CHAPTER

1

The Form and Functions of Neural Circuits in the Olfactory Bulb

G. Lepousez, P.-M. Lledo

Institut Pasteur, Paris, France; Centre National de la Recherche Scientifique, Paris, France

OUTLINE

1.1 INTRODUCTION

Sensory systems are specialized biological devices by which organisms perceive the external sensory space. Sensory perception allows the deconstruction of this external world and the subsequent emergence of an internal percept. Following this Aristotelian principle, animals can discriminate and recognize an enormous range of physical and chemical signals in their environment, which may profoundly influence their behavior and provide them with vital information for reproduction and survival.

Several sophisticated sensory channels are available for that purpose, but all of them rely on a specific set of rules by which information is transposed from one dimension to another. For the chemical senses, this transposition concerns the ways in which chemical information gives rise to specific neuronal responses in a dedicated sensory organ (Ache and Young, 2005). In comparison to other sensory stimuli, odorant molecules, that is, volatile molecules that are perceived as odors, are infinite in terms of molecular formulae and cannot be classified with only objective dimensions such as frequency in the case of auditory stimuli (Laurent, 2002). The task of perceiving an odorant is made even more complex because a single odor usually is composed of many types of molecules (e.g. chocolate contains more

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than 600 types) and is still perceived as one unique object, distinct from its components (a process called pattern completion). In addition, odor intensity (i.e., molecular concentration) can vary without changes in the perceived quality (a process called perceptual stability; Gottfried, 2010).

The origin of chemical detection (also called chemosensation) certainly dates back to the beginning of prokaryotes. It has evolved into distinct modalities in vertebrates to meet crucial needs such as locating potential food sources, detecting dangers such as predators, and mediating social and sexual interactions. Despite these functions, which are highly conserved throughout the evolution of species, interest in audition and vision has largely dominated the sensory research field in neuroscience, leaving behind the understanding of the more primitive chemical sense. Nevertheless, during the last two decades, neuroscience has made considerable progress in understanding how the brain perceives, discriminates, and recognizes odorant molecules so precisely. In 1991, the description of a multigene family of olfactory G-protein-coupled receptors provided a molecular basis for odor recognition (Buck and Axel, 1991). This discovery was of great significance to the neurobiology of olfaction and later was recognized with the Nobel Prize in 2004 (Mombaerts, 2004a). Since then, olfaction has attracted the attention of neuroscientists who started to investigate the different stages of chemosensory systems. As a result, converging approaches including anatomy, neurogenetics, biochemistry, cellular biology, neurophysiology, psychology, and computational neuroscience have contributed to provide a picture of how chemical information is processed in the olfactory system, starting from the periphery to higher brain regions.

Although still incomplete, today we have a fairly comprehensive picture about how chemicals interact with their cognate receptors to initiate signal transduction in the sensory receptor cells. We also know how the olfactory sensory information is first transduced in the sensory neurons located in dedicated olfactory sensory organs (Mombaerts, 2004b). Among the different elements along the olfactory pathway, local circuits in the second- and third-order central areas are key elements that process the simple monophasic sensory signal conveyed by the sensory neurons and convert it into a multidimensional content (Figure 1.1) (Gottfried, 2010; Wilson and Sullivan, 2011).

Below, we discuss how the chemical information is encoded and processed at the first central relay of the olfactory system, the main olfactory bulb, as well as the functions of the bulbar neural circuits that are relevant for triggering specific behavioral responses. In addition to the main olfactory bulb, which relays odorant information detected by sensory neurons of the olfactory epithelium, a similar structure called the accessory olfactory bulb, located in the caudal part of the olfactory bulb, relays pheromonal information detected in the vomeronasal organ. Because of space constraints, this chapter focuses exclusively on the main olfactory bulb and odor coding in rodents.

1.2 SYNAPTIC ORGANIZATION OF THE MAMMALIAN OLFACTORY BULB

The olfactory system is responsible for correctly coding sensory information from thousands of odorous stimuli. To accomplish this complex task, odor information is

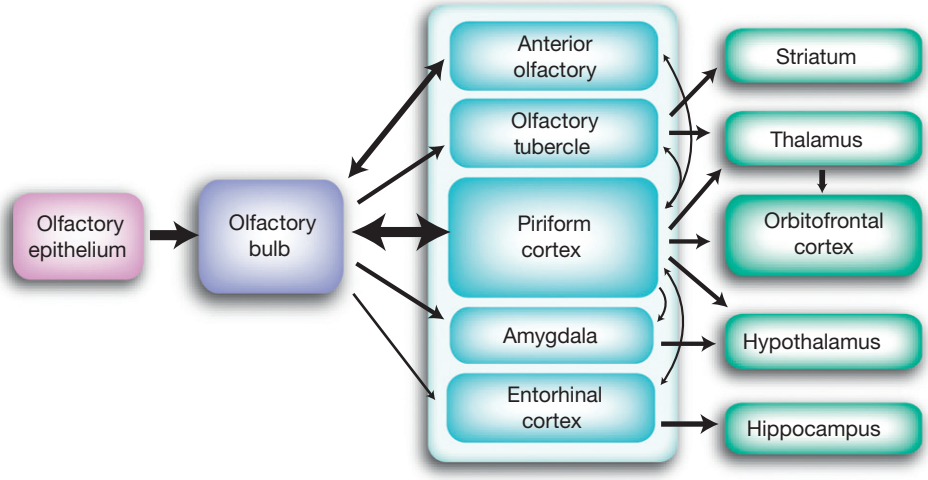

FIGURE 1.1 Schematic representation of the olfactory system. The olfactory system is composed of a sensory organ, the olfactory epithelium, followed by the olfactory bulb, the first central relay of odor information. The olfactory bulb then projects to different olfactory cortical areas involved in olfactory processing and behavior. Structures in blue that receive direct inputs from the output neurons of the olfactory bulb composed together the so-called 'olfactory cortex.'

processed through distinct units. At each of these units, a modified representation of the odor stimulus is generated. Following a bottom–up approach, we will start our description from the olfactory sensory organ located in the nasal cavity.

1.2.1 Organization of Sensory Inputs

The ability to process correctly the physical and statistical properties of chemical information is constrained by the functional architecture and the synaptic organization of some dedicated neural circuits. As our knowledge about the neurobiology of olfaction grows, it is becoming evident that the main olfactory systems of animals in disparate phyla share many striking features regarding the functional architecture and the synaptic connectivity (Bargmann, 2006; Hildebrand and Shepherd, 1997). For instance, mammals and invertebrate olfactory systems display common organizational features and functional characteristics (Wilson and Mainen, 2006). In all cases, the initial event shared by virtually all odorant detection systems is the requirement of specific interaction of odorant molecules with specific receptors expressed on the cilia of sensory olfactory neurons before conveying information to central structures (Ache and Young, 2005; Bargmann, 2006; Mombaerts, 2004b). Essentially, there are four different features that are common to all olfactory systems: (1) The presence of soluble odorant binding proteins in the mucus overlying the receptor cell dendrite, (2) the existence of G-protein-coupled receptor acting as specific odorant receptors, (3) the use of a two-step signaling cascade in odorant transduction, (4) the presence of functional anatomical structures at the first central target in the olfactory pathway called glomeruli (reviewed by Bargmann, 2006; Firestein, 2001; Mombaerts, 2004b). If these common features represent adaptive mechanisms that have evolved independently, their study might bring valuable knowledge about the way the nervous system extracts information from olfactory space.

In mammals, olfactory transduction starts with the activation of some of the thousand different types of odorant receptors located on the cilia of bipolar olfactory sensory neurons that comprise the olfactory neuroepithelium (1000–1300 genes in the mouse; Buck and Axel, 1991; Mombaerts, 2004b). It is believed that these sensory neurons recognize more than a thousand airborne volatile molecules called odorants. A general principle is that these receptors exist as separate information channels, because most sensory neurons express only one type of olfactory receptor. Because of the broad chemical tuning of these receptors (Araneda et al., 2000), the general coding principle is "one odor = one set of receptor activations" (Firestein, 2001; Mombaerts, 2004b). The olfactory epithelium then projects to the first central relay of the olfactory system: the main olfactory bulb (referred to below as the olfactory bulb). As advances in understanding olfactory transduction progressed, interest in deciphering some of the olfactory bulb functions grew concomitantly. This heightened interest has been spurred on, at least in part, by the discovery of the way in which the sensory organ connects to the olfactory bulb. We know now that the sensory neurons that express the same odorant receptor project their axons centrally to one or two spherical modules in the olfactory bulb called glomeruli (Zou et al., 2009). Here, sensory information is transmitted to higher brain centers via output neurons called mitral/tufted cells. The discrete and spherical glomeruli are morphological units made of distinctive bundles of neuropil (Figure 1.2). This terminology reflects both the homogeneity of the sensory inputs (they all express only one odorant receptor) and the degree to which the olfactory bulb neurons connected to the same glomerular unit display a similar receptive field (Dhawale et al., 2010; Tan et al., 2010). Recently, dramatic progress has been made in understanding of how olfactory sensory neurons develop and how they express only one odorant receptor. This discovery prompted the use of genetic tools to probe and manipulate specific populations of sensory neurons, resulting in several major breakthroughs

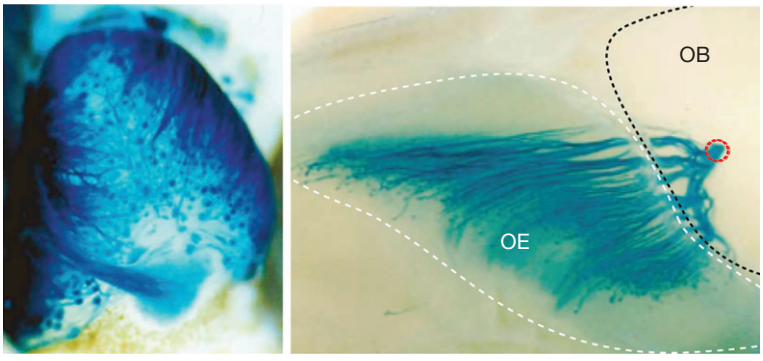

FIGURE 1.2 Convergence of the olfactory sensory neuron axons into glomeruli. (a) Olfactory sensory neurons labeled in blue project their axons on the surface of the olfactory bulb (note the single glomeruli). (b) Whole-mount view of the olfactory epithelium (OE) and the olfactory bulb (OB). Olfactory sensory neurons expressing the olfactory receptor P2 in the olfactory epithelium (OE) project the axons towards a single glomerulus (red dashed circle) on the surface of the olfactory bulb (OB). *Adapted from Mombaerts P, Wang F, Dulac C, et al. (1996) Visualizing an olfactory sensory map.* Cell *87: 675–686, with permission.*

regarding axon guidance, axon sorting and axon positioning (Sakano, 2010; Zou et al., 2009).

In different species, each glomerular structure results from the convergence of 5 to 40 thousand axon terminals of sensory neurons that express the same odorant receptor (Figure 1.2). Therefore, the glomerular layer can be considered as a two-dimensional anatomical representation of the olfactory receptors' repertoire (also called 'chemotopic map'; Johnson and Leon, 2007; Wachowiak and Shipley, 2006). Because one odor can activate several olfactory neurons, odor information is first encoded by the combinatorial patterns of glomerular activation. Odorants activate a specific array of olfactory sensory neurons that lead to a chemotopically fragmented map of activated glomeruli on the surface of the olfactory bulb (Meister and Bonhoeffer, 2001). Remarkably, the precise projection pattern can be reproduced from one animal to another and even between different rodent species (Soucy et al., 2009). Distinct odorants activate different combinations of glomeruli and two odors are more difficult to discriminate when these show a greater overlap in this glomerular chemotopic map (Linster et al., 2001). Nevertheless, if such a spatial pattern coding scheme were only applicable to several odors, it would not be able to provide a sufficiently large coding space to discern between the millions of potential odors or mixtures of odor present in our environment (Laurent, 2002).

The sensory neurons project to paired olfactory glomeruli on both the medial and lateral aspects of the olfactory bulb, thus creating two mirror-symmetric maps (Mombaerts et al., 1996). As each group of glomerulus-specific output neurons is odorant receptor-specific, glomeruli form a morphological as well as functionally defined network somewhat analogous to barrels in the somatosensory cortex (Johnson and Leon, 2007). In mammals, the convergence ratio of sensory neurons to olfactory bulb output neuron is very large: about 1000:1 (Zou et al., 2009). A bulbar output neuron thus forms its responses to odors from very large numbers of converging inputs, ensuring detection of faint signals, increase signal-to-noise ratios and temporal noise average.

1.2.2 Synaptic Processing Within Olfactory Bulb Microcircuits

Because of its relatively simple anatomical organization and easy access, the olfactory bulb has been a privileged model system for deciphering the principles underlying network processing of sensory information. There, odors elicit a well-organized pattern of glomeruli activation across the surface of the olfactory bulb, but the mechanisms by which this chemotopic map is processed into an odor code by the bulbar circuitry has recently attracted more attention. With the advance in recent years of *in vitro* brain slice preparation, as well as *in vivo* recording techniques that were applied on behaving animals, the complex processing of the olfactory information is starting to be revealed. Since Cajal's pioneering studies, it has been known that the main output neurons of the bulb, the so-called mitral cells, are located in a single lamina, the mitral cell layer (Figure 1.3). A second population of output neurons, namely tufted cells, are scattered in the external plexiform layer (EPL). The primary (or apical) dendrite of mitral and tufted cells, extending vertically from its soma, contacts one glomerulus, whereas their multiple long secondary dendrites spread in the EPL.

About 50–100 output neurons (mitral/tufted cells) emanate from each glomerulus and project to a number of higher centers that compose the olfactory cortex (see Figure 1.1). Output neurons are the backbone of two serial intrabulbar microcircuits: one between primary apical dendrites and juxtaglomerular cells and the other between secondary dendrites and granule cells. The main difference between juxtaglomerular 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 (Figure 1.3). Therefore, two potential distinct 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 EPL, where reciprocal dendrodendritic synapses are heavily distributed between dendritic spines of local interneurons and the dendrites of output neurons. These two inhibitory microcircuits are also under the control of centrifugal fibers coming from cortical and neuromodulatory area.

1.2.2.1 Synaptic Transmission at the First Synapses

The glomerular layer constitutes a first site of integration for olfactory information. In this layer, axonal termini of olfactory sensory neurons synapse directly onto output neurons (50–100 cells per glomerulus) and also onto local neurons, namely juxtaglomerular cells (1000–2000 cells per glomerulus). The olfactory nerve-evoked excitatory responses of both neuron types comprise fast amino-3-hydroxy-5-methyl-4-isoaxozole-propionic acid (AMPA) and slow *N*-methyl-D-aspartate (NMDA) components. The latter is particularly long-lasting and may play an important role in the bulbar output by maintaