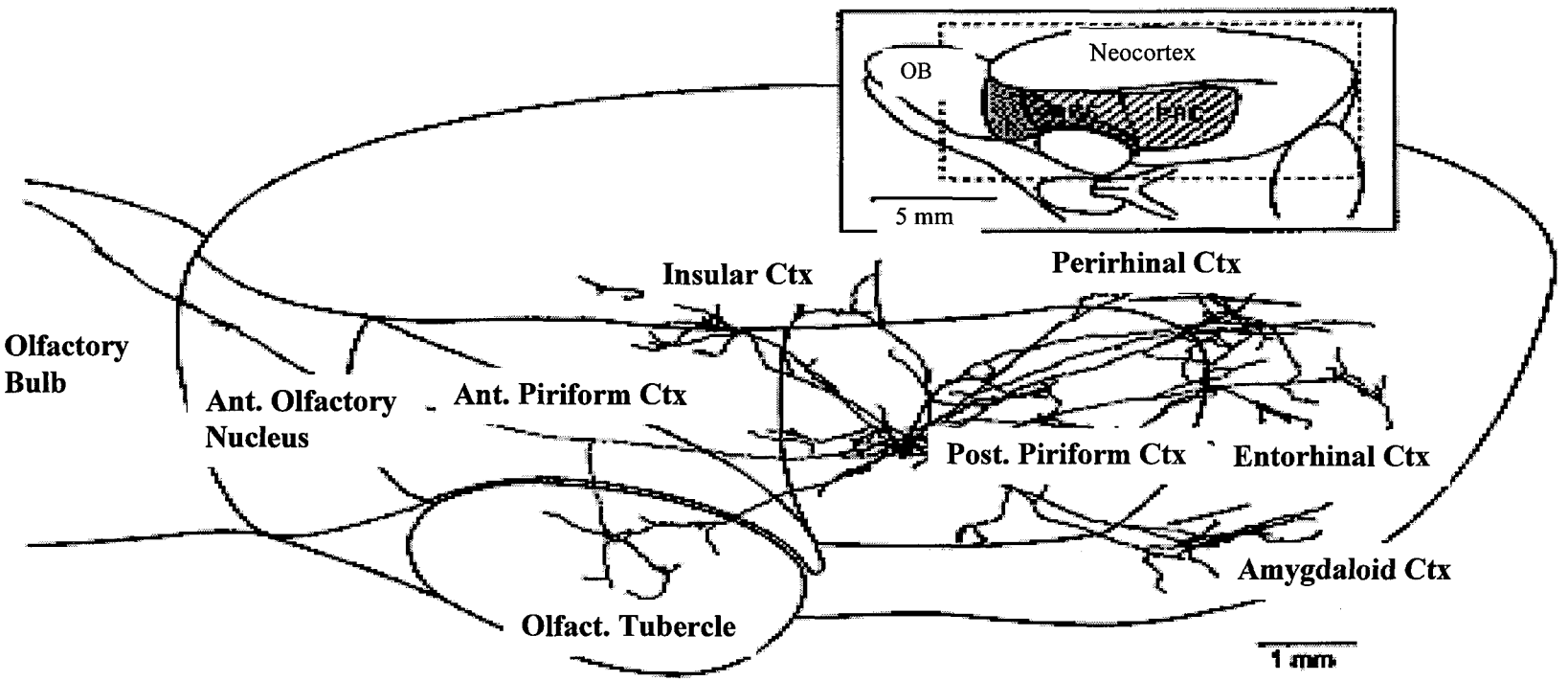
The olfactory system - 21 - Spatio-temporal code?



Spatio-temporal code in which both elements can be modulated and can carry independent information



Central olfactory pathways



adapted from Haberly, L.B. Chemical Senses (in press)

Johnson D.M. et al., J. Neurosci. 20(18): 6974-82 (2000)

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.

References

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3. B. W. Ache, *Semin. Cell Biol.* **5**, 55 (1994).
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13. C. I. Bargmann, *Science* **282**, 2028 (1999).
14. E. R. Troemel, B. E. Kimmel, C. I. Bargmann, *Cell* **91**, 161 (1997).
15. C. Dulac and R. Axel, *Cell* **83**, 195 (1995).
16. Y. Pilpel and D. Lancet, *Nature* **398**, 285 (1999).
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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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REVIEW

The Olfactory Bulb: Coding and Processing of Odor Molecule Information

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Olfactory sensory neurons detect a large variety of odor molecules and send information through their axons to the olfactory bulb, the first site for the processing of olfactory information in the brain. The axonal connection is precisely organized so that signals from 1000 different types of odorant receptors are sorted out in 1800 glomeruli in the mouse olfactory bulb. Individual glomerular modules presumably represent a single type of receptor and are thus tuned to specific molecular features of odorants. Local neuronal circuits in the bulb mediate lateral inhibition among glomerular modules to sharpen the tuning specificity of output neurons. They also mediate synchronized oscillatory discharges among specific combinations of output neurons and may contribute to the integration of signals from distinct odorant receptors in the olfactory cortex.

The sensory input to the olfactory system is mediated by odor molecules that represent an amazingly diverse range of structure. How can the mammalian olfactory system detect and discriminate such a large variety of odor molecules? Recent studies have begun to elucidate the molecular and cellular mechanisms for the reception of odor molecules at the level of olfactory sensory neurons in the nose (*1–5*). To cope with the diverse odor molecules, mammals have developed up to 1000 odorant receptors (*3, 4, 6*), which are expressed on the cilial membrane surface of sensory neurons in the olfactory epithelium (OE).

The central olfactory system receives the odor molecule information through axons of sensory neurons. The information is processed and integrated as the olfactory quality of objects. The human perception of the olfactory image is characteristic in that it usually associates with pleasant or unpleasant emotions. Because a single object, such as the flower of jasmine, emits a specific combination of dozens of different odor molecules, the central olfactory system has to integrate signals from a large variety of odorant receptors. This poses an interesting but daunting question as to how the central olfactory system combines or compares signals among 1000 types of odorant receptors. Recent progress has begun to unravel the basic cellular mechanisms for processing the molecular information at the first relay station of the central olfactory system, the main olfactory bulb (MOB) (*7*).

The mammalian MOB has a relatively simple cortical structure, containing thousands of signal-processing modules called

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"glomeruli" (*8*). Glomeruli are relatively large spherical neuropils (100 to 200 μm in diameter), within which axons of olfactory sensory neurons form excitatory synaptic connections on dendrites of mitral and tufted cells, the output neurons of the MOB (*9*) (Fig. 1). An individual glomerulus can be viewed as an olfactory axon convergence center for inputs originating from one type of odorant receptor; the odorant receptor–specific signal is transmitted to mitral and tufted cells innervating the glomerulus. In mice, each glomerulus receives converging axonal inputs from several thousand olfactory sensory neurons and is innervated by primary dendrites of ~20 mitral cells (*10*) (Fig. 1). If we refer to a glomerulus together with its associated neurons as a glomerular module, the architecture of the mouse MOB can be simplified as being composed of 1800 such modules. The odor molecule information is processed by the local neuronal circuits that mediate synaptic interactions within the module as well as among these modules in the MOB. Axons of mitral and tufted cells then send the information to the olfactory cortex (Fig. 1).

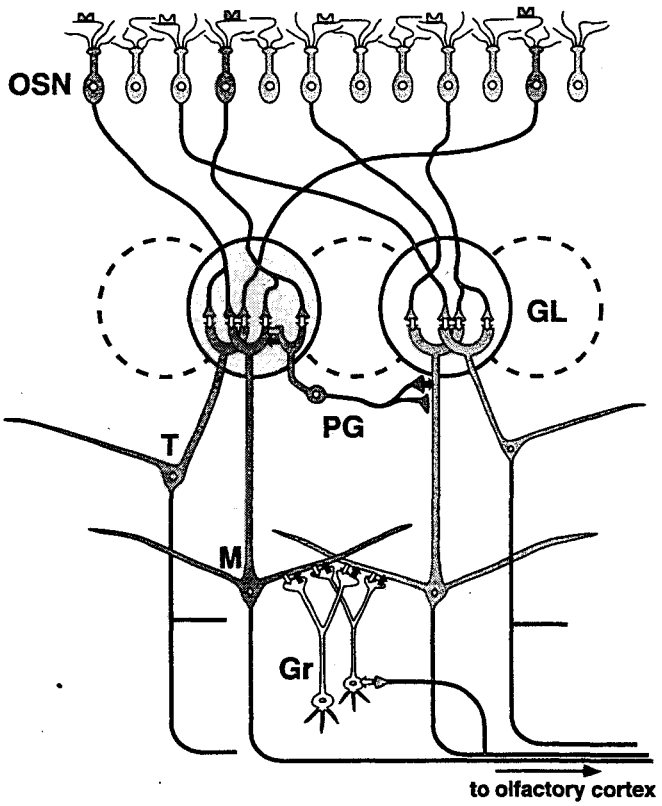

Fig. 1. Basic circuit diagram summarizing the synaptic organization of the mammalian MOB. Two glomerular modules (brown and blue) represent two different types of odorant receptors. Mitral cells (M) and tufted cells (T) are output neurons, and granule cells (Gr) and periglomerular cells (PG) are local interneurons. OSN, olfactory sensory neuron; GL, glomerulus. Short white arrows denote excitatory synapses, and short black arrows denote inhibitory synapses.

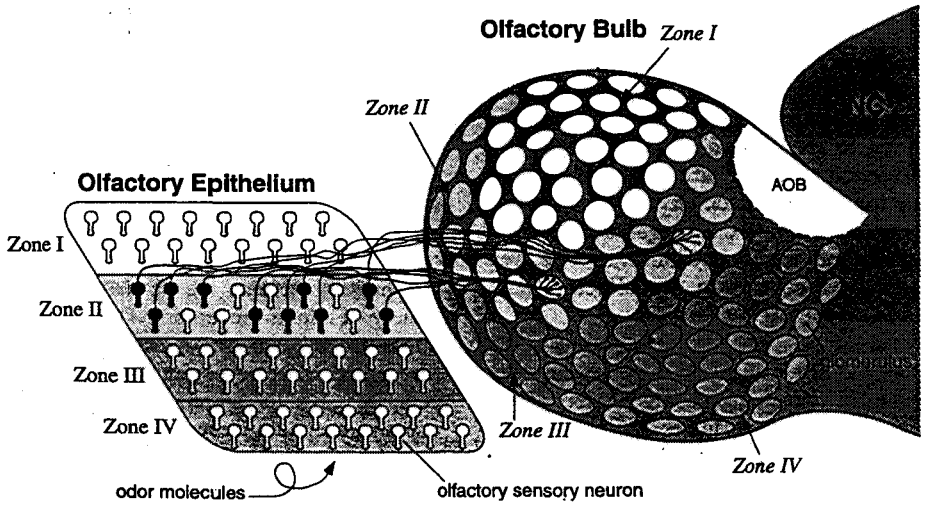

Fig. 2. Schematic diagram illustrating the axonal connectivity pattern between the nose and the MOB. The OE in mice is divided into four zones (zones I through IV) that are defined by the expression of odorant receptors. Olfactory sensory neurons in a given zone of the epithelium project to glomeruli located in a corresponding zone (*zones I* through *IV*) of the MOB. Axons of sensory neurons expressing the same odorant receptor (red or dark blue) converge to only a few defined glomeruli. NC, neocortex; AOB, accessory olfactory bulb.

Axonal Connection Between Nose and Olfactory Bulb

In mice, the OE contains more than 2 million sensory neurons. Individual olfactory sensory neurons express only one type of odorant receptor gene (*11–13*) out of a repertoire of up to 1000 genes. This suggests that individual sensory neurons respond to a range of odor ligands that bind to the expressed receptor (*13–15*). However, it is still unknown as to which range of odor molecules individual sensory neurons are tuned to (*13–16*). Each neuron projects a single axon into a single glomerulus in the MOB. How is the axonal connection functionally organized between the OE and the MOB? Two basic principles of the olfactory axon projection have been demonstrated: "zone-to-zone projection" and "glomerular convergence."

Zone-to-zone projection. Odorant receptors are classified into four groups, according to their expression patterns in the OE. A given type of odorant receptor is expressed in one of four circumscribed zones in the OE (*12, 17*) (Fig. 2) (zones I, II, III, and IV are arranged from dorsomedial to ventrolateral parts of the OE) (OE zones are given in roman type, and MOB zones are given in italic type). Within a given zone, neurons expressing different receptors intermingle, showing widely dispersed distribution. Structural comparison of various odorant receptors, in relation to their expression zones, revealed that the odorant receptors with highly homologous amino acid sequences tended to be localized in the same zone of the OE (*13*).

Such zonal organization is preserved to some extent in the MOB. The presence of zones in the glomerular sheet of the MOB was first shown in rabbits (*18*) and then in rats (*19*) with immunohistochemical studies using R4B12 and RB-8 antibodies, respectively. The antigen molecule recognized by these antibodies turned out to be a cell adhesion molecule, OCAM/RNCAM (*20*), which is expressed by axons of olfactory sensory neurons in zones II, III, and IV of the OE. Axons of zone I sensory neurons do not express OCAM. Tracing of OCAM-expressing olfactory axons to their terminals in the glomeruli showed zonally segregated projections of olfactory axons; OCAM-negative zone I axons project to

glomeruli in the rostrodorsal *zone I* of the MOB, whereas OCAM-positive zones II, III, and IV axons project selectively to caudoventral *zones II*, *III*, and *IV* of the MOB (Fig. 2). A complementary pattern was reported in the expression of CC2 carbohydrate epitope, which is only positive for zone I axons (*21*). Although molecular markers that distinguish glomeruli among *zones II*, *III*, and *IV* are still lacking, in situ hybridization studies of MOB sections with odorant receptor probes (*22*), together with studies of anatomical tracing of olfactory axons (*23*), suggest that the MOB may comprise four spatially segregated zones corresponding to the four zones in the OE. Thus, odor information received by sensory neurons in a given zone of the OE is thought to be transmitted to glomeruli and then transferred to mitral and tufted cells in the corresponding zone of the MOB.

Glomerular convergence. The olfactory axons can find their specific target glomeruli in the MOB. Recent studies have unraveled the highly ordered glomerular convergence pattern of olfactory axon projection: Olfactory sensory neurons expressing a given odorant receptor converge their axons onto a few defined glomeruli (Fig. 2).

Physiological studies had suggested the glomerular convergence pattern as one of the plausible models for explaining the tuning specificity of olfactory bulb neurons (*24–27*). The glomerular convergence has been visualized by two types of experiments. In situ hybridization analysis showed the presence of odorant receptor messenger RNA (mRNA) in the olfactory axon terminals in glomeruli, indicating that the sensory neurons expressing a given odorant receptor mRNA converge their axons to particular glomeruli (*22*). Evidence that is more conclusive of the glomerular convergence was presented by using a gene-targeting technique, knock in, a method of replacing a particular gene with another gene construct (*28–30*).

Tuning of Individual Glomerular Modules to Specific Molecular Features

The glomerular convergence does not necessarily indicate that all olfactory axons converging onto a single glomerulus derive from the same type of sensory neurons expressing the same type of odorant receptor. It is possible that individual glomeruli receive mixed inputs from multiple types of odorant receptors. This issue was examined in the P2 odorant receptor–IRES-tauLacZ knock-in mice (IRES, internal ribosomal entry site) (*30*). In these mice, all olfactory axons innervating the P2 glomerulus expressed β-galactosidase, indicating that the P2 glomerulus receives olfactory axon inputs exclusively from sensory neurons expressing the P2 odorant receptor (*31*). With an extrapolation of this result, it appears likely that each glomerulus is devoted to a single odorant receptor. However, the "one glomerulus–one receptor" hypothesis needs to be examined experimentally for each glomerulus, and it is possible that convergence of inputs from multiple types of receptors occurs in some glomeruli of the MOB.

Functional importance of the glomerular convergence was examined with physiological methods (*32*), including single-unit recordings of spike responses from mitral and tufted cells to odor molecules (*24–26, 33*). Because individual mitral and tufted cells project a single primary dendrite to a single glomerulus, the tuning specificity of given mitral and tufted cells strongly reflects that of the glomerulus they innervate.

Detailed characterization of the tuning specificity of individual mitral and tufted cells was obtained in the rabbit MOB using a battery of odor molecules with systematic variations of molecular conformation (*25, 26*). The results demonstrated that single mitral and tufted cells show excitatory spike responses to a range of odor molecules with similar molecular conformation (Fig. 3). In other words, the molecular receptive range (MRR) (*26, 27, 34*) of individual mitral and tufted cells consists of a range of odor molecules that share characteristic structural features. The characteristic features include (i) the overall stereochemical structure of the hydrocarbon chain (Fig. 3) and (ii) the type and position of the attached functional group. These characteristics of odor molecules are similar to epitopes in the antigen-antibody interactions in the immune system (*35*) and are thus called "odotopes" (*36*). In agreement with the single-unit studies, optical imaging of odorant responses in rat MOBs showed that glomeruli were tuned to detect particular molecular features (*37*).

Mitral and tufted cells that presumably belong to different glomerular modules show different MRRs (*25–27*). The MRRs of two mitral cells located in the ventromedial part of the rabbit MOB are shown in Fig. 3. The mitral cell in Fig. 3A discriminates among different stereochemical isomers of disubstituted benzenes and is tuned selectively to detect those odor molecules that have two side chains in para position. However, the mitral cell in Fig. 3B does not discriminate among different isomers and is tuned to detect disubstituted benzenes that have short side chains in any position (ortho, meta, or para). This suggests that different glomerular modules are tuned to detect different molecular features. In Fig. 3, the odor molecule "*para*-xylene" (shown by an asterisk) is detected by both mitral cells, presumably because it is para-isoform with short side chains.

An individual glomerular module can thus be viewed as a molecular feature–detecting unit. Because an individual odor molecule typically exhibits several molecular features, it may activate a specific combination of the molecular feature–detecting units. This is supported by the results of spatial mapping of glomerular activity after stimulation of the OE with a

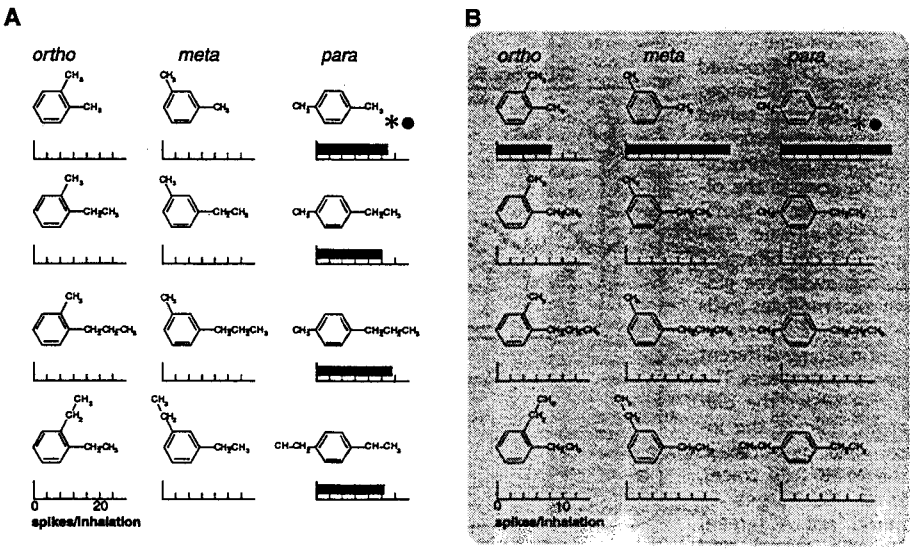

Fig. 3. Different glomerular modules detect different molecular features. Response specificity of two mitral cells (**A** and **B**) to a number of odor molecules made of isomeric disubstituted benzenes. Solid bars indicate the mean number of spikes per inhalation cycle elicited by stimulation with respective odor molecules. The molecular structure of odor molecules is shown above each graph. The neuron in (A) is tuned selectively to para-isomers of disubstituted benzenes, whereas the neuron in (B) responds selectively to disubstituted benzenes with short side chains. Asterisks indicate *para*-xylene, which in this case activates both neurons. Modified from (*26*).

single odor compound as measured by 2-deoxyglucose uptake, c-*fos* expression, functional magnetic resonance imaging, and optical imaging (*37–39*). The quality of an individual odor molecule is thus coded by a combination of activated glomerular modules. This is also the case for a mixture of odor molecules; dozens of odor molecules released from a particular object may activate a selective set of glomerular modules. Regardless of the complexity of odor molecules emitted from a given object, its olfactory quality may be coded by a specific combination of activated glomerular modules at the level of the MOB.

Spatial Arrangement of Glomerular Modules in the MOB

How are the glomerular modules spatially arranged in the MOB? Glomeruli are parceled into four zones in the MOB (Fig. 2). Examination of tuning specificity of mitral and tufted cells suggests that glomeruli representing odorant receptors with similar tuning specificity are assembled in a local region within a specific zone. For example, mitral and tufted cells in the dorsomedial region in *zone I* of the rabbit MOB show similar MRRs covering *n*-fatty acids or *n*-aliphatic aldehydes or both. In contrast, these neurons rarely respond to *n*-aliphatic alcohols, and they never respond to alkanes (*24, 25, 27*). Glomeruli or mitral and tufted cells in a given region show varying overlapping MRRs (*15, 27, 37*). The local assembly of glomerular modules with varying overlapping specificities to odor molecules seems to be crucial for processing molecular information in the MOB.

An integration into a coherent map of the results of spatial arrangement of glomeruli obtained from in situ hybridization studies (*22*) and odorant receptor-tauLacZ studies (*28, 29*) suggests that each MOB represents two symmetrical sensory maps of odorant receptors, one in the lateral hemisphere and the other in the medial hemisphere of the MOB. The idea of two symmetrical maps is in agreement with mediolateral symmetric distribution of 2-deoxyglucose uptake foci after stimulation with particular odor molecules (*2, 38*). The functional meaning of the possible dual sensory maps in the MOB remains to be elucidated.

Interaction Among Molecular Feature–Detecting Glomerular Modules

The glomerular modules in the MOB interact with each other through neuronal circuits by local interneurons, granule cells, and periglomerular cells. Mitral and tufted cells project secondary dendrites tangentially for long distances and make numerous dendrodendritic reciprocal synapses with granule cell dendrites (Fig. 1). The reciprocal synapse consists of a mitral-to-granule glutamate-mediated excitatory synapse and a granule-to-mitral γ-aminobutyric acid–mediated inhibitory synapse (*8, 40*). Thus, activation of a mitral and tufted cell results in feedback inhibition of the cell, as well as lateral inhibition of neighboring mitral and tufted cells (*8, 40, 41*). The primary dendrites of mitral and tufted cells form dendrodendritic reciprocal synapses with periglomerular cells within the glomerulus. Some of the periglomerular cells send inhibitory projections to the dendrites of neighboring mitral and tufted cells, suggesting that periglomerular cells also provide lateral inhibition of mitral and tufted cells. Accumulating evidence suggests that interactions among mitral and tufted cells through these interneurons play a central role in the processing of olfactory information (*33, 42, 43*).

Enhancement of tuning specificity by lateral inhibition. Of particular interest is the lateral inhibition mechanism by which activation of mitral and tufted cells associated with one glomerular module results in the inhibition of mitral and tufted cells associated with neighboring glomerular modules (*8, 33, 44*). Single-unit recordings from mitral and tufted cells in the rabbit MOB showed that spike activity of an individual cell is inhibited by a defined subset of odor molecules with structure that is closely related to the excitatory odor molecules (*26, 42*). A pharmacological blockade of the dendrodendritic synapses between mitral/tufted and granule cells greatly reduces the odor-induced lateral inhibition. The lateral inhibition through the dendrodendritic reciprocal synapses with granule cells may enhance the contrast between strongly activated and faintly activated glomeruli and thus sharpen the tuning specificity of individual mitral and tufted cells to odor molecules. The second-order mitral and tufted cells may thus be more sharply tuned to specific molecular features than olfactory sensory neurons are (*34, 42*).

Synchronized oscillatory discharges of mitral and tufted cells and binding of different glomerular modules. At the level of the MOB, the quality of stimulus odor is encoded by a specific combination of activated glomerular modules. How does the local neuronal circuit in the MOB contribute to the combination and integration of signals received by different glomerular modules? A recent physiological study (*43*) raised the possibility that the local neuronal circuit generates synchronized oscillatory discharges (*45*) of bulbar output neurons, mitral and tufted cells, thereby contributing to the combining of signals from different glomerular modules at the level of olfactory cortex (Fig. 4). Synchronized oscillatory discharges are thought to play an important role in the insect central olfactory system (*46*).

Inhalation of odor molecules elicits a prominent oscillation (30 to 80 Hz) of local field potentials (*47*), imply that many mitral and tufted cells respond with synchronized spike discharges. Dendrodendritic synaptic connections between mitral/tufted cells and granule cells are thought to be responsible for generating the oscillatory local field potentials (*8, 40, 48*). Simultaneous recordings from two mitral/tufted cells located 300 to 500 μm apart (*43*) showed that synchroniza-

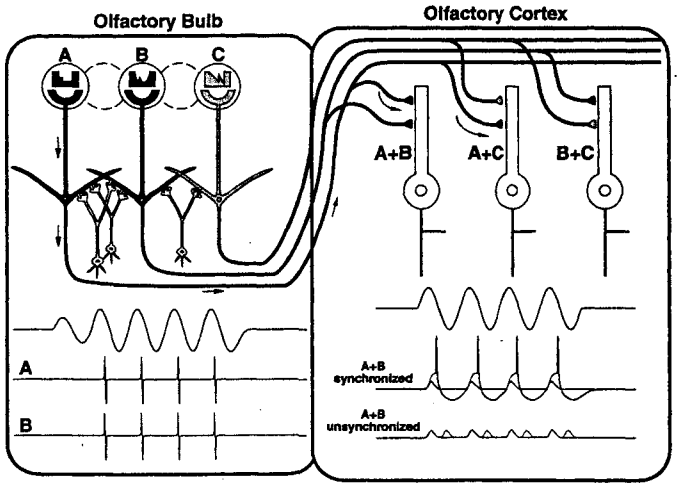

Fig. 4. Synchronized oscillatory discharges of mitral and tufted cells and presumptive combination-detecting neurons in the olfactory cortex. **(Left)** The schematic diagram of the olfactory bulb shows three glomerular modules (cells A through C) representing three different odorant receptors. The traces under the diagram indicate the local field potential in the MOB (top trace), spike discharges of mitral cell A (green) (middle trace) and spike discharges of mitral cell B (orange) (bottom trace). Spike discharges are synchronized between cells A and B. **(Right)** Diagram of the olfactory cortex indicates presumptive convergence of mitral cell axons onto individual cortical neurons. The traces indicate oscillatory local field potential in the olfactory cortex (top trace), synaptic and spike potentials in the hypothetical cortical neuron (A + B) when the inputs are synchronized (middle trace), and synaptic potentials when the inputs are unsynchronized (bottom trace). In the middle trace, temporal summation of synaptic inputs from mitral cells A and B gives rise to spike discharges of this cortical neuron.

tion of spike discharges occurs during odor stimulation among specific pairs of mitral/tufted cells that are associated with different glomerular modules (Fig. 4, left); a clear synchronization was observed in about one-fourth of the mitral and tufted cells examined.

If axons of two mitral/tufted cells belonging to different glomerular modules converge onto the same target neuron in the olfactory cortex, the cortical neuron may serve as a combination detector whose activity represents combined activation of the two glomerular modules (Fig. 4). Synchronization of spike discharges of the bulbar output neurons may greatly enhance the probability of driving the target cortical neuron because of the temporal summation of synaptic inputs from the two mitral/tufted cells (the trace shown by A + B synchronized in Fig. 4, right). Thus, synchronization of two mitral/tufted cells associated with different glomerular modules might serve as a mechanism for the temporal binding of signals from different odorant receptors. During inhalation of odor molecules emitted from a specific object, synchronized spike responses may occur in a number of mitral and tufted cells associated with a specific subset of glomeruli representing a selective combination of odorant receptors.

The above discussion leads to the hypothesis that the strength of the dendrodendritic reciprocal synaptic connections with granule cells that bridge two different mitral/tufted cells may determine the degree of spike synchronization. If this is the case, dendrodendritic reciprocal synapses can serve as a substrate for mediating the temporal and functional binding of signals from different odorant receptors. Of particular interest is the possibility that a plastic change in the strength of the dendrodendritic synapses may result in a change in the strength of the functional binding of signals among different odorant receptors. It has been suggested that at least a part of olfactory or pheromonal (or both) memory trace resides in the dendrodendritic reciprocal synapses (*49*). One of the basic mechanisms for olfactory memory might be to change the strength of the dendrodendritic synaptic connections among specific subsets of mitral and tufted cells. This may cause changes in the efficacy of driving selective subsets of odorant receptor combination–detecting neurons in the olfactory cortex.

Conclusion

The finding of a large multigene family of odorant receptors (*6*) has triggered rapid advances concerning the functional organization of the mammalian olfactory nervous system. The initial step was an understanding of the functional roles of individual sensory neurons in the OE. Next came the elucidation of the axonal projection patterns of sensory neurons to the MOB. This led to the notion that the functional logic for discrimination among different odor molecules is determined by the pattern of olfactory axon connectivity to the MOB, the glomerular convergence. We now know of the following neuronal mechanisms for the processing of odor molecule information in the MOB: (i) Individual glomerular modules function as a molecular feature–detecting unit, and (ii) local neuronal circuits mediate lateral inhibition and synchronized spike discharges among mitral and tufted cells that belong to different glomerular modules.

However, we still lack basic knowledge of the detailed functional organization of the axonal projection of mitral and tufted cells to the olfactory cortex and of the neuronal circuits in the olfactory cortex (*50*). Thus, the challenge is to understand neuronal mechanisms as to how the olfactory cortex combines or compares signals from 1800 glomerular modules. Newly developed techniques, including transsynaptic labeling of selective neuronal pathways by plant lectin transgenes (*51*), might provide a clue for understanding the axonal connectivity pattern between the MOB and the olfactory cortex. When our knowledge of the olfactory cortex and higher olfactory centers advances, we might be able to determine why roses have a pleasant scent, whereas sweaty socks smell bad.

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