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# Information Processing in the Mammalian Olfactory System

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**Lledo, Pierre-Marie, Gilles Gheusi, and Jean-Didier Vincent.** Information Processing in the Mammalian Olfactory System. *Physiol Rev* 85: 281–317, 2005; doi:10.1152/physrev.00008.2004.—Recently, modern neuroscience has made considerable progress in understanding how the brain perceives, discriminates, and recognizes odorant molecules. This growing knowledge took over when the sense of smell was no longer considered only as a matter for poetry or the perfume industry. Over the last decades, chemical senses captured the attention of scientists who started to investigate the different stages of olfactory pathways. Distinct fields such as genetic, biochemistry, cellular biology, neurophysiology, and behavior have contributed to provide a picture of how odor information is processed in the olfactory system as it moves from the periphery to higher areas of the brain. So far, the combination of these approaches has been most effective at the cellular level, but there are already signs, and even greater hope, that the same is gradually happening at the systems level. This review summarizes the current ideas concerning the cellular mechanisms and organizational strategies used by the olfactory system to process olfactory information. We present findings that exemplified the high degree of olfactory plasticity, with special emphasis on the first central relay of the olfactory system. Recent observations supporting the necessity of such plasticity for adult brain functions are also discussed. Due to space constraints, this review focuses mainly on the olfactory systems of vertebrates, and primarily those of mammals.

## I. INTRODUCTION

Animals discriminate and recognize numbers of chemical signals in their environment, which profoundly influence their behavior and provide them with essential information for survival. In higher organisms, while chemosensitivity involves both taste and smell, most animals mainly rely on olfaction as the principal chemosensory modality. As a result, the mammalian olfactory system regulates a wide range of multiple and integrative func-

tions such as physiological regulation, emotional responses (e.g., anxiety, fear, pleasure), reproductive functions (e.g., sexual and maternal behaviors), and social behaviors (e.g., recognition of conspecifics, family, clan, or outsiders). To achieve this large variety of functions, two anatomically and functionally separate sensory organs are required (56, 127, 186, 238, 313, 321). First, the vomeronasal organ is specialized to sense chemical compounds (e.g., pheromones), specific regarding the origin of the source (227). By transferring information through

the accessory olfactory bulb, this sensory organ provides information about the social and sexual status of other individuals within the species (111). However, recent evidence also suggests some cross-talk between the main and accessory systems. Recent molecular and neurophysiological approaches have offered new insights into the mechanisms of pheromone detection in rodents and into the sensory coding of pheromone signals that lead to gender discrimination or aggressive behavior, for example. They have also shown that the vomeronasal organ does not have an exclusive function with regard to pheromone recognition, but it responds also to molecules other than pheromones, at least in rodents (280). Thus it is highly debated today, to what extent only the vomeronasal organ can detect pheromones, and also to what

extent it can only detect pheromones (46). For more details about the vomeronasal organ and the accessory olfactory bulb, we refer the reader to previous reviews that have specifically addressed their organization and functions (46, 115, 217, 307, 308, 313).

In mammals, the second sensory organ is represented by the olfactory epithelium, which recognizes more than a thousand airborne volatile molecules called odorant compounds (or odorants) (Fig. 1). This neuroepithelium is connected to the next central station for processing olfactory information: the main olfactory bulb (referred to below as the olfactory bulb). While advances in understanding olfactory transduction were taking place, interest in the olfactory bulb was also intensified. This growing interest has been spurred on by discovering

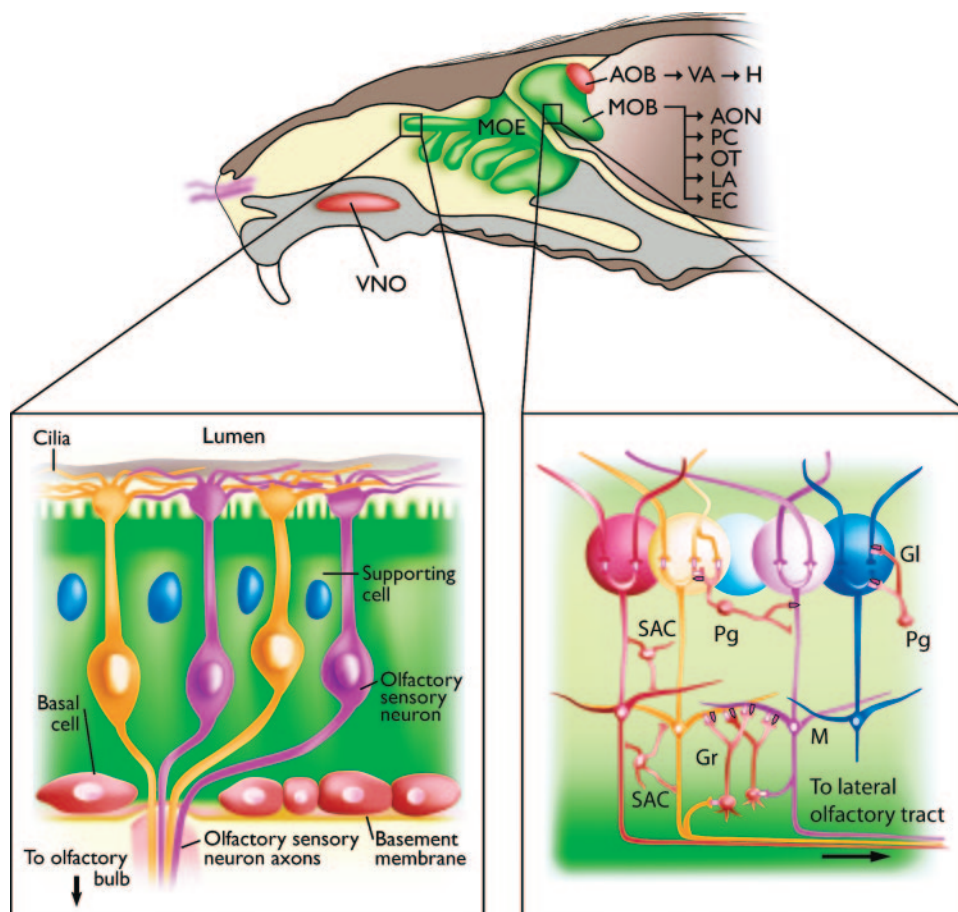


FIG. 1. The olfactory system in rodent. *Top*: a simplified sagittal view of the rat head. The main olfactory system is highlighted in green, and the accessory olfactory system appears in red. The presence of turbinates in the main olfactory epithelium (MOE) increases the surface area of the sensory organ. Axons of sensory neurons in the MOE project to the main olfactory bulb (MOB), and axons of sensory neurons in the vomeronasal organ (VNO) project to the accessory olfactory bulb (AOB). Information provided by pheromone signals is then transmitted to the vomeronasal amygdala (VA) before reaching specific nuclei of the hypothalamus (H). Output projections of the MOB target the primary olfactory cortex that include the anterior olfactory nucleus (AON), the piriform cortex (PC), the olfactory tubercle (OT), the lateral part of the cortical amygdala (LA), and the entorhinal cortex (EC). *Left inset*: schematic illustration of the olfactory epithelium, showing the three major cell types. Note that basal cells constitute a truly neuronal stem-cell population in the adult. *Right inset*: basic circuitry of the main olfactory bulb. Olfactory sensory neurons that express the same odorant receptor gene project their axons to either of two glomeruli (Gl) in the olfactory bulb. Four populations of sensory neurons, each expressing a different odorant receptor gene, are depicted in different colors. Their axons converge on specific glomeruli, where they synapse with the dendrite of local interneurons (periglomerular neurons, Pg) and second-order neurons (mitral cells, M). The lateral dendrites of mitral cells contact the apical dendrites of granule cells (Gr). Short axon cells (SAC) are bulbar interneurons that contact both apical and lateral dendrites of mitral cells. In this *inset*, short white arrows indicate excitatory inputs while red ones inhibitory contacts.

the way the sensory organ connects to the olfactory bulb. Finally, whereas the power of olfactory stimuli in memory and the control of animal behavior have long been recognized, the neural mechanisms underlying these processes have only recently received new interest. Here, we summarize the richness and the kinds of interactions that take place in special areas throughout the olfactory system, emphasizing the more recent results from mice, rats, and humans.

## II. EVOLUTIONARY ASPECTS OF OLFACTION

Sensory perception is a process by which information from the external world is subsequently reformatted into an internal state. A number of very different but sophisticated ways, based on distinct sensory channels, have risen according to the phylogenetic position of the species. Among them, communication with the environment and other organisms through chemical cues is an essential process for the survival of all multicellular systems.

Indeed, chemosensation is a fundamental process shared by most organisms, as it is responsible for recognizing external chemical signals that influence behavior. The origin of molecule detection dates back to prokaryotes and has evolved into four distinct modalities in most vertebrates. The main olfactory system, the accessory olfactory system, the gustatory system, and the so-called common chemical sense mostly carried by trigeminal sensory neurons, all differ with respect to receptor molecules, receptor cells, and wiring of the receptor cells with the central nervous system. The main olfactory system detects only volatile odorants, whereas the accessory system picks up less volatile or even water-soluble odorants (418, 476). It is generally thought that the accessory system specializes in pheromone detection, whereas the main system detects common odorants (56; but see Refs. 109, 204, 375, 436, 443).

Olfaction is applied to chemosensory systems that detect chemicals emanating from a distant source. In contrast, when chemosensory systems require physical contact with the source for detection, they are called gustatory. Because vertebrates have anatomically separate olfactory and gustatory systems, only olfaction will be considered here in analogous systems belonging to different phyla.

In terrestrial environments, chemical signals can be either volatile or nonvolatile. Accordingly, terrestrial vertebrates have two functionally and anatomically distinct olfactory systems: one detecting volatile cues (the main olfactory system) and another thought to process mostly nonvolatile signals (the vomeronasal system) (Fig. 1). Such a dichotomy has been brought into play to support the long-standing hypothesis according to which the

vomeronasal system evolved as an adaptation to terrestrial life (51). Today, accumulated evidence rather contests this assumption. For instance, we now know that modern amphibians and amniotes also possess vomeronasal organs. It is thus likely, but yet not demonstrated, that their last common ancestor also possessed a vomeronasal organ. Furthermore, two families of fully aquatic, nonmetamorphosing salamanders, were shown to possess vomeronasal systems, implying that the emergence of the vomeronasal system preceded that of terrestrial life (120). The evolution of a vomeronasal system in aquatic species might rather provide a selective advantage for terrestrial life, and consequently, it could have been retained in many species of terrestrial vertebrates. In spite of this, anatomical studies, and most recently molecular studies, indicate that the selective pressure to retain vomeronasal chemosensory input has been lost in higher primates. As a result, Old World primates, apes, and humans might not have retained a functional vomeronasal system (115, 308). Alternatively, species without a distinct vomeronasal system may still have an accessory olfactory system intermingled within the main system. Thus it is yet possible that the accessory system did not "arise" at some point of the vertebrate evolution, but rather it just became anatomically separated from the main system.

As our knowledge about the neurobiology of olfaction is growing, it is becoming incredibly evident that the main olfactory systems of animals in disparate phyla have many striking features in common (121, 194, 253). For instance, vertebrate and insect olfactory systems display common organizational and functional characteristics. Further recent works that were undertaken to broaden this scope to include nematodes, mollusks, and crustaceans have only strengthened this assumption. Existence of these similarities either results from sharing inheritance or might come from independent evolution through convergence (1, 194, 431). Whatever the mechanism is, the initial common event, shared by all odorant detection systems, requires the specific interaction of odorant molecules with specific receptors expressed on the cilia of sensory olfactory neurons before conveying information to central structures.

Basically, four features are shared by all olfactory systems. They include 1) the presence of odorant binding proteins in the fluid overlying the receptor cell dendrite; 2) the requirement of G protein-coupled receptors as odorant receptors (even though some sensory neurons may use transmembrane guanylate cyclase receptors such as in *Caenorhabditis elegans* and mammals); 3) the use of a two-step signaling cascade in odorant transduction; and 4) the presence of functional structures at the first central target in the olfactory pathway (194). All these characteristics may represent adaptations that have evolved independently, and therefore might provide us with valuable information about the way the nervous



system processes odorant stimuli. Alternatively, these shared properties may instead reflect underlying homology or could have arisen independently due to similar constraints (121).

The detection capacity of a wide variety of olfactory systems arises from invariant series of information-processing steps that occur in anatomically distinct structures. In mammals, the olfactory epithelium contains several thousands of bipolar olfactory sensory neurons, each projecting to one of several modules in the olfactory bulb. These discrete and spherical structures, called olfactory glomeruli, are considered to be both morphological and functional units made of distinctive bundles of neuropil (416) (Fig. 1). This term reflects both the homogeneity of the sensory inputs received by the cells in the glomerular unit and the degree to which the neurons in the same glomerular unit are interconnected. Their number varies in different species: rodent olfactory bulbs contain several thousand glomeruli, and fish and insects have 10-fold fewer. In different species, each glomerular structure results from the convergence in the olfactory bulb of 5,000–40,000 axon terminals that establish synapses with dendrites of bulbar output neurons and of various classes of local bulbar interneurons. Because each group of glomerulus-specific output neurons is odorant receptor specific, they form a morphological defined network somewhat analogous to ocular-dominance columns in visual cortex or to barrels in the somatosensory cortex. It is also worth noting that a number of mechanisms have evolved to ensure that only a single odorant receptor is expressed per sensory cell. In rodents, tight transcriptional control results in the choice of one among a possible thousand odorant receptor genes (292). This extremely large repertoire of odorant receptors is undergoing rapid evolution, with at least 20% of the genes lost to frame-shift mutations, deletions, and point mutations that are the hallmarks of pseudogenes (81, 383; reviewed in Refs. 313, 454). Facing a changing environment, this characteristic may reflect the pressure made on a gene family to diversify and generate large numbers of new receptors that might confer new selective advantages. Interestingly, ~50% of human odorant receptor genes carry one or more coding region disruptions and are therefore considered pseudogenes (157, 291, 384). In fact, this massive pseudogenization of the odorant receptors repertoire in humans and Old World primates is preceded by a moderately high level of pseudogenes (~30%) (153). In contrast, of the thousand odorant receptor sequences in the mouse genome, ~20% are pseudogenes (158, 490). Thus there has been a decrease in the size of the intact odorant receptor repertoire in apes relative to other mammals, with a further deterioration of this repertoire in humans (153, 383). Because such decline occurred concomitant with the evolution of full trichromatic vision in two separate primate lineages, it has recently been proposed that the weaken-

ing of olfaction might result from the evolution of full color vision in our primate ancestors (154).

### III. FROM ODORANT MOLECULES TO CORTICAL CENTERS

The olfactory system sits at the interface of the environment and the central nervous system. It is responsible for correctly coding sensory information from thousands of odorous stimuli. To accomplish this, odor information has to be processed throughout distinct levels. At each one, a modified representation of the odor stimulus is generated (247, 261). To understand the logic of olfactory information processing, one has first to appreciate the coding rules generated at each level, from the odorant receptors up to the level of the olfactory cortex. In mammals, the initial event of odor detection takes place at a peripheral olfactory system, the olfactory epithelium of the nasal cavity, which is located at the posterior end of the nose. This area is exquisitely tuned to detect an immense variety of volatile molecules of differing shapes and sizes that are often present in miniscule quantities in the environment (55, 126, 150, 194, 382). Olfactory transduction then starts with about a thousand different types of odorant receptors located on the cilia of sensory neurons that comprise the olfactory neuroepithelium (490). The sensory neurons project to a small number of olfactory glomeruli paired on both the medial and lateral aspects of the olfactory bulb. About 20–50 second-order neurons emanate for each glomerulus and project to a number of higher centers, including the olfactory cortex. Using a trans-synaptic tracer expressed in olfactory receptor neurons under the control of two specific olfactory receptor promoters, it has been shown that the projection of bulbar output neurons receiving sensory inputs from homologous olfactory neurons, form reliable discrete clusters in different regions of the olfactory cortex (496). Within the anterior piriform cortex, such clusters were partly overlapping, but clearly distinct between the two olfactory receptor promoters used. A certain overlap between more diffuse projections to higher olfactory centers may constitute the anatomical basis for cross-talk between information strands emanating from different odorant receptors. This characteristic is probably helpful to integrate multiple modules of olfactory information into a composite gestalt, specific for a particular scent made of numerous chemical compounds.

#### A. Olfactory Sensory Neurons and Signal Transduction

The olfactory sensory organ is made of a specialized olfactory neuroepithelium that directly interacts with inhaled odorants (116, 127, 312). This organ is exquisitely

tuned to recognize an immense variety of molecules, different in shape, size, or chemical function that will be further encoded by neuronal circuits. It is made up of three major cell types: sensory neurons, supporting sustentacular cells, and several types of basal cells including the olfactory stem cells (Fig. 1). The former are unusual in that they are short-lived cells that exist for only 30–60 days (174, 326). Once mature, the sensory bipolar neurons extend a single dendrite to the neuroepithelial surface from the apical pole. Numerous cilia protrude from this dendrite and extensively invade the mucus lining of the nasal cavity. Odor molecules that dissolve in the nasal mucus bind to specific receptors on the cilia of olfactory sensory neurons. Therefore, the first step takes place at the interaction between odorant molecules and their respective receptors in sensory neuron dendrites (56, 57, 312, 313, 490). Odorant receptors can bind a number of volatile compounds with rather moderate affinity despite the overall high sensitivity of the system (230). Because each individual receptor is substantially cross-reactive for different ligands, the receptor repertoire might evolve according to the concentration and the mixture of odorants (113). Odorant receptors belong to the family of the G protein-coupled seven-transmembrane proteins (382), and several findings suggest that these receptors signal through the tissue-specific downstream components, the heterotrimeric G protein subunit  $G_{olf}$  (368), type III adenylyl cyclase (348, 381, 423), and a cyclic nucleotide-gated ion channel (78, 130, 265, 330, 497) to mediate odor detection. In addition to this major pathway, several other second messenger cascades [e.g.,  $Ca^{2+}$ , inositol trisphosphate ( $IP_3$ ), or cGMP] that are activated upon odorant detection are thought to regulate secondary events such as odorant adaptation for instance (159, 401).

According to recent genome-wide analysis, there are between 1,000 and 1,300 odorant receptor genes, with an intact open reading frame number, in the mouse. This constitutes the largest gene family so far in the mammalian genome, perhaps in any genome (482, 490, 491). These genes have a compact gene structure and are scattered throughout the genome in clusters of various sizes. Olfactory receptor genes have been isolated from several vertebrate species including rat, mouse, human, catfish, zebrafish, dog, frog, chicken, pig, opossum, mudpuppy, and lamprey. Homologies are not recognizable between insect and vertebrate olfactory receptors (455) and are rather minor between fish and mammalian receptors (335, 462).

Olfactory receptor genes form also the largest category of genes with monoallelic expression. This principle was originally demonstrated by single-cell reverse transcription-polymerase chain reaction (RT-PCR) on pools of olfactory sensory neurons using limiting dilution and polymorphic alleles (81) and led to the one receptor-one neuron hypothesis. However, an alternative model proposing that a single neuron expresses during differentia-

tion zero, one, or a few odorant receptor genes has recently challenged this view. According to this hypothesis termed "oligogenic expression," the developmental phase of oligogenic expression is followed by positive and negative selections resulting in cells with one expressed receptor (314).

Once expressed in the membrane of the sensory neuron, the activation of olfactory receptors induces a cascade of intracellular events resulting in an influx of both  $Na^+$  and  $Ca^{2+}$  (129, 331) that culminate in the generation of a graded receptor potential in the soma of the sensory neuron (151, 347). Electrophysiological studies indicate that odorant sensitivity and the odorant-induced current are uniformly distributed along the cilia, suggesting that all the components of the immediate responses to odorants are localized to the cilia. From its basal pole, the sensory neuron sends a single axon through the basal lamina and cribriform plate (of the ethmoid bone) to terminate in the olfactory bulb, the first central relay (Fig. 1). The unmyelinated sensory neuron axons merge into densely packed fascicles to form the olfactory nerve, which transmits the electrical signals to the bulb. Throughout the olfactory pathway, a unique population of glia, the ensheathing cells, forms the bundles of axons that make up the olfactory nerve. The gathering of sensory axons may lead to ephaptic transmission that allows synchronizing action potential in neighboring fibers, with submillisecond precision, by extracellular electrical field (38). Upon reaching the olfactory bulb, axon terminals from olfactory sensory neurons that express the same odorant receptor converge on a specific glomerulus (310) and arborize to form ~15 synapses with target dendrites (184, 242). Axonal projections from the sensory neurons to the olfactory bulb form reproducible patterns of glomeruli in two widely separated regions of each bulb, creating two mirror-symmetric maps of odorant receptor projections (311). Surprisingly, it has been shown that odorant receptor identity in epithelial neurons determines not only glomerular convergence and function, but also organizes the neural bulbar circuitry (29).

It is important to note that there is no strict spatial relationship between the arrangement of excitatory projections of the olfactory sensory neurons in the olfactory bulb and the regions of mucosa from which they originate. This feature contrasts with the spatial organization of other sensory systems where afferent inputs are organized in a rather precise topographical mode. Similarly, as described below, much evidence indicates that bulbar outputs do not have point-to-point topographical projections to their target structures, which are characteristic of all other sensory systems. In mammals, the convergence ratio of sensory neurons-to-olfactory bulb output neuron is very large: ~1,000:1. A bulbar output neuron thus forms its responses to odors from very large numbers of converging sensory inputs, ensuring that postsynaptic aver-

aging increases signal-to-noise ratios. Interestingly, it has recently been shown that the mechanism underlying the extensive organization and targeting, between the olfactory sensory neurons and the olfactory bulb, implicates an activity-dependent mechanism. With the use of random inactivation of the X-chromosome in a genetic model to establish competition between normal and channel-deficient olfactory neurons, an activity-dependent competition between sensory neuron terminals was indeed revealed (492). Experience-dependent selection for trophic factors, as has been described in other neuronal systems, could account for this selection process (369). Two recent reports highlight further mechanisms based on spontaneous and odorant-evoked neuronal activity in the establishment and maintenance of the sensory projections. First, it was proposed that spontaneous activity of olfactory sensory neurons plays a permissive rather than instructive role in this process (483). Then, it was demonstrated that neuronal activity could also help to weed out weak synaptic connections, thereby contributing to spatial refinement and plasticity of the sensory projections (495). Clearly, more work will be needed to clarify the mechanism by which neuronal activity might be able to refine and stabilize sensory projection to the olfactory bulb.

## B. Synaptic Transmission at the First Processing Stage

Unlike other sensory neurons, axonal termini of olfactory sensory neurons synapse directly onto second-order neurons within the forebrain (90, 173, 325). There, they form synapses impinging onto both output (second-order) neurons and local interneurons of the olfactory bulb (124, 250). At least in mammals, this makes the olfactory bulb the major site of integration for the olfactory information. The topography of these connections has been the subject of extensive studies revealing that sensory neurons expressing a given receptor project to a given subset of glomeruli (Fig. 1). It was concluded that the processing of olfactory information adheres to a certain spatial distribution, at least between sensory neurons and the olfactory bulb itself (see below), and remarkably such topographical organization is conserved in different species across phyla.

### 1. Characteristics of sensory inputs onto bulbar neurons

In the glomeruli, olfactory nerve terminals form excitatory glutamatergic synapses with the apical dendrites of the bulbar output cells (16, 32, 124), and with periglomerular interneurons (22, 235, 249, 357). These two olfactory nerve-evoked excitatory response types comprise fast amino-3-hydroxy-5-methyl-4-isoaxazole-propionic acid (AMPA) and slow *N*-methyl-D-aspartate (NMDA) compo-

nents (16, 22, 32, 80, 85, 124). The latter is particularly long lasting and thus plays an important role in the bulbar output by maintaining a pattern of sustained discharge of output neurons (69, 193).

It should be kept in mind that a given glomerulus can respond to multiple odorants, and a given odorant activates multiple glomeruli. As a result, odor identity is represented rather combinatorially by patterns of glomerular activation that might rely, at least in part, on the properties of synaptic transmission between sensory neurons and their postsynaptic targets in the bulb.

Since the olfactory system can detect extremely faint sensory signals, some mechanisms might occur to reliably transmit information contained in the odorant-evoked firing of sensory neurons to the brain. In other sensory systems, some devices such as the synaptic ribbons in the retina or the cochlea indeed enable sustained and reliable synaptic transmission (147, 350). Because such a presynaptic specialization is not present in the terminals of olfactory sensory neurons, other features supporting a reliable synaptic transmission might be involved. Detailed analyses of olfactory nerve-evoked excitatory responses in olfactory bulb slices have shown a marked paired-pulse depression, supporting that glutamate release from sensory neuron terminals is high under normal conditions (17, 200, 235, 328, 409). The presence of presynaptic cyclic nucleotides (both cAMP and cGMP) provides a mechanism by which afferent inputs to the bulb are highly reliable (328). To characterize this feature, the properties of transmitter release from olfactory nerve terminals have been further examined. With the use of stationary fluctuation analysis of AMPA receptor excitatory postsynaptic currents (EPSCs) and the progressive blockade of NMDA receptor EPSCs by (5*R*,10*S*)-(+)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-10-imine hydrogen maleate (MK-801), it was demonstrated that the probability of glutamate release from nerve terminals is unusually high ( $\geq 0.8$ ) (327). This suggests that olfactory nerve terminals have specialized features that may contribute to the reliable transmission of sensory information from the olfactory sensory organ to the first central relay. This might be critical to amplify extremely faint signals. In the presence of threshold odorant concentrations, such features would serve to ensure transmission of information contained in the sparse firing of sensory neurons. In contrast, the strong paired-pulse depression likely constrains the saliency of bursts evoked by high concentrations of odorant to the first spike. Supporting the notion that the probability of release from olfactory nerve terminals is near maximal when odorants evoke action potentials is the fact that activation of any presynaptic metabotropic receptors, known to be present on olfactory nerve terminals, has been shown, so far, to reduce but never strengthen the synaptic transmission between olfactory sensory neurons



and the olfactory bulb (e.g., Refs. 17, 123). Hence, periglomerular local neurons release dopamine and GABA within olfactory bulb glomeruli (301, 425). These local neuromodulators, which reduce both the transmitter release from olfactory nerve terminals and paired-pulse depression, via activation of presynaptic D<sub>2</sub> dopamine and GABA<sub>B</sub> receptors (17, 123, 200, 328), could further maintain relative response magnitudes across a wide range of input intensities, reduce sensory noise, and improve contrast between neighbor-activated glomeruli.

In addition to this unique presynaptic feature of olfactory receptor neurons, an alternative mechanism for signal amplification coming from the sensory organ itself relies on synchronizing glutamate release from sensory neuron terminals together. This might occur when presynaptic action potentials are synchronized (38). The mammalian olfactory nerve is arranged in configurations that may favor such synchronization. These axons lack myelin, and they are arranged in densely packed fascicles (94, 110, 175). Each fascicle contains between 10 and 200 axons (297), with each axon having a diameter of ~0.2  $\mu\text{m}$  (175). Axons within a fascicle are oriented parallel to each other and do not branch before they reach their termination site in the glomeruli of the olfactory bulb (94, 317). The high packing density and the geometry of these axons suggest that neighboring axons can be synchronized with each other through several forms of interactions. Although there are no known chemical synapses between sensory neurons, there are other potential means of communication between these nonmyelinated axons, including gaseous messengers (44), gap junctions (488), ephaptic interactions (direct transmission of electrical signals) (38), and extruded potassium (36). Such synchronization might help to produce an oscillatory drive onto bulbar output neurons (188, 296) that is subsequently filtered and amplified by intrinsic subthreshold voltage oscillations occurring in the depolarized state of bistable output neurons (193).

## 2. Synaptic processing within olfactory bulb microcircuits

Because of its relatively simple anatomical organization and easy accessibility, the olfactory bulb has been a favored model system for investigating neural processing of sensory information. Odors elicit a well-organized pattern of activation in glomeruli across the surface of the olfactory bulb, but the mechanisms by which this map is transformed into an odor code are still unclear. With the advance in recent years of *in vitro* brain slice preparation, as well as *in vivo* techniques that can be applied on live animals, recently complex processing of the olfactory information has started to be revealed.

Since Cajal's pioneering studies, it is known that the main output neurons of the bulb, the so-called mitral cells,

are located in a single lamina, the mitral cell layer. Their primary (or apical) dendrite, extending vertically from its soma, contacts one glomerulus (at least in mammals), where massive interactions with bulbar interneurons and olfactory nerve terminals occur. Most of the local interneurons have dendrites restricted to one glomerulus and impinge onto olfactory nerve terminals or mitral cell primary dendrites. In contrast to the primary dendrite, mitral cell secondary (or basal) dendrites radiate horizontally, up to 1,000  $\mu\text{m}$ , to span almost entirely the olfactory bulb (318, 346). In the external plexiform layer, they interact with inhibitory axonless interneurons, named granule cells, the most numerous cellular populations within the bulb. Both sensory excitatory inputs and the intrabulbar circuit, which mainly includes two distinct connections, between primary dendrites and periglomerular cells, and between secondary dendrites and granule cells (415), tightly controlled the firing activity of output neurons. The main difference between periglomerular and granule cells is that the former mediate mostly interactions between cells affiliated with the same glomerulus while granule cells mostly mediate interactions between output neurons projecting to many different glomeruli. However, periglomerular neurons might exert also a distant action by interacting with another class of bulbar interneurons. The functional consequences of this synaptic organization will be described below.

The synaptic mechanisms that play a key role in the circuits of the olfactory bulb have two unusual features. First, many bulbar neurons communicate via reciprocal dendrodendritic synapses (357, 361, 365). The reciprocal circuit provides inhibition that forms the basis for a reliable, spatially localized, recurrent inhibition (365). A mitral cell's synaptic depolarization, driven by the long-lasting excitatory input from the sensory neurons, triggers glutamate release by dendrites and thus depolarizes interneuron dendrites and spines (118, 208, 402, 444). This, in turn, elicits the release of GABA directly back onto output neurons (208, 210, 339, 402). Second, several bulbar neuronal types are known to modulate their own activity through the transmitters that they themselves release (207, 403, 425), and transmitter release might occur, in some cell types, through an action potential-independent manner (208, 210, 402).

Because secondary dendrites have large projection fields and extensive reciprocal connections with interneurons (415), each bulbar local neuron may contact the dendrites of numerous output neurons. This suggests that not only do dendrodendritic interactions provide a fast and graded feedback inhibition, but they also offer a unique mechanism for lateral inhibition between output neurons that innervate different glomeruli (208, 295, 402, 404, 407, 481). Consequently, it has been demonstrated that bulbar projecting neurons connected to different glomerular units, and which respond to a wide range of



related odor molecules, also receive inhibitory inputs from neighboring glomerular units via lateral inhibition at dendrodendritic connections (321). Thus the propagation of action potential into the lateral dendrites, and the possible spread of excitation through granule cell dendrites, contribute to a "spatial" contrast mechanism that sharpens the tuning of output neuron odorant receptive fields (447, 481, but see Refs. 258, 260).

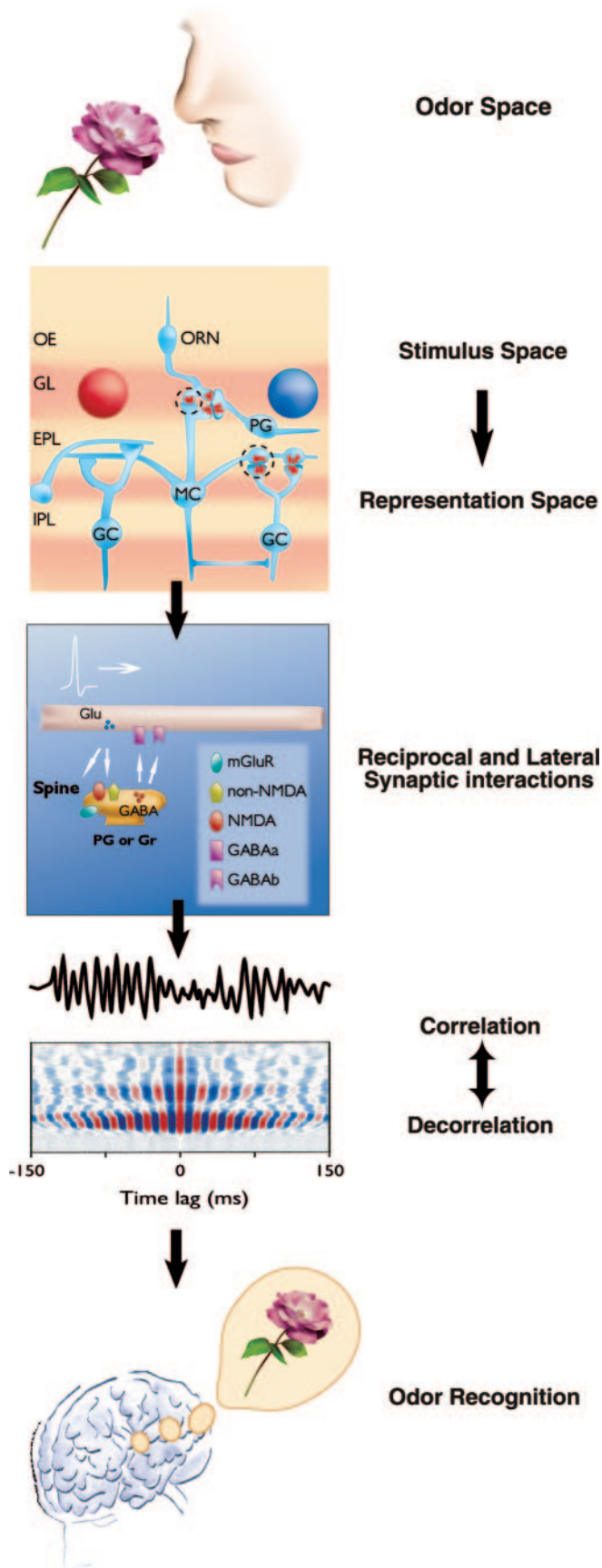
More recently, a distinct and novel intrabulbar network was found to fulfill a similar function. The so-called "short axon" cells, located near glomeruli, send interglomerular axons over long distances to excite inhibitory periglomerular neurons (20). This interglomerular center-surround inhibitory network, along with the mitral-granule-mitral inhibitory circuit above described, forms a serial, two-stage inhibitory circuit that could enhance spatiotemporal responses to odors. In this case, information is transmitted not only vertically across the glomerular relay between sensory neurons and output neurons, but also horizontally through local interneuron connections that are activated in odor-specific patterns. Such a model based on lateral connection, originally introduced into neuroscience to explain visual contrast enhancement in the retina (187), has been mathematically extensively characterized (14, 148, 451, 453). Both anatomical and functional analyses support the existence of lateral inhibitory mechanisms, in the olfactory bulb, through which activity in few stimulated output neurons may lead to suppression of other neighboring neurons innervating distinct glomeruli. This inhibition was proposed to refine the process of odor information. For instance, examination of the responses of individual bulbar neuron to inhalation of aliphatic aldehydes reveals that many individual cells are excited by one subset of these odorants, inhibited by another subset, and unaffected by yet a third subset (321). Glomerular unit has thus the potential to respond to a wide range of related odorants but also receives inhibitory inputs from neighboring glomerular units through lateral inhibition. The quality of the odor stimulus is first encoded by a pattern of sensory input activity across glomeruli that are, at least in first approximation, not shaped by inhibition. The odor stimulus is further encoded by mitral cell activity patterns within the olfactory bulb by a specific combination of activated mitral cells that critically depend on GABAergic inhibition.

In addition to the lateral inhibition model, the long-range projections of secondary dendrites could support a novel perspective that has emerged recently and views bulbar microcircuits as a nonlinear dynamical system (260). According to this view, the olfactory bulb transforms stationary input patterns into time-varying output patterns, moving along input-specific trajectories in coding space. In this framework, the main function of bulbar microcircuits would be to enable odor-specific dynamics that can decorrelate input patterns. Such a decorrelation

function would distribute clustered input patterns more evenly in coding space, thus optimizing the use of the coding space for discrimination and other olfactory tasks (Fig. 2). It is here important to note that not only decorrelation can be achieved by lateral inhibition but also that inhibition is crucially involved in the decorrelation. Supporting this notion is the fact that the bulbar inhibition is not restricted to near neighbors, but can extend at least over medium spatial ranges. In other words, because secondary dendrites project to long distances, the olfactory bulb networks aim to reformat combinatorial representations so as to facilitate their readout by downstream centers. This model is consistent with experiments showing that GABAergic reciprocal inhibition contributes to synchronizing the output neuron activity (60, 100, 228) mainly through granule cell spine activity (254).

By regulating the extent of back-propagation of action potential into the dendrites, different subsets of dendrodendritic synapses might be recruited. Invasion of output neuron dendrites by back-propagating axosomatically initiated action potentials provides the depolarization required to recruit the local inhibitory circuit (35, 79, 83, 208, 278, 295, 477). Dual patch-clamp recordings have revealed that back-propagation, from the soma into the primary dendrite, does not attenuate (35), but this is less clear for the propagation into secondary dendrites. Some reports have shown that single spikes were attenuated as they propagate out into the dendrite (83, 278, 295) while others have demonstrated a more reliable propagation (477). These apparently contrasting observations might result from different experimental conditions that regulate dendritic back-propagation such as intrinsic membrane properties, ionic channel modulation, or the level of dendrodendritic inhibition (277). Nevertheless, morphological observations, indicating a progressive tapering of secondary dendrites, support a reliable propagation of action potential into the distal dendrite (318). In agreement with this, *in vivo* two-photon calcium imaging indicates that under physiological conditions 40-Hz spike trains can indeed access the full length of the dendrites without significant attenuation (76, 97).

In addition to inhibitory inputs arising from granule cells, it has been reported that output neuron secondary dendrites receive large excitatory inputs when either inhibition was antagonized or magnesium was removed from the external medium (18, 142, 207). In fact, the first evidence for self-excitation in mitral cells came from the turtle olfactory bulb, when injection of a depolarizing current into a mitral cell elicited a prominent glutamate receptor-dependent afterdepolarization (337). On the basis of its resistance to blockade of action potentials with tetrodotoxin, it was suggested that self-excitation originated from dendrodendritic synapses rather than from recurrent axon collaterals. Patch-clamp studies have shown that both AMPA and NMDA glutamate receptors



can mediate self-excitation (393, 405) on both primary and secondary dendrites (393). More recent studies performed in slices have demonstrated that mitral cells receiving synaptic inputs within a common glomerulus laterally excite one another through chemical and/or electrical transmission (69, 207, 406, 448). Thus secondary dendrites also serve the more classical function of somatic input devices, integrating both excitation and inhibition from nearby local interneurons. In mammals, excitatory synapses onto mitral cells have been localized exclusively to the apical dendritic tufts that receive primary sensory afferents (249, 357, 411). However, glutamate autoreceptors have been localized anatomically on output neurons near dendrodendritic synapses (316), but their exact location with respect to the glutamate release site is still not known (395). The origin of the excitatory inputs to the secondary dendrites is therefore highly debated. It has been proposed that glutamate released from mitral cells could activate glutamate autoreceptors that can in turn enhance their firing (142, 207, 393). Self-excitation can drive an afterdischarge in output neurons that last for hundreds of milliseconds, reflecting the fact that a significant component of the response is mediated by slow NMDA autoreceptors (403). In addition, using a combination of in vitro whole cell recordings and immunogold detection of glutamate, it was demonstrated that ionotropic glutamate receptors on secondary dendrites of bulbar output neurons could also be activated by interneurons located in the granule cell layer (101).

It is noteworthy that remote synaptic contacts on the secondary dendrite are probably electronically decoupled from the soma and have minimal impact on somatic firing, but they might nevertheless affect local outgoing spikes. Supporting this view is the finding that inhibitory synaptic events, elicited by stimulating subjacent granule cells, completely abolish spike propagation (477). Alternatively, by participating in spike traffic, the excitatory synaptic

FIG. 2. Schematic representation of early computations carried out at the first information processing stage. *Top panel*: from the external world, airborne volatile molecules act on a sensory organ located in the nasal cavity where chemical information is transduced into electrical information. *Three middle panels*: odorant molecules react with olfactory receptors expressed by olfactory receptor neurons (ORN). The same type of sensory neurons segregate en route to the glomeruli to excite both periglomerular neurons (PG) and mitral cells (MC). The stimulus space is then converted into a representation space through the activity of a dense synaptic network between MC and GABAergic granule cells (GC). The intense reciprocal (dashed circles) and lateral synaptic connections lead to pattern dynamics in the olfactory bulb. Over time, the temporal format then evolves into spatiotemporal patterns of neuronal activation where decorrelation follows correlative activity. *Bottom panel*: bulbar responses based on afferent inputs provide information relevant for perceptual odor identification (perception), while the dynamic processing within the olfactory bulb, in which GABAergic transmission leads to active reformatting, facilitates categorization (recognition). OE, olfactory epithelium; GL, glomerular layer; EPL, external plexiform layer; IPL, internal plexiform layer.

events received by secondary dendrites might be considered as safety factors for propagation of action potentials. Together, dual excitation-inhibition responses impinging onto secondary dendrites might offer a unique mechanism for stability of bulbar network activity to recruitment of additional glomeruli with increasing odorant concentration (144, 303, 389, 456). The relative amplitudes of both excitatory and inhibitory responses received by output neurons during odor responses *in vivo* depend on their activation states and the network of granule cells (295).

Taking into account all these findings, it is obvious that the balance between excitation and inhibition in the olfactory bulb, and thus the interplay between local interneurons and output neurons, provides a combinatorial device to the representation of olfactory information. Contacts mediated by local interneurons and bulbar output neurons may contribute together to a global reformatting of odor representations, in the form of a stimulus-dependent, temporal redistribution of activity across the olfactory bulb (Fig. 2). Depending on which sensory neuron afferents are stimulated and which local interneuron connections become active as a result, different topologies of inhibitory circuits are expected to assemble. From this framework, two combinatorial encoders that take part in information processing within the bulbar network could be distinguished (260). The first one consists of the olfactory receptor repertoire expressed by the sensory neuron ensemble that transduces receptor activation patterns into glomerular odor maps throughout a highly reliable synaptic transmission (stimulus space; Fig. 2). The secondary encoder lies in the intricate interneuron network that extracts, or at least prepares representations, for higher order features, from the odor images to convert them as timing relationships across the firing output neuron ensemble (e.g., whether neurons are simultaneously active or not) (representation space; Fig. 2).

Finally, the organization of pattern activity in the bulb that relies on a proper synaptic interaction between local interneurons and output neurons depends on precise ontogenetic mechanisms that tightly control the bulbar wiring. Recent studies have brought some new insights into how intrabulbar connections are fine-tuned by neuronal activity (29, 274). According to these works, the extraordinary specificity of sensory axon convergence in the olfactory bulb was recapitulated in additional aspects of the bulb connectivity. Using a combination of genetically tagged receptors and focal dye injection into glomeruli, it was demonstrated that not only bulbar output neurons project axons across the medial-lateral axis of the bulb to a similar region on the opposing side, a finding previously reported (271), but also that they were extremely flexible according to the degree of sensory inputs. These authors reported that the intrabulbar circuit was rewired with the arrival of novel olfactory sensory neu-

rons (271). It was therefore proposed that the postsynaptic targets of sensory neurons are not prespecified but instead are instructed and organized by their presynaptic partners. Altogether, the ability of the odor environment to affect the projection and survival of sensory neurons as well as the intrabulbar connectivity suggests that evoked activity contributes to the connectivity as well as the maintenance of the olfactory circuit (369, 483, 495).

### C. Decoding Information in Higher Olfactory Centers

Odor information received by the olfactory bulb is first processed and refined before being transmitted to downstream centers. As described above, two potential sites of odor processing can be distinguished according to the topographical organization of the bulbar circuit. The first one resides in the glomeruli where local interneurons shape excitatory inputs coming from sensory neurons. The second one lies in the external plexiform layer of the olfactory bulb where reciprocal dendrodendritic synapses, between dendritic spines of local interneurons and the dendrite of output neurons, are heavily distributed. The final processing occurs in higher-order brain structures comprising the primary and accessory olfactory cortex. The axons of bulbar output neurons project in the olfactory tract to higher-order brain structures without contacting the thalamus. These higher centers include the anterior olfactory nucleus, which connects the two olfactory bulbs through a portion of the anterior commissure, the olfactory tubercle, the piriform cortex (considered to be the primary olfactory cortex), the cortical nucleus of the amygdala, and the entorhinal area (416). Nevertheless, olfactory information is ultimately relayed through the thalamus to the neocortex, similar to other sensory systems. The olfactory tubercle projects to the medial dorsal nucleus of the thalamus, which in turn projects to the orbitofrontal cortex, the region of cortex thought to be involved in the conscious perception of smell (377).

Olfactory information must be relayed from convergent synapses in the olfactory bulb to higher brain centers, where it is decoded to yield a coherent odor image. Experiments in mice that traced the olfactory circuitry of olfactory sensory neurons expressing a given odorant receptor suggest a distributed olfactory code in the olfactory cortex (496). This study employing genetically encoded transneuronal tracers in the mouse olfactory system has shown that output neurons which receive input from a single glomerulus project to defined regions of the piriform cortex that are more extensive than the glomerular segregation. These tracing studies are consistent with functional studies that demonstrate a characteristic response property of individual mitral cells that reflects the molecular receptive range of the glomerulus from which it



receives olfactory input (281). Overlap between the projection patterns of different glomeruli affords the opportunity for integration of olfactory information at higher olfactory centers. In both the olfactory bulb and higher centers, odor information seems to be encoded by activity across the entire neuronal network. This divergent connectivity is reminiscent of the persistence in discriminating odorants even after ablation of a large fraction of the olfactory bulb (279).

Despite recent progress, considerable functional analysis has yet to be performed before we will completely understand how odorant molecules are represented in higher olfactory centers. The nature of the olfactory stimulus itself seems crucial for olfactory processing in higher centers. For instance, the lateralization of odor information processing in the human brain is thought to depend on odor identity. Most odorants simultaneously activate two systems: the olfactory system, which generally projects ipsilaterally, and the trigeminal system, most of which crosses to the contralateral side. Thus hemispheric asymmetry for olfactory function strongly depends on the quality of the nasal stimulus, more specifically its potential olfactory or trigeminal stimulating properties (42).

#### IV. EARLY COMPUTATIONS AT THE FIRST INFORMATION PROCESSING STAGE

Sensory perception amounts to the deconstruction of the external world and subsequent reconstruction of the internal representation. A number of sophisticated sensory modalities available for that purpose all rely on a specific coding. We define here a code as a set of rules by which information is transposed from one form to another. For the sense of smell, it concerns the ways by which chemical information is transposed into neural responses. Sensory information is first transduced in the olfactory system by specialized receptor neurons located in the nasal epithelium. Local circuits in the second- and third-order brain areas then process the simple monophasic sensory signal conveyed by the sensory neurons to convert it into a multidimensional code (reviewed in Refs. 145, 258, 259, 321).

Among the different relays along the olfactory pathway, the olfactory bulb first plays a central role in relaying information from the sensory organ to several central targets (55, 114, 127, 312, 321). There has been some controversy over the relative importance of spatial versus temporal patterns of odor-induced activity (see, for instance, Refs. 56, 108, 248, 258, 260). The following issue reviews some recent findings regarding both spatial and temporal dimensions in the mammalian olfactory bulb. Because a critical or comprehensive assessment of all studies is not provided here, the reader may want to

consult one of several recent reviews for a more complete perspective on this area (82, 143, 146, 182, 230, 247, 253, 259, 261, 469).

#### A. Odor Maps

For all species, sensory stimuli are detected by specialized receptors located in sensory organs, and the signals hence generated flow through multiple and interconnected centers of the brain where they are analyzed and processed into sensory perception. Such a process requires the coding of sensory inputs into specific patterns of neuronal activity. A common mechanism for sensory information coding is provided by the topographic organization of sensory neurons and their axonal projections, such that sensory centers represent an internal map of the external sensory world: the body surface, the frequency of sounds, and the visual world. In that manner, the nature of sensory stimuli is encoded by the spatial coordinates of neuronal activity in high sensory centers of the brain, and the discrimination between sensory signals results from the stimulation of topographically distinct subsets of neurons.

Inputs and local circuitry of several sensory systems are organized in modular fashion (e.g., the rodent barrel cortex), with similar inputs being received by groups of cells that are highly interconnected. In the olfactory system, while other parameters are likely to be as important, spatial activity patterns have been hypothesized to play a key role in sensory information encoding. Several studies have provided experimental evidence illustrating the relationship between spatial patterns of olfactory bulb activity and features of odor stimuli (reviewed in Refs. 232, 312, 442, 478). The analyses of the glomerular convergence of olfactory axons using genetically modified mice suggest that individual glomeruli represent only one or at most a few type(s) of odorant receptors. The axonal projections of sensory neurons expressing the same receptor converge onto a few spatially fixed glomeruli within a large glomerular array on the surface of the bulb, thus creating a stimulus-specific two-dimensional spatial representation of olfactory receptor activation (56, 311, 315). According to this spatial map, signals from different types of odorant receptors are sorted into different glomeruli and individual output neurons associated with a single glomerulus are tuned to specific features of odor molecules (205, 320, 322).

Together, these findings support the idea that olfactory image of a given odorant object is coded by a specific combination of activated glomeruli. In mammals, odor-specific spatial activation patterns have been reported using several distinct methods including analysis of immediate early gene expression such as *c-fos*, *c-jun*, *zif268* and *Arc* (21, 177–179, 206, 215, 400), 2-deoxyglucose map-



ping (19, 88, 212–214, 219, 387, 417, 422, 429), and functional magnetic resonance imaging (fMRI) (427, 479). More recently, optical imaging based on intrinsic signals (28, 281, 303, 389, 446), calcium signaling (41, 456), or voltage-sensitive dye (235, 428) have been successfully applied to map individual glomeruli. These physiological approaches revealed that the initial mapping of olfactory stimuli across the spatial dimension of the olfactory bulb arises from the precise convergence of receptor neurons expressing the same odorant receptor onto only two glomeruli located in a stereotyped manner. They also demonstrated that physiological responses of the bulb were odor specific, bilaterally symmetric, reproducible over multiple trials, conserved among conspecifics (suggesting precise ontogenetic control), and independent of the context of a given odor in an odor sequence. Third, they demonstrated that the specific detection of odorant is achieved using devices of rather low specificity. Nevertheless, the combination of responses of several receptors, each with low but different specificity, generates a unique fingerprint for each odorant or odor mixture (303, 389). With these characteristics taken into account, it has been possible to link map differences to differences in perception within the vertebrate olfactory system (268, 390, 400). Only perceptually distinguishable olfactory stereoisomers elicit recognizably different odor images (268), supporting the relevance of spatial activation patterns in encoding olfactory information. In addition, imaging data indicate that higher odor concentrations increase glomerular response intensity and recruit additional glomeruli (303, 389, 429), consistent with the observation that bulbar output neuron responses change both quantitatively and qualitatively with odor concentration (231, 461). Remarkably, single vertebrate olfactory receptor neurons are reported to have a dynamic range of only one to two log units (128, 370, 445), yet optical recordings often showed continuous increases in receptor neuron input spanning nearly three log units (457). Individual sensory neurons expressing the same odorant receptor may have identical odorant response profiles but differing thresholds, thus increasing the dynamic range of population terminals converging into a single glomerular (86, 128).

In fact, odor encoding is a spatially distributed process. It was initially thought that olfactory stimulation evokes distributed, odor-specific spatial patterns of activity in the olfactory bulb (177, 212–214, 216, 320, 321, 429). However, because single odors can activate broad overlapping regions, it is clear that individual neurons can be activated by many odorants, including ones that belong to different chemical families, underlying different odor qualities. Calcium imaging on dissociated olfactory sensory neurons (41, 292) and older studies *in situ* (150, 222) are consistent with such results. Furthermore, recent imaging studies indicated that the spatial pattern of bulbar

activity is not only distributed but also extremely dynamic, thus providing a picture of how odor identity and concentration could be represented by a combination of spatial and temporal coding (285, 303, 389, 446, 480). In this way, action potential timing or rate could code non-temporal stimulus features such as quality or intensity of odorants. More recently, detailed insights into these patterns have come from measuring changes in membrane potential within populations of neurons using a voltage-sensitive dye that nonselectively stains all olfactory bulb neurons (428). In this study, the dye signal, which is thought to primarily reflect postsynaptic neuronal activity, revealed that odor-evoked responses were widespread and not localized to individual glomeruli. The extensive nature of the voltage-sensitive dye signals may reflect the widespread lateral branching of bulbar output secondary dendrites, and further supports the hypothesis that processing of olfactory input involves distributed activity across much, if not all, of the bulb. In addition, they showed that odorant-evoked spatial patterns were not simply repeated during the breathing cycle (428). Some glomeruli responded less strongly during the second breathing cycle, suggesting that adaptation occurs, whereas others responded more strongly, indicating that other processes also contribute to the dynamics observed. Together, these results demonstrate that activity patterns in the bulb are not static, but rather evolve within a respiration cycle and from one cycle to the next.

In summary, odors generally activate an array of receptor types and, hence, elicit a well-organized pattern of activation in glomeruli distributed across the surface of the olfactory bulb. Different odors activate different combinations of glomeruli; the odor identity code across population of sensory neurons thus possesses a critical combinatorial component. These activity patterns depend on the identity of the active glomeruli and have to be considered as a function of time. Such odor map dynamic may be shaped by synaptic interactions within glomeruli, between neurons in adjacent glomeruli, or between neurons in subglomerular layers, as the olfactory input is transferred to higher-order neurons, during learning for instance. As a result, both spatial distribution and the temporal structure of neuronal activity should therefore not be studied in isolation but rather considered as a single entity of the same coding process.

## B. Temporal Coding

Several experimental and theoretical points clearly argue against the single-neuron coding hypothesis for the sense of smell (23). One of the most obvious reasons relies on the number of neurons in the olfactory system, which is simply insufficient to represent the tremendous amount of information that an animal processes in its

lifetime. In contrast, the biased allocation of channel bandwidth in favor of timing is especially useful for sensory systems that rely on large populations of neurons to convey the signal: one can readily increase the precision of the stimulus estimate by simply pooling more neurons (for reviews of population coding, see Refs. 61, 345). It is noteworthy that coding sensory information by cell assemblies (392, 465) offers four important advantages: 1) overlapping set coding of information items (according to this property, the same neuron is a part of many different assemblies made of overlapping sets of neurons that encode different information); 2) sparse coding of information items; 3) dynamic coding implying correlation and decorrelation since neurons are interconnected by flexible functional synapses that evolve with time; and 4) dynamic reverberant property since activation of a cell assembly persists for a time much after the offset of sensory inputs. This long-lasting effect results from complex feedback synaptic interactions. As we shall see below, the four characteristics apply to the olfactory system circuit.

### 1. Network dynamics in the olfactory system

Since the pioneering work of Lord Adrian (2), it has been proposed that the coding of odor information requires the activation of a large fraction of bulbar output neurons (232, 260, 321). Subsequently, numerous studies have shown that odor molecules are able to activate numerous glomeruli and a large number of output neurons, each broadly tuned to odor molecules (84, 144, 151, 389, 446). This led many authors to propose that spatial assembly of activated output neurons encodes odors in the olfactory bulb. The existence of a precise topography of glomeruli supports this view (55, 315, 452) and implies that a specific assembly of output neurons whose activity is determined by its connectivity can code each odor. However, stimulation of the olfactory epithelium with a mixture of odorant compounds or, even with a single compound, causes activation of bulbar output neurons that are, in many cases, distributed over several discrete regions of the bulb (322, 412, 429). Thus already at the first central stage that processes sensory inputs, the neuronal circuitry cannot be viewed only as a passive relay of odor-related information but rather as richly interconnected circuits in which excitation and inhibition are physically widespread. As a consequence, its global mode of action might not be captured accurately by either static or isolated samples.

Electrophysiological studies have revealed many forms of temporal patterning of activity of the bulbar output neurons that are relevant of the olfactory pattern-recognition task (60, 289, 306, 324, 461). Through such spatiotemporal patterns of neuronal activation, the circuit dynamic offers a large coding space that spreads odor

representations of chemically related odor (e.g., acting as a decorrelator) and simultaneously optimizes this distribution within it throughout oscillatory synchronizations (e.g., formatting odor space) so that odor representations can be sparsened in the next olfactory station.

In general, changes in the format of sensory-related information rely on coordinated neural firing patterns in large-scale neural networks (122, 420, 441). The coordinated electrical activity emerges from collective behavior of neurons across large groups of neurons (165), and it is reliably correlated with a variety of behavioral states and cognitive processes such as attention, working memory, or perception (155, 167, 269, 450). In sensory systems, evoked oscillations are thought to encode stimuli (329, 420; reviewed in Refs. 260, 419) and to participate in fine discrimination (430). They have been reported in neural assemblies of various sensory systems such as vision (e.g., Ref. 333 for the retina and Ref. 166 for the visual cortex), audition (e.g., Ref. 98), and olfaction (reviewed in Ref. 257). The temporal correlation hypothesis from the "binding" theory remains a matter of active debate. Among the contentious issues are how prevalent are the oscillatory activities in evoked neural responses, and to what extent neural oscillations are correlated with sensory stimulation (410, 419). Before answering these questions, it is important to note that temporal patterning comprises different components. Some are imposed onto odor stimuli by the dynamics of the carrier medium and by active sampling, whereas others are generated internally by neuronal dynamics in the olfactory bulb. Odor information in the bulb is represented not only by the combination of active neurons in the network, but also by the slow temporal sequence of activity patterns and by the synchronization of neuronal subpopulations (143). Another property of population activity that can subserve odor processing is the chemotopic spatial format (146). There is no doubt that exploring the extent to which these features of population activity are decoded by the brain, and by what mechanisms, will be the major issues for the near future.

### 2. Temporal features of olfactory responses

By recording the local field potential (LFP), which is an indirect reflection of neuronal activity since it is generated by current flows through the extracellular space linking inward and outward membrane currents, both spontaneous and odor-induced LFP oscillations were found to be a universal feature of olfactory processing systems from a wide variety of vertebrates (2, 3, 50, 72, 134, 347, 396, 405, 434). For a given odor stimulus, the "induced rhythm" (as first termed by E. D. Adrian) is synchronized transiently in time and only among a neural subpopulation that is selectively responsive to that particular odorant. The inhalation of odor molecules has first

been reported to trigger oscillations in the olfactory bulb with different frequency ranges (e.g., Refs. 2, 47, 50, 117, 137–139, 168, 233). A robust pair of fast oscillations defined by their frequencies as gamma (30–80 Hz) and beta (15–40 Hz), as well as a slower one called theta rhythm (3–12 Hz), are classically observed in the olfactory system. Whereas gamma and beta waves are induced by odor inputs, the theta frequency band seems rather to be phase-locked with respiration (3, 47, 50, 117, 131, 138, 233). This respiration-coupled theta rhythm displays spatiotemporal dynamics in response to odor stimuli (428) and is also present in downstream piriform cortex (49, 467, 468), indicative of a potential function in the representation of odor stimuli.

The amplitude and frequency of these oscillations may reflect previous olfactory experience and the behavior of the animal (37, 48, 72, 134, 140, 233, 366). Hence, previous studies focusing on gamma frequencies have shown that the amplitude of oscillatory bursts associated with odor sampling defined maps over the bulbar surface. Yet, those maps were more related to the behavioral content of the odor than to its chemical nature (48, 103, 138). More recently, LFP recordings revealed that odor sampling enhanced oscillatory activity in beta frequency range when odors were experimentally associated with a reward (37, 366) or after repeated presentations of the same odor (72, 168). It is worth noting that gamma and beta frequency bands never coexist in response to odorant stimulation. Hence, recent studies examining spatiotemporal evolution of odor-induced LFP oscillations in the bulb during training, reported an alternation of the two rhythms during odor processing (59, 298, 334). From these studies, it is clear that odor sampling and learning are associated with a decrease in gamma burst power followed by an increase in beta oscillatory activity.

Interestingly, all rhythms observed in the first relay of mammals have also been seen in their functional analog in invertebrates and are thought to encode stimuli (reviewed in Ref. 260) as well as to participate in the fine discrimination of close stimuli (430). Extension of the results obtained in the olfactory bulb to include analysis of olfactory cortical neurons should provide us with a clue for understanding cellular mechanisms for the integration and decoding in the olfactory cortex of odor information. In this respect, oscillations have been explored, and a gamma rhythm was found in the piriform cortex of awake animals (37, 47, 135, 233) or of anesthetized rodents (131, 334). The synchronized spike discharges provide a basis for the integration at the level of olfactory cortex of signals originated from different odorant receptors. If axons of the two output neurons were to converge on the same target neuron in the olfactory cortex, the synchronization of spike discharges may greatly increase the probability of driving the target neuron because of temporal summation of synaptic inputs from the two cells.

Thus the transient synchronization of spike responses, at the first central relay, might contribute to temporal binding of input signals from different receptors. The firing of neurons of the olfactory system is highly constrained by these oscillations to occur within narrow time frames (117, 228). As a result, it is expected that a distinct set of synaptic responses occurs within each cycle of fast oscillation (237), a mechanism highly important for sensory information processing (421).

Another functional implication of the multiple time scales of neuronal activity is the possible modulation of membrane potentials of a subset of output neurons (66, 145, 281, 296). Such oscillations could serve as time references for temporal coding. An elegant model has proposed that a simple mechanism could translate the strength of glomerular activation into a temporal variable, namely, the phase of the first output neuron spike relative to the ongoing oscillation cycle (198). However, there is so far no experimental evidence supporting a phase code (with respect to the LFP) for odor concentration. Experimental results indicated rather that the spike phase relative to the fast oscillation is invariant (117, 145, 228, 260), whereas a strong correlation between spike number and latency to the initial action potential was established (296). Together, this supports the idea that oscillatory activity does not carry odor information by itself. Rather, fast oscillations might serve other functions as correlation and subsequent decorrelation of activity patterns (in insects, see Ref. 354). In contrast, the slow, respiration-driven oscillation might indeed be useful for phase coding (66, 131, 296, 428) and for synchronicity of bulbar output neurons connected to the same glomerulus (405). The olfactory receptor neurons, glomerular and output neuron responses are focused on the periodic inspiration peak in the respiratory cycle (73, 75, 356, 426, 428), thereby presumably driving all odorant-related responses to arrive in the cortex simultaneously. Such a system would provide a temporal filtering device that would eliminate responses arriving outside the synchronized temporal window as neural noise, throughout the olfactory pathway. In line with this, it has been demonstrated that oscillations induced by olfactory stimulation with certain organic solvents, or components of predator secretions, are coherent between the olfactory bulb, the piriform cortex, the entorhinal cortex, and the dentate gyrus (74, 449, 494). However, the functional role of the widely distributed oscillations across the olfactory system remains to be characterized. It has been hypothesized that they serve to constrain the firing periods of neurons to narrow time frames, with defined temporal relationships between the firing times of different populations of cells. This would determine the relative timing of convergent synaptic inputs (237), as well as the timing relationships between synaptic inputs and the generation of a postsynaptic spike. These temporal relationships would affect how the postsynaptic cell integrates its multiple inputs and adjusts the weights of



its synapses (224, 421). Different ranges of oscillations would thus support different cellular computations.

In summary, synchronized oscillations could be involved in learning, in creating a periodic clock by which neurons follow the phase in which they fire, in filtering noise, in refining the coding space of a response, and in fine-tuning between odorants that use overlapping spatial representations in the olfactory bulb. Alternatively, neuronal oscillations may be epiphenomenal. The development of more specific hypotheses will require a determination of the firing times of various populations of cells relative to the field potentials as well as a cautious examination of the correlation between the induced oscillations and the related behavior of awake animals.

### 3. Odorant-induced slow oscillations

It has been hypothesized that the beta oscillation is generated by a loop formed by bulbar output neurons, pyramidal cells of the piriform cortex, and the granule cells in the olfactory bulb. The beta oscillation may be generated also by a feedback loop or intrinsic mechanism within the piriform cortex or other cortical areas (334). The available data are yet insufficient today to distinguish between these two possibilities, nor are they mutually exclusive. Furthermore, some authors have reported the existence of slow delta oscillations in the olfactory bulb of several species (see for instance Refs. 99, 255). In rodents, they can be revealed under pharmacological conditions allowing higher excitability of the network (e.g., in the presence of low external magnesium concentration, bicuculline, or NMDA) (363, 405). These slow synchronized oscillations were shown to result from recurrent excitation occurring in the glomerular layer. Consistent with this, it has been found that many neurons recorded in the periglomerular layer (~60%) exhibited slow oscillatory discharge patterns after olfactory nerve stimulation. This slow activity that emerges from the membrane intrinsic properties of local bulbar neurons (302, 363) may play a role in the long-lasting depolarization of the bulbar network, allowing a sustained depolarization of the entire network.

### 4. Odorant-induced gamma oscillations

Field gamma waves and phase-locked discharge of neurons are observed in a large number of brain structures. A gamma cycle may be considered as an information quantum, allowing the exchange of information among the linked members in a phase-locked manner. This cyclic mode of operation may be a unique solution to temporarily segregate and link neuronal assemblies to perform various operations. From this perspective, the gamma oscillation is a computational process that brings together activity of sensory- and/or memory-activated neurons in time, thereby affecting behavioral output and

plasticity. Examples of these operations include phase reset of the cycle by sensory stimulation (62, 156, 439), phase locking of motor activity (58, 408), memory encoding and retrieval, and synaptic potentiation of sequentially activated place neurons. In the olfactory bulb, the evoked gamma oscillations arise during a depolarized state triggered by olfactory nerve stimulation and a prolonged firing in bulbar neurons. Such prolonged network activity may result from numerous intrinsic and synaptic factors such as 1) polysynaptic amplification of olfactory nerve inputs occurring in the glomerular layer (36, 69, 363, 405), 2) recurrent excitation between neighboring mitral cells (207, 393), and 3) the existence of bistability of mitral cell potentials that can prolong their initial depolarization (193). After olfactory nerve stimulation and when GABAergic inhibition subsides, the long-lasting excitatory synaptic responses received by the primary dendrite allow several output neurons to be synchronized.

Because bulbar output neurons are endowed with numerous voltage-dependent ionic conductances and intrinsic resonant membrane properties, sequential activation of voltage-dependent channels during the gamma cycle may set constraints for excitability and plasticity. Exploration of the significance of the cyclic conductance changes in future experiments is a necessary step to provide an insight into the physiological role of gamma in the olfactory system. During the gamma oscillation, the dendrites of bulbar output neurons can depolarize, thus potentially activating/inactivating a host of voltage-gated channels. The sequential activation and inactivation of the numerous conductances may offer clues to the physiological significance of the gamma oscillations in the synaptic transmission and plasticity.

Although the extracellularly recorded field potentials reflect the summed activity of membrane currents over a relatively large volume of neurons, active neurons may contribute disproportionately more to the field than non-spiking cells. In the near future, large-scale recordings spanning across different central regions should be used to reveal whether subsets of active neurons behave differently from the "average" population. The coherent oscillations of cell assemblies during gamma rhythm provide an ideal mechanism for temporal coding and decoding (458). Further research is required to determine whether phase coding and rate coding are redundant or whether they are used to register different types of information. On the basis of the efficient and tunable output neuron-local interneuron feedback, it is possible that such feedback loop allows active output neurons, and their common interneurons, to beat at a slightly different frequency and phase than the "master clock" rhythm of gamma. As a result, the phase differences can segregate assemblies of neurons that are assigned to different representations. Addressing many of these issues requires the analytical power of patch-clamp recordings applied



on in vitro preparations. The dynamic relationship between output neuron discharge and the postsynaptic response of the various interneuron classes should be worked out in detail. On the other hand, a coordinated effort is needed to compare the physiological relevance of the in vitro observations to the intact brain. Furthermore, in addition to physiological experiments, several topics could benefit from computational models. For example, modeling extracellular current flow using networks of neurons may yield insights into the relative contribution of spiking and nonspiking neurons to local field potentials.

#### 5. *Generating odorant-induced gamma oscillations through intrinsic membrane properties*

In the olfactory system, the induced gamma rhythm originates already at the first central relay. It is abolished in the piriform cortex following bulb removal (27) and preserved in the bulb when conduction through the olfactory peduncle is blocked by cooling (168) or by surgical disruption (334). These observations are consistent with previous findings indicating that oscillatory activity emerges from intrinsic properties of the bulbar neuronal network.

Single neurons in the central nervous system are endowed with intrinsic resonant membrane properties that depend on a large repertoire of voltage- and calcium-gated ion channels, distributed across the dendritic and somatic membrane, and which give rise to complex neuronal dynamics (273). In general, oscillation occurs in a single cell when a strong fast positive feedback (generating the rising phase of membrane voltage) interacts with a slower negative feedback (producing the decay phase of the cycle). Activation of voltage-gated inward currents or activation of outward potassium currents can provide positive feedback within a cell. In the olfactory bulb, it is remarkable that the output neurons are especially prone to voltage-dependent oscillations. Subthreshold oscillations, ranging from 15 to 60 Hz, are generated from a tetrodotoxin-sensitive sodium conductance that operates within a range of voltages above and below spike threshold (100) and are crucial for spike timing as well as for filtering excitatory postsynaptic potentials. Once again, the presence of membrane resonance and voltage-dependent subthreshold oscillations in bulbar output neurons indicates that these neurons are not passive relays of incoming synaptic events, but rather participate in sculpting their final output owing to their regenerative properties.

The role of other voltage-dependent conductances in the generation of gamma waves has yet to be disclosed. During the gamma cycle, the magnitude of the membrane potential can change considerably; therefore, distinct nu-

merous voltage-dependent conductances may be activated sequentially. In turn, their activation exerts an important effect on the firing patterns of the principal cells. Whatever the different ionic channels implicated, the subthreshold oscillatory activity of the membrane potential might precisely control the timing of spiking activity and thereby provide a mechanism by which the firing of output neurons is synchronized.

How could intrinsic subthreshold oscillations of cell assemblies be synchronized? In the mammalian brain, a neural circuit consists of two major cell types: excitatory principal neurons and inhibitory interneurons. It follows that three types of synchronization mechanisms by chemical synapses are conceivable: recurrent excitation, mutual inhibition between interneurons, and feedback inhibition through the excitatory-inhibitory loop. Theoretical models have suggested that the gamma rhythm in the mammalian olfactory cortex (472) and the olfactory bulb (134, 168, 319, 364) is generated by a negative-feedback loop between bulbar output neurons and local inhibitory interneurons. The phase relationship between unit activity and the field potential in the olfactory bulb is consistent with this hypothesis (117, 228). Mechanisms other than that operating within the dendrodendritic synapses between output neurons and granule cells may also be involved in the generation of the synchronized oscillatory spike discharges. For example, the synchronization might be mediated by dendrodendritic synaptic connections with periglomerular cells, or by the local circuit via axon collaterals of output neurons. Nevertheless, the fact that granule cells are found to be the major key players to synchronize bulbar output neurons (254) might result from several intrinsic properties of the olfactory bulb circuit. First, some granule cells impinge onto output neurons very close to their cell body. Thus granule-to-mitral cell synapses are more likely to control their spiking activity than remote synapses made by distinct local interneurons. Second, output neuron secondary dendrites that extend as far as one-third of the length of the olfactory bulb (346, 361, 365) should provide a rather long horizontal connectivity necessary for synchronizing a large population of output neurons. Third, local neurons from the granule cell layer are capable of releasing not only GABA but also glutamate (101). Hence, glutamatergic feedback excitation could provide an effective mechanism for both temporal and spatial coding in the olfactory bulb. Fourth, the existence of electrical coupling between granule cells (371) could enable their synchronizing effect on output neurons. The report showing that gamma frequency oscillations were impaired in other brain structures obtained from connexin36-deficient mice supports this assumption (199).

### 6. *Functional implications of synchronization in highly distributed systems*

The functional importance of oscillations towards odor encoding has been concluded from the use of GABA<sub>A</sub> receptor antagonist that desynchronized projection neurons (287, 288, 430). This treatment altered the ability to distinguish between aliphatic alcohols of different chain length, but left discrimination of more widely differing odorants unimpaired. Other experimental findings also support the notion that bulbar oscillations play a key role in odor discrimination and that GABAergic inputs to principal neurons are crucial for network synchrony and odor perception (see below). This finding and previous studies highlighting the plastic nature of the dendrodendritic synaptic connections both in the accessory and main olfactory bulbs (45, 221) indicate that the degree of synchronization among specific subsets of output neurons might change according to the history of previous sensory inputs. In other words, a plastic change in the dendrodendritic synaptic interactions might result in a modification in the strength of temporal binding of signals originating from different odorant receptors. Taken together, temporal dynamics of neuronal representation of odors may have several functions, conceivably in the readout of bulbar output neuron activity, and possibly in fine-tuning the basic machinery for odorant recognition and distinction.

A correct level of inhibition is therefore important for olfactory coding, but within a framework that differs from conventional lateral inhibitory rules. Rather, inhibition here is proposed to be a mechanism that regulates the complex dynamics of olfactory network responses. The interplay between local interneurons and resonant properties of output neurons appears as an encoding device that optimizes information processing within the bulb. Each odor representation can be thought of as a high-dimensional vector of output neuron states evolving with time, in a stimulus-specific manner controlled by local interneurons. A previous study of olfactory coding in invertebrates attempted to show that correlated neural activity, as revealed by field potential oscillations, was necessary for fine olfactory discrimination (reviewed in Refs. 257, 258). This study was accomplished by pharmacologically desynchronizing a population of neurons without affecting their individual firing properties and showing that olfactory discrimination was impaired. With the use of a different approach to reduce the level of GABAergic inhibition, a specific loss of odor discrimination in mutant mice was reported when the number of interneurons was reduced (152) or when GABA<sub>A</sub> receptor-mediated synaptic inhibition was altered (341). The olfactory bulb synchronization in the gamma frequency band might thus give a context to the evolving content carried by output neuron firing patterns, thus allowing postsynaptic

cells in the olfactory cortex to decode the spatiotemporal information carried by transient synchronized assemblies. In line with this, the piriform cortex has been proposed to function as a content-addressable memory (180). The presence of recurrent architecture and the demonstration of long-term potentiation in the afferent and associative pathways in the piriform cortex support this idea (225). Finally, it should be mentioned that a model of olfactory memory based on altering GABAergic inhibition in the olfactory bulb has also been proposed (267), and several studies have indeed demonstrated the plastic nature of dendrodendritic reciprocal synaptic connections (reviewed in Refs. 45, 221). Thus the degree of synchronization among specific subsets of output neurons might change during the learning process, resulting in changes in the strength of temporal binding of signals originating from different odorant receptors.

In summary, the studies aimed at examining the information processes in the olfactory bulb teach us three lessons. First, the neural synchronization across bulbar output neurons may enhance the representation of a complex olfactory stimulus by integrating the different signal streams activated by the odor into a unified olfactory "image" at the level of the sensory cortex. It seems likely that olfactory information is coded both spatially and in time. Thus the combination of spatial coding and correlated spike activity may, during odor stimulation, synchronize spike responses in the output neurons throughout a much more dynamic process than previously thought. Second, the activation of neuronal assemblies in the bulb acts to modulate neuron groups in the forebrain, and some olfactory signal decoding mechanism must be present. One of them has been proposed stating that the olfactory forebrain could use coincidence detector neurons to identify the various activity patterns observed in the bulb (321). This model proposes that synchronized oscillations would be a mechanism whereby signals from different olfactory neurons are bound in time to be detected. Finally, even a paleocortical structure such as the olfactory bulb plays an integral part in higher cognitive processes rather than acting simply as a relay station whose sole functions are the improvement of signal-to-noise ratio and contrast enhancement. The bulbar neurons that relay activity to the brain interact extensively with each other, both directly and through a network of coupled inhibitory and excitatory interneurons. With these unique features, the olfactory bulb might be able to solve two important problems related to pattern recognition: odor perception and recognition.

### C. *Roles of Local Inhibition in Active and Dynamical Networks*

At the first processing stage of odor information, local inhibitory interneurons (periglomerular and granule

cells) interconnect excitatory second-order neurons at two separate locations. At the more superficial one, periglomerular cells provide a local inhibition within a glomerulus or between neighboring glomeruli (20, 30, 229, 340, 357, 362) while at a deeper part, granule cells mediate a widespread inhibition onto the secondary dendrites of output neurons (112, 361). Thus, in contrast to periglomerular cells, granule cells may interconnect bulbar output neurons whose input glomeruli lie millimeters apart (415).

Ample evidence supports the critical involvement of the bulbar local interneurons in rhythmic oscillations. First, theoretical and experimental studies have focused on how oscillatory activity can arise between mitral cells and inhibitory granule cells coupled through reciprocal dendrodendritic synapses (135, 136, 208, 365). Second, genetic manipulation of granule cell excitability enhances field oscillations and alters discrimination (341). In line with this, we have reported how individual mitral cells can generate gamma-frequency activity as a result of intrinsic electrical properties of output neurons interacting with GABAergic synaptic transmission (100, 254). Third, current source-density analysis indicated that the field potentials in the bulb were generated by synaptic currents in granule cells. In light of these results, it has been shown recently that oscillatory activity in the olfactory bulb is associated with increased firing in inhibitory granule cells (334).

Remarkably, a population activity in local inhibitory networks coupled by electrical synapses has been proposed to be involved in generating the fast oscillations (141). Supporting this view, experimental and theoretical studies in other brain regions have demonstrated a prominent role for gap junction coupling in many types of fast inhibitory network oscillations. For instance, enhanced neuronal synchronization has been suggested for cortical fast-spiking interneurons that are coupled both through gap junctions and fast GABAergic synaptic transmission (299). There is anatomical evidence for the presence of electrical synapses onto interneurons in the olfactory bulb. Gap junction coupling between granule cells has been shown by both electron microscopy and dye coupling (371). Furthermore, a protein that mediates interneuronal coupling in cortical networks (e.g., connexin36) is highly expressed in the granule cell layer of the olfactory bulb (87). Freeze-fracture electron microscopy (256, 309) and dye-coupling (351) experiments suggest that gap junctions also exist between bulbar output neurons and granule cell membranes. Based on immunohistochemical and in situ hybridization labeling, the gap junction protein forming these electrical synapses is likely to be connexin43 (309, 351), although there is also some recent evidence for connexin45 expression in bulbar output neurons (489).

Because bulbar interneurons are key players in inducing and maintaining the induced oscillations, they con-

stitute the primary target of centrifugal fibers to the bulb (283, 290), including excitatory input from the olfactory cortex (181, 332, 359) and inhibitory input from the nucleus of the horizontal limb of the diagonal band (252). Thus not only the olfactory bulb processes sensory information from the external world, but it also integrates signals propagated via centrifugal projections from numerous central structures (for reviews, see Refs. 185, 415, 416). In line with this, it is noteworthy that a noradrenergic input from the locus coeruleus synapses mainly in the mitral cell and granule cell layers, whereas cholinergic input from the horizontal limb of the diagonal band of Broca innervates all layers of the olfactory bulb, especially glomerular and granule cell layers (for reviews, see Refs. 185, 290). Granule cells indeed receive the majority of cortical feedback to the bulb (359, 360), and they receive a centrifugal projection from cortical pyramidal cells onto their basal dendrites (283). Because centrifugal input arrives largely onto the basal dendrites of granule cells, it is likely that one of its functional consequences is either to enhance putative mutual inhibition via excitatory input to the granule cells or to inhibit the granule cells via direct GABAergic input.

Together, these neuromodulator inputs to the olfactory bulb play important roles in olfactory functions, including odor detection and discrimination, and are critical for learning formation and/or recall of specific olfactory memories. Several distinct forms of memory might involve higher centers, since interactions between fibers of central origin (mainly noradrenergic and cholinergic) and granule cells have been shown to occur in local mechanisms of neuronal plasticity related to olfactory memory (for instance, see Refs. 220, 262, 266, 367, 432, 470, 471). The spatial and temporal coincidence of centripetal and centrifugal afferents might constitute the required conditions for the triggering of bulbar interneuron plasticity. The centrifugal higher influences provide contextual information required for sensory formatting of odor representations by early olfactory circuits (233, 234, 349). Finally, it is noteworthy that in addition to the neuromodulation, the activity of the bulbar interneuron network is regulated throughout a continuous adult neurogenesis. As a result, because of their massive centrifugal modulation and their continuous production, GABAergic interneurons are positioned in a strategic position to amplify their key function in controlling the dynamical bulbar processing.

## V. NEURONAL REPLACEMENT IN THE ADULT OLFACTORY SYSTEM

There is a growing interest in studying olfactory plasticity. The reasons for such interest are manifold. First, olfaction is a sensory modality already functioning at early embryonic stages. It is a primary mechanism for



receiving information about the world, and early olfactory experience and learning are crucial for survival. Second, the high dimensionality of the system offers multiple sites for regulation. Finally, the olfactory system exhibits life-long turnover of both peripheral sensory neurons and bulbar interneurons. We will summarize the current knowledge of this neurogenesis in the adult olfactory system.

### A. Neurogenesis in the Adult Olfactory System

There are at least two germinative zones present in the adult olfactory system. The first one is located in the sensory organ where, like in other epithelia, cell renewal persists throughout adult life to replace olfactory sensory neurons (64, 65, 171–173, 325) while the second area resides near the ventricle of the forebrain. The former site of neurogenesis is made possible by the presence of globose and horizontal basal cells found deep in the olfactory epithelium, near the basal lamina that separates the epithelium from the underlying lamina propria (63, 64, 170, 173). The mature sensory neurons have only a limited life span of ~90 days (286), but if mice are reared in a laminar flow hood to prevent rhinitis, sensory neurons can survive as long as 12 mo, close to the life span of the animals (196). Thus the turnover of sensory neurons, and by extension, the rate of neurogenesis in the olfactory epithelium, is tightly regulated by environmental factors. In fact, its mitotic rate is subjected to a bidirectional regulation. Neurogenesis is enhanced by ablation of the olfactory bulb (71), while blocking airflow through one side of the nasal cavity causes an ipsilateral reduction in cell proliferation. This plasticity, coupled with the fact that there are a limited number of cell classes in the olfactory epithelium, makes this area exquisite for studying mechanisms that control the rate of neuronal production. In addition, differentiated neurons send back regulatory signals to inform progenitor cells about the number of new neurons that need to be produced to maintain cell population equilibrium.

What could be the functional meaning of this neurogenesis? Mature sensory neurons that have been damaged by exposure or by pathogens, and immature ones that cannot find adequate synaptic target in the olfactory bulb, are two obvious candidates to support the existence of the neurogenesis in the sensory organ. Once mature, sensory neurons must extend along a long route to the correct glomerulus. As odor quality remains constant throughout life, the glomerular array must be constant to a certain degree. Apoptotic cell death has been observed in cells representing all stages of regeneration, implying apoptotic regulation of neuron numbers at all levels of the neuronal lineage. Currently, there is a considerable interest in chemical factors that inhibit or promote neurogenesis, neuronal differentiation, or actively produce apoptotic cascades.

The idea that the olfactory bulb of mammals could integrate newborn neurons was puzzling since a decade ago the adult brain was considered as totally devoid of neurogenesis despite early works (6–8, 10). Although some debates still persist (163, 246), it is now definitively admitted that there are at least two sites of neuronal production in the adult mammalian brain: the subventricular zone (SVZ), which lines the lateral walls of the ventricles, and the subgranular zone of the dentate gyrus of the hippocampus. These two regions are considered as vestiges of the developmental program of the central nervous system. In the embryo, bulbar interneurons are derived from neuronal precursor cells that migrate from the lateral ganglionic eminences (464). Postnatally, they are derived from neuronal precursor cells that migrate in the rostral migratory stream (RMS), from the SVZ (9, 26, 89, 195, 275, 276, 282; reviewed in Ref. 438).

Within the SVZ, the neural precursor cells are considered to be stem cells since they proliferate and give rise to several different cell types (104, 176, 211, 323, 372, 373; reviewed in Refs. 353, 438) (Fig. 3). The continuous generation of SVZ neurons in mammals has been found not only in rodents (9, 10, 26, 195, 275, 276) but also in primates, including New World monkeys (300), Old World

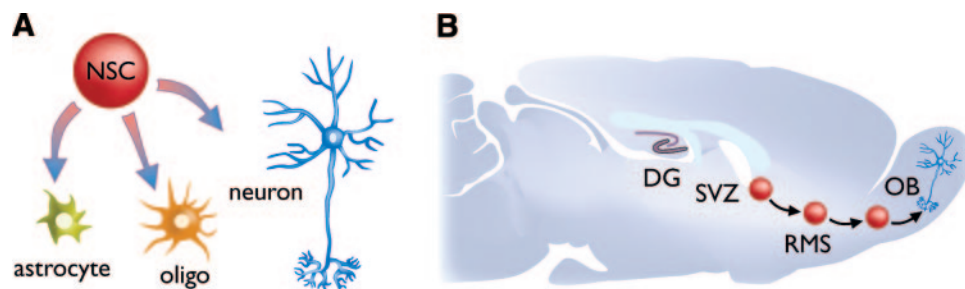


FIG. 3. Neurogenesis and neural stem cells (NSC) in the adult mammal central nervous system. A: NSC from adult brains produce all cell types from the neuronal lineage: astrocytes, oligodendrocytes, and neurons. B: the two neurogenic zones in the adult brain that host NSC are the dentate gyrus (DG) of the hippocampus and the subventricular zone (SVZ). From the SVZ, neuroblasts migrate to the olfactory bulb (OB) via the rostromigratory stream (RMS), where they differentiate into bulbar interneurons.



monkeys (163, 226, 246, 263, 352), and humans (251, 358, 459). In primates, SVZ neurons have to migrate several centimeters to reach the olfactory bulb (246, 352).

Several *in vitro* studies have indicated that forebrain periventricular stem cells exhibit multipotency (149, 437, 438). However, other approaches performed *in vivo* have demonstrated that neural stem cells were endowed with a rather limited cell fate. For example, *in vivo* SVZ precursors were found to generate primarily committed neuronal precursors that can either die or give rise to neuronal progenitors (149, 437, 438). Those precursors are unusual in that they display neuronal characteristics revealed by labeling with neuronal markers. In addition, unlike other immature neurons, precursor cells of the SVZ migrate tangentially without the aid of radial glial cells and continue dividing during their migration along the RMS, to populate the olfactory bulb where they differentiate into local neurons (275, 282). Analyses of *in vitro* results gave rise to the current view that adult SVZ generates stem cells capable of producing the three major cell types of the central nervous system (e.g., oligodendrocytes, astrocytes, and neurons) (reviewed in Ref. 460). When the neuroblasts reach the olfactory bulb, they migrate radially, and of those that survive, ~90% differentiate into GABAergic and 10% into dopaminergic interneurons of the glomerular and granule cell layers (33).

### 1. The subventricular zone of rodents and nonhuman primates

Significant progress has been made in investigating the molecular, cellular, and organizational composition of the SVZ during these last years. This appears as a crucial step for determining the mechanisms that promote division and differentiation of neural stem cells. According to ultrastructural criteria, it has been established that four main cell types compose the SVZ (105). A layer of ependymal cells lines the lateral ventricle. It separates a first type of cells called type B cells from the ventricle. Type B cells are astrocytes, and some of them may occasionally extend a single cilium between ependymal cells and contact the lateral ventricle (104). SVZ neuroblasts (type A cells) migrate along the wall of the lateral ventricle in homotypic chains ensheathed by type B cells (276, 463). In addition to the previous cell types, the SVZ contains clusters of a fourth, rapidly dividing, type C cell present along the chains of type A cells. Convincing evidence arose from the work of Alvarez-Buylla and colleagues (105) who designated the astrocytes (type B cells) as the SVZ neural stem cells. They infused the antimetabolic drug cytosine- $\beta$ -D-arabinofuranoside (Ara-C) into the adult mouse brain and thus temporally depleted the SVZ of proliferating type A and type C cells. After removal of Ara-C, they observed that glial fibrillary acidic protein (GFAP)-expressing cells repopulated the SVZ and gave rise to type C cells, which

in turn gave birth to neuroblasts (type A cells). In the same vein, using transgenic mice expressing the receptor for an avian leucosis virus under the GFAP promoter (106), it was possible to show that SVZ astrocytes labeled with this method generate neuroblasts migrating to the olfactory bulb. A more recent study reported some evidence of an extravascular basal lamina composed of stems terminating in bulbs adjacent to the ependymal layer (305). Although the precise functions of this basal lamina have not been fully investigated, it is suggested that it constitutes a critical component of the adult neurogenic stem cell niche (13, 107, 305).

### 2. The human case

The similarity of the organization and the processes taking place in the SVZ between rodents and human has not been extensively explored. In the human SVZ, it is possible to detect the presence of epidermal growth factor receptor (EGF-R) mRNA and protein (459). Molecular analyses of the human SVZ also revealed the expression of the polysialylated neural cell-adhesion molecules (PSA-NCAM) that characterize migrating neuroblasts, and the neuronal marker class III  $\beta$ -tubulin and Hu proteins that are both expressed in immature neurons. These observations demonstrate that dividing neuroblasts are present in potentially neurogenic regions of the human brain (rostral SVZ). Interestingly, the authors showed that EGF-R mRNA positive cells in the SVZ were significantly higher in subjects under 1 year of age compared with adults and that no cluster of PSA-NCAM or class III  $\beta$ -tubulin-positive cells could be detected in the teen, young adult, and adult SVZ.

Another study has revealed the precise description of the organization of the human SVZ (394). Under appropriate conditions, single SVZ astrocytes taken from the lateral walls of the anterior horn, the body, and temporal horn of the human SVZ generate *in vitro* neurospheres that differentiate into astrocytes, oligodendrocytes, and neurons. One of the main observations of this study concerns the subventricular organization that is unique compared with other vertebrates. The human SVZ astrocytes form a ribbon along the lateral walls of the ventricles, and this strip of astrocytes is separated from the ependyma by a gap. The authors did not find any evidence of the presence of a RMS, from the SVZ to the olfactory bulb, as classically described in other species (394). Nevertheless, although rare individual cells expressing specific markers of immature neurons were reported in this study, these neuronal precursors were never organized into clusters of migrating chains. Together, these findings raise critical questions about the destination and fate of the human SVZ astrocytes, about their functions, and their potential interest for autotransplantation in brain regions of clinical relevance.

### 3. Guiding newborn neurons in the adult brain

Although neuronal migration has been demonstrated in several regions of the brain (125), the olfactory bulb constitutes the more extensively used model to understand a process of general importance for the adult brain (9–11, 26, 160, 195, 241, 275, 282, 304, 464). It is a central region that offers the unique opportunity to study the migration and integration of newborn neurons into already functional neuronal circuits (reviewed in Refs. 12, 272).

A) TANGENTIAL MIGRATION. PSA-NCAM is important for SVZ migration (40, 77, 91, 202, 344, 385, 440, 463). Recent evidence suggests that Slit, a secreted repellent for axons (52, 239, 264, 474), is expressed in the septum and ventricular zone (475, 493) and can repel both the postnatal SVZ neurons (201, 475) and embryonic neurons (493). More recently, it was shown that the olfactory bulb contains a diffusible attractant for the SVZ cells that was not identifiable (270). This result contrasts with previous findings revealing that the olfactory bulb has neither attractive nor repulsive activities (202, 240). In mammals, diffusible proteins such as Slits (197, 209, 485) and their Rundabout (Robo) receptors (52, 264, 485) are implicated in driving newborn neurons from the SVZ (493). Slit1 and Slit2 are expressed in the septum and the ventricular zone (475, 493), and *in vitro* studies revealed that secreted factors from the caudal septum repel SVZ neurons (201, 336, 475). With the use of septum and choroids plexus explants from wild-type mice and Slit1- and/or Slit2-deficient mice in diffusion assays, it has been shown that septum repulsive activity results from a combination of Slit1 and Slit2 and that only Slit2 represents a chemorepulsive factor release from the choroids plexus (336). In addition to its expression in the septum, Slit1 is expressed in the RMS. Slit receptors such as Robo2 and Rig-1/Robo, but not Robo1, are also highly expressed in the SVZ and along the RMS. Multiple labeling with specific markers performed by the same group revealed that rapid dividing precursor cells (type C cells) and migrating neuroblasts (type A cells) are the source of Slit1 in the SVZ and all along the RMS.

B) RADIAL MIGRATION. Once in the olfactory bulb, newborn neurons turn radially out of the RMS to reach outer layers where they differentiate and functionally integrate into adult circuitries (272). How these neurons achieve their radial migration remains unresolved. However, two recent papers have provided substantial evidence that at least two extracellular matrix molecules contribute as microenvironmental signals to initiate radial migration processes. Reelin has been identified as a secreted glycoprotein that induces neuroblasts to detach from chains and start their radial migration (183). This protein is highly expressed in the mitral cell layer and in the external plexiform layer. *In vitro* experiments demonstrated

that reelin promotes the dispersal of chain-migrating PSA-NCAM-positive cells into individual neuroblasts. These data were corroborated *in vivo* by examining the density of neuroblasts at the entrance of the olfactory bulb in *reeler* mice. As expected, it was found that the accumulation of PSA-NCAM positive cells is larger in mutants than in wild-type mice. Furthermore, green fluorescent protein (GFP)-positive neuronal precursors grafted into the olfactory bulb of mutant *reeler* mice do not migrate radially. With the use of a similar approach, a critical role of a different component of the extracellular matrix molecule tenascin-R has been demonstrated (391). This protein is absent within the RMS and exclusively detectable in the granule cell and the internal plexiform layers of the olfactory bulb. Similar to reelin, tenascin-R induces the detachment of neuroblasts when they are leaving the RMS and invading the olfactory bulb. Here again, the examination of the most anterior extension of the RMS in tenascin-R-deficient mice revealed a greater accumulation of neuroblasts than in wild-type mice. However, in contrast to reelin, tenascin-R has the property to orient migrating neuroblasts. Grafting tenascin-R expressing cells near the RMS, in regions that are never populated by neuroblasts or express tenascin-R, induces a radial migration of newborn cells out of the RMS. Finally, it has been shown that the expression of tenascin-R is dependent on the bulbar activity, since unilateral odor deprivation resulted in a decrease in both tenascin-R mRNA and protein in deprived bulbs. Identifying more precisely the molecular processes occurring during the radial migration of neuroblasts, before reaching their final position, may have critical clinical impact for neurodegenerative diseases.

## B. Maturation and Functional Integration of Newborn Neurons

### 1. Maturation of newborn interneurons

Using a replication-defective retrovirus expressing alkaline phosphatase and [<sup>3</sup>H]thymidine labeling of the newborn neurons, a previous study (355) investigated the time course of, respectively, the maturation and survival of olfactory interneurons as they migrate along the RMS and populate the adult olfactory bulb. Retrovirus injection was processed into the SVZ and used to stain the entire membrane of the soma and dendritic processes of the labeled cells, thus offering the opportunity to assess their structural morphology during their tangential and radial migration. Five morphological stages, and their timing, were described. Class 1 cells appear 2–7 days after viral injection and represent migrating neuroblasts found in the RMS. Between 7 and 9 days after viral injection, most of the labeled cells were observed migrating radially in the granule cell layer. These class 2 cells have an elongated cell body and a leading process with multiple ram-

ifications. Class 3 refers to labeled cells located in the granule cell layer, 9–11 days after viral injection. Their cell bodies are aligned with those of resident granule cells, suggesting that at this stage newborn interneurons have completed their migration. These maturing granule cells show growing dendritic processes that do not extend beyond the mitral cell layer. Class 4 cells appear between 11 and 15 days after viral injection. These cells show an elaborate dendritic arborization that extends in the external plexiform layer. Finally, class 5 cells appear 3 wk after viral injection, displaying a complex dendritic arborization with numerous spines. By *day 30*, all labeled cells belong to class 5.

## 2. Newly generated interneuron survival and death

Quantitative examination of long-term survival of newborn neurons incorporating the olfactory bulb has been recently assessed (34, 355, 473). Obviously not all neuroblasts coming from the SVZ reach the olfactory bulb, and ~50% of newborn neurons die after their migration. Dynamics of programmed cell death of young neurons varies according to the methodology used and has been reported to mainly occur during the first 6–12 wk after labeling. It was found that surviving newborn cells could live up to 12 mo (355) and more (473). The incorporation of adult bulbar interneurons is critically regulated by cell death. The time window of apoptosis seems to occur when most of the cells have developed dendritic arborization, suggesting that they had already been connected with their targets (i.e., mitral and tufted cells). However, double-labeling of TUNEL with doublecortin also gives support to the fact that immature neurons also undergo apoptosis (473). The lack of metabolic and electrical activities dramatically reduces the survival of newborn cells. With the use of anosmic mice, it has been found that incoming activity affects survival once the newborn interneurons have incorporated the granule cell layer and achieved structural maturation (355). In contrast, neuronal activity does not influence proliferation and migration of newborn cells along the RMS. This is in agreement with other findings showing that olfactory deprivation does not cause a decrease in cell proliferation (93, 133). Such a selective survival outlines the necessity to know better how newborn neurons are functionally integrated into adult networks.

## 3. Physiological properties of newborn interneurons

Taking advantage of the property of a pseudorabies virus expressing green fluorescent protein to pass transsynaptically into connected neurons, this virus was injected into the piriform cortex of adult mice exposed to bromodeoxyuridine (BrdU) through their drinking water (67). BrdU and viral colabeling of periglomerular and granule cells demonstrated that new neurons reach the

olfactory bulb. Furthermore, triple labeling of newborn neurons showed that some BrdU-NeuN colabeled cells were also positive for *c-fos* induction in adult mice exposed to odorants. Such results unequivocally support the notion that newborn olfactory neurons are functionally integrated into adult circuitries. A more recent study went further by analyzing the calendar of appearance of different transmitter receptors and the electrophysiological properties of new neurons incorporating the olfactory bulb (68). Class 1 neurons predominantly express extrasynaptic GABA<sub>A</sub> receptors and to a lesser extent AMPA receptors, but lack NMDA receptors. Contrary to the developing brain, no spiking activity occurs in these newborn neurons as they leave the RMS. No NMDA receptors were detected in newborn neurons until they become class 2 cells. First synaptic events emerge shortly after new neurons have completed their radial migration (class 3 and more mature neurons). Consistent with the earlier expression of GABA<sub>A</sub> receptors, inhibitory events (GABAergic synapses) occur before excitatory ones (glutamatergic synapses). Class 4 neurons are the first to establish reciprocal synapses with mitral cells. Although most of them express Na<sup>+</sup> channels, only a minority of class 4 neurons show fully developed Na<sup>+</sup> currents. Finally, spiking activity does not occur until neurons reach the most mature stage (class 5). This later point emphasizes that newborn neurons quietly integrate into existing circuits, connect target cells of the neural network, and only thereafter fire action potentials. Such a process of a delayed excitability may spare the existing bulbar circuitries some detrimental neurotransmitter release and functional disruptions.

## C. Functional Properties Brought by Adult-Generated Interneurons

### 1. The olfactory bulb as a locus of memory

Neurobiological studies have provided strong support to designate the olfactory bulb as a critical structure implicated in several types of learning and memory, especially in transient memory storage (45, 139, 164, 169, 284). The constitutive and inducible replacement of bulbar interneurons provides a rationale for the transfer of memories out of the olfactory bulb (reviewed in Ref. 284). It remains unknown whether a loss of interneurons takes place after the transfer of the memories held by these neurons to other parts of the brain or, alternatively, if the olfactory bulb is necessary for temporary processing of the information that is sent elsewhere for storage, in which case a rejuvenating population of neurons capable of rapidly forming synaptic connections may be well suited to participate in such a function. Questions about the functional significance of bulbar neurogenesis in the



adult brain necessitate determining which integrated functions such a process supports.

## 2. Newly generated neurons and behavior

A general physiological mechanism seems to operate within the olfactory bulb during olfactory learning in different contexts and different species (45). It has been shown, in the main olfactory bulb as well as in the accessory olfactory bulb, that the ratio of excitatory to inhibitory neurotransmitters is significantly decreased in different situations (memory of the mating male's pheromone, olfactory learning in neonatal rats, olfactory conditioning in adult mice). Again, these physiological changes emphasize the interest to uncover the real contribution of the newborn inhibitory interneurons. The use of situations of ethological relevance constitutes an important approach that undoubtedly should help the improvement of our understanding of the functions of adult neurogenesis. Some recent studies have attempted to examine olfactory neurogenesis in adulthood according to different ethological contexts.

For instance, in monogamous species, such as prairie voles, pair bond formation between partners occurs following mating (mate recognition), and social affiliation involves olfactory learning. In such a context the permanent supply of newborn neurons within the bulb could represent a potential support of social attachment in this species. Exposure to a male behind a wire mesh for 48 h induces an increase of newborn neurons in the SVZ and in the RMS of female prairie voles (424). The increase of neuron proliferation is suppressed in ovariectomized female prairie voles and can be partly reinstated by estrogen treatment. Of course, the functional benefit from the bulbar neurogenesis should not be considered to be acute (132), since it takes several weeks to generate a functionally integrated new interneuron.

Pair bond formation may also occur between adults and their offspring. In this sense, the selective maternal care of sheep toward their own lambs represents an interesting model to explore a potential role of the adult olfactory neurogenesis in attachment. In support of this hypothesis, it has been shown that the infusion of an antagonist of GABA<sub>A</sub> receptors, in the olfactory bulb of the ewe, prevents recognition of the lamb (236). The ablation of newborn neurons by injecting antimitotic drug within the SVZ would enable determination of involvement of adult olfactory neurogenesis in the learning and recognition processes of the lamb odor. As described below, pregnancy, care of young, and lactation behavior in mice are associated with an increase in olfactory neurogenesis. This supports the idea that we could learn much more by exploring different ethologically relevant contexts in which adult neurogenesis may occur.

We have investigated the effects of an odor-enriched environment on the regulation of bulbar neurogenesis in adult male mice (374). We assumed that bulbar activity may have an inductive, facilitative, and/or maintenance function in the neurogenesis of interneurons, which in turn may affect behavioral functions. Exposure to an odor-enriched environment (i.e., daily exposure for 24 h to different aromatic fragrances for 40 days) increased the rate of survival but not the rate of proliferation of newborn bulbar interneurons in enriched mice. In addition, behavioral analyses revealed that when submitted to different olfactory tasks, odor-enriched mice displayed a longer and stronger (i.e., resistant to retroactive interference) short-term olfactory memory compared with standard mice. Such a regulation of olfactory neurogenesis by odor stimulation is restricted to the olfactory bulb and does not modify the rate of hippocampal neurogenesis. Therefore, sensory inputs into the olfactory bulb appear as critical processes for the survival of newly generated olfactory interneurons (see also Ref. 355). Yet, the physiological factors governing this effect remain to be identified.

## D. Adult Neurogenesis as an Adaptive Function

According to the different uses of the term *function* in biology, one must ask what could be the advantages of the bulbar neurogenesis in term of fitness. A trait has survival value if it contributes to the survival, reproduction, and fitness of the organism. Because adult neurogenesis is a rather conserved biological phenomenon, its adaptive functions deserve to be explored. However, most of the studies have as yet focused on the physiological processes underlying adult neurogenesis and, except for the seminal papers in song birds and black-capped chickadees, very few experiments have addressed the question of its adaptive role (24, 25, 161, 338). Due to the seasonal variation in the availability of food, some bird species store it in different locations. In these food-storing birds, winter survival critically depends on their cache-recovery ability, and lesions of the hippocampus have been shown to impair their spatial memory (413). Moreover, it has been reported that these species display a larger hippocampus volume than nonstoring birds (190, 191). It was further found that free-ranging adult black-capped chickadees display a high seasonal (in fall) recruitment of newborn neurons in the hippocampal complex, i.e., at a time when birds are storing food (25). Such a behavioral context strongly suggests a high survival value of the recruitment of newborn neurons. Some other studies have also explored adult neurogenesis in terms of functional significance, as in the case of the recent study (414). The authors investigated bulbar neurogenesis during pregnancy and lactation in the mouse. They observed



that neurogenesis rates increased in the first third of gestation and during the first week of lactation, as well as following mating. Among the different stimulating maternal hormones, prolactin (PRL) appeared as a key factor triggering bulbar neurogenesis in the dams. Chronic subcutaneous or intracerebroventricular administration of PRL increased BrdU-positive cells in the SVZ and in the olfactory bulb. Conversely, the authors reported a significant reduction in the density of neuroblasts in the forebrain SVZ of mated females heterozygous for the PRL receptor. The authors did not directly assess the functional significance of this increase in olfactory neurogenesis in the pregnant and lactating mice, but proposed that it may participate in maternal care and offspring recognition at parturition and during lactation. Further behavioral investigations are needed to assess these functional aspects, especially to assess enhanced olfactory offspring discrimination in lactating females.

Olfactory neurogenesis during early pregnancy and lactation give rise to several other speculations in terms of adaptive functions. First, the first week of pregnancy is reminiscent of the time period during which female mice form an olfactory memory to pheromones of a stud male following mating (53, 54). However, it has been shown that such memory depends on the accessory olfactory bulb. Although adult neurogenesis has also been shown to occur in the accessory olfactory bulb (40), changes in this region have not yet been explored during early pregnancy (414). In case of a stimulated neurogenesis in the accessory olfactory bulb following mating, one may wonder whether the olfactory memory of the pheromones of the male with which female mate requires an increase in the density of newborn neurons into the accessory olfactory bulb. Second, house mice have been reported to nest communally in the laboratory, under semi-natural conditions as well as in the field (293, 294, 399, 466). Communal nests means that several females give birth and nurse indiscriminately offspring and nonoffspring (245). It has been shown that female mice nest communally with other females possessing a similar major histocompatibility complex, or more generally, when communal nesting partners tend to be kin (293, 294). Even if mothers recognize their own pups, it is unlikely that in mixed-litter nests such ability may serve lactating females to nurse only their pups while blocking access to nonoffspring. Thus, in terms of adaptive fitness, it has been proposed that mother mice reduce the cost of sharing milk with nonoffspring by nesting with closely related conspecifics (244; for a review, see Ref. 189). It is thus possible that the increase in olfactory neurogenesis during early gestation and lactation might facilitate the ability of females to assess the relatedness of potential nesting partners when sharing a nest.

## VI. FROM THE EXTERNAL WORLD OF ODORS TO THE INTERNAL STATE OF AFFECTS

The olfactory system is the first sensorial canal to become active in newborns. In mammals, the sense of smell becomes operational with the first respiratory movements of the newborn. Even in humans, during the first hours of life in the open air, the newborn child behaves like a macrosomatic animal. Meanwhile, the human being is totally dominated by affect. During the rest of the development period and all of adult life, olfaction will remain the sense that opens the most direct route to the affective sphere. This is in contradiction to the philosophical opinion purported by Kant in which intellectual influence is superior to affect: he sees in olfaction the dregs of the inferior faculty of knowledge because "the more the senses are strongly affected in relation to a constant level of stimuli, the less they teach us" (223).

To achieve this privileged relationship between olfaction and affect, the two olfactory systems connect different areas. The vomeronasal system projects to the hypothalamus and amygdala that are known to control innate endocrine or behavioral responses. In contrast, in the main olfactory system, information is processed in cortical area, which may give rise to the conscious representation of odorant molecules. In primates, the projections from the olfactory bulb reach medial olfactory areas including the piriform (primary olfactory) cortex, entorhinal cortex, cortico-medial nucleus of the amygdala, and olfactory tubercle. From the piriform cortex, projections reach area 13, a part of the caudal orbitofrontal cortex, and from there on to different orbitofrontal areas (70, 343). Populations of neurons in the primate (macaque) orbitofrontal cortex have olfactory responses to odors (379, 433, 435), which in many cases reflect the reward value of the odor (92, 378, 379).

The development of functional imaging techniques, such as positron emission tomography (PET) and fMRI, has made it possible to determine, in vivo, brain regions influenced by odors, as well as by behaviors associated with olfaction (e.g., sniffing). Application of these techniques has provided several new insights into various olfactory functions. One is that sniffing and smelling engage separate subsystems in the human olfactory cortex. Another is that perception of odorants is mediated by a set of core regions, which are partly different for pure olfactory than for olfactory plus trigeminal odorants. Thus, depending on the task associated with odor perception, the core regions are recruited together with other circuits, in a parallel and hierarchical manner. In addition, fMRI studies demonstrated, in accordance with basic psychological observations, that the right hemisphere may be more specialized than the left for central olfactory processing, particularly regions within the orbitofrontal cortex.

Interestingly, PET neuroimaging studies in humans found that the perception, discrimination, and recognition of odors activate the orbitofrontal, cingulate, and insula cortices (398) and that the right orbitofrontal cortex was associated with familiarity judgments (386). They also showed that the orbitofrontal cortex is activated by odors such as vanilla (positive valence) and hydrogen sulfide (negative valence) (486, 487).

Odors are important in emotional processing, yet relatively little is known about the representation of the affective qualities of odors in the human brain. Recent results suggest that there is a hedonic map of the sense of smell in brain regions such as the orbitofrontal cortex. These results have implications for understanding the psychiatric and related problems that follow damage to these brain areas. It is indeed remarkable that among all the senses, olfaction possesses a particular link with the limbic system that was taken to be the "nose-brain." Today, it is clear that the primary olfactory cortex projects to the entorhinal area, which in turn projects to the hippocampus. Thus we see reintroduced, after years of fervent affirmation followed by years of fervent denial, the idea that the hippocampus receives olfactory inputs. The pathway that links olfaction to the limbic system seems to be privileged. The path from the olfactory epithelium is more direct than the path from sensory surfaces such as the skin. Moreover, the primary olfactory cortex projects to the amygdala, in large part onto a particular cell group, the lateral nucleus of the amygdala, by bypassing the neocortex. However, while it is clear that the olfactory bulb projects to the amygdala in rodents, one wonders whether such a connection is still present in humans. For instance, the vomeronasal organ and the corresponding region of the accessory olfactory bulb are thought to form an apparatus dedicated to the processing of sexually significant odors, but in the fully formed human body, none of these structures has been identified (308). Finally, to emphasize the privileged link between olfaction and the limbic system, it has to be mentioned that the primary olfactory cortex projects also to the hypothalamus.

All animal and human behaviors are organized around two fundamental affective states: pleasure and aversion. The emotions can be defined as basic affects that assist the power of action in terms of maximizing rewards and minimizing punishments (376). The olfactory system has direct anatomical input connections with the formerly so-called rhinencephalon, a part of the brain that plays a major role in the mechanisms of emotions. It is not surprising, therefore, that odors act as potent stimuli for emotional reactions in animals and humans. Most odors possess an affective valence and are labeled as pleasant (positive hedonic value) or unpleasant (negative hedonic value). Taking account of hedonic tone, some researchers hypothesized two separate systems mediating positive and negative emotions (95, 96). The right hemisphere is

involved in encoding negative affects while the left one in encoding positive affects (31). Research studies using fMRI have confirmed this assumption by demonstrating that odors may be processed differently in the brain according to their negative or positive valence (380). On the one hand, pleasant but not unpleasant odors activate the medial part of the rostral orbitofrontal cortex. It is interesting to note that this region is close to the one found to correlate with monetary wins (342). On the other hand, a correlation between the unpleasantness rating of odors was found in regions of the left and more lateral orbitofrontal cortex. Activation was also detected in the anterior cingulate cortex with a middle part activated by both pleasant and unpleasant odors and a more anterior part of the anterior cingulate cortex showing a correlation with subjective pleasantness ratings.

The intensity of the affective experiences of an odor is differentially appreciated from its valence. With the use of event-related fMRI, it was shown that amygdala activation is associated with intensity, but not valence, of odors. In fact, the experience intensity is differentially appreciated from its valence. Activity in the orbitofrontal cortex, in contrast, was associated with affective valence independently of intensity (15). More recently, dissociation between intensity and valence was also observed, but intensity ratings of the odors were not correlated with activation in the orbitofrontal cortex but rather with the signal in the primary olfactory cortex (including the piriform and anterior entorhinal cortex) (380). Neural correlates of responses to emotionally different valenced sensorial stimuli were comparatively examined using PET studies to analyze the regional cerebral blood flow (rCBF) during presentation of both pleasant and unpleasant stimuli, respectively, for olfaction, vision, and audition. For all of these, emotionally valenced stimuli led to increased rCBF in the orbitofrontal cortex, the temporal pole, and the superior frontal gyrus in the left hemisphere. Emotionally valenced olfactory and visual but not auditory stimuli induced bilateral rCBF increases in the amygdala. These results indicate that pleasant and unpleasant emotional stimuli recruit the same neural networks in the left hemisphere regardless of the sensory modality. Finally, the data suggest a more potent activating effect of emotionally valenced olfactory cues over visual and auditory stimuli on the amygdala (388). Although compelling, these observations are contradictory with the results of another study (162). In this latter study, authors use event-related fMRI in an olfactory version of a classical conditioning paradigm; neutral faces were paired with pleasant neutral or unpleasant odors under 50% reinforcement. By comparing paired (odor/face) and unpaired (face only) conditions, odor-evoked neural activation could be isolated specifically in the primary olfactory cortex. A nonhabituating response in the posterior piriform cortex was turned

to all odors, whereas activity in the anterior piriform cortex reflected sensitivity to odor affect.

Studies using the response of the autonomic nervous system have been also used to examine the differential processing of pleasant and unpleasant odors. On one hand, some experiments found reverse effects for pleasant and unpleasant odors using the electrodermal response (4, 5, 43). On the other hand, studies using recordings of the startle reflex have only observed specific effects of unpleasant odors (119). In addition, many studies have focused their interest on the fact that the differential reactivity pattern to pleasant versus unpleasant odors depends on the nostril stimulated. For instance, chemosensory evoked potentials suggest the existence of differential processing of affective valence of odors when the right or the left nostril is stimulated (243). Responses (amplitude of the P2 wave) tended to have greater amplitude when the right nostril was stimulated by an aversive odor (hydrogen sulfide), while the reverse pattern was observed with a pleasant odor (vanillin). Furthermore, a study using response times indicated that unpleasant odors were rated faster than pleasant ones when the right nostril was stimulated (31). This right-side advantage for brain processing of unpleasant affect in olfaction is however in contradiction with previous observations showing the predominance of the left orbitofrontal cortex response to unpleasant odors (380).

As seen before, olfactory function is bilateral at the first relays but becomes predominantly ipsilateral in projection. This means that odor information received through one nostril is projected to the ipsilateral primary cortex, but finally, the right orbitofrontal cortex is going to be more activated than the contralateral homologous orbitofrontal cortex, whereas the medial temporal lobes were symmetrically activated (487). This suggests the hypothesis that some right hemisphere structures may be more specialized than corresponding structures in the left hemisphere in encoding olfactory information. An intriguing discovery is that odors are perceived as more pleasant when sniffed through the right nostril and are named more accurately when sniffed through the left (192). Research on olfactory lateralization in humans suggests that the process is influenced by the nature of the olfactory stimulus. In a comparative study of odors that produced right trigeminal stimulations (i.e., mustard oil) and odorants with high hedonic valence (i.e., phenyl-ethyl alcohol which has a roselike smell), it was concluded that basic olfactory perception and particularly the emotional and hedonic aspects are more lateralized to the right hemisphere and irritative aspects to the left (42). Finally, when studying lateralization effects on emotional perception of odors, right-handed subjects scored higher on hedonic scoring of odors; they also showed the right nostril/right hemispheres to produce a higher hedonic score. The studies did not find the left-handers to show any lateralized

effect, but they gave lower hedonic scores on average compared with the right-handers. Remarkably, handedness appeared to interact with gender, the difference between right and left being less significant in women (102).

Taken together, these noninvasive functional imaging studies of the human olfactory system revealed that the sense of smell is organized similarly to other sensory modalities and that the specific psychological characteristics of olfaction should be attributed to an early involvement of the limbic system rather than a conceptually different mode of processing (398). Taking into account the high connectivity of limbic structures and the fact that activation of the amygdala immediately induces emotions and facilitates the coding of memories, one should not be so surprised to uncover the special relationship that links olfaction with emotions.

## VII. CONCLUSIONS

Remarkable progress has been made in the past decade in understanding the function of the olfactory systems. The development of experimental and new theoretical approaches has already generated important new insights into the neural substrates of olfactory processing and explained how the brain recognizes and discriminates odors. This has spurred an awakening of the scientific community exploring the sensory systems to the importance of studying olfactory processing to better understand how external stimuli are encoded and stored in higher brain centers. It is clear today that olfaction is a synthetic sense par excellence. It enables pattern learning, storage, recognition, tracking, or localization and attaches emotional and hedonic valence to these patterns. Previous studies dedicated to investigating olfactory processing have postulated the convergence of information from deconstructed patterns in the olfactory bulb to "cardinal cell assemblies" located at the top of a hierarchical perceptual system in higher brain centers. However, the notion of grandmother cells (23) located in the first central relay has been revisited today, in part because the olfactory bulb is more than a passive relay of odor-related information. In fact, sensory information is encoded in the temporal patterns of spiking activity embedded within highly organized spatial maps. This first stage of the process behaves rather as an active nonstationary system with complex and correlated activity patterns of neural assemblies, across space. For such a dynamic, local inhibitory interneurons of the first olfactory central relay appear as key players. The modulation of granule cell neurogenesis by ongoing environmental changes and centrifugal fibers offers a unique means for the olfactory bulb circuit to optimize olfactory information processing.



As a result of unprecedented developments in methods for examining the structure, development, function, and neurochemistry of olfactory system circuits, research in olfaction has already progressed dramatically in recent years, leading R. Axel and L. Buck to be awarded the 2004 Nobel Prize in physiology or medicine for their pioneering work on the sense of smell. Although the duo's work has answered important questions about olfaction, it has also posed additional puzzles. Applying new technologies, including those of molecular biology, neurophysiology, and functional imaging, should help us to unravel the mysteries of both peripheral and central coding. These coming advances should lead, within the next decade, to a rather complete understanding of olfactory system function. We now have the feeling that after digging deeply, we are starting to release exquisite fragrances of knowledge.

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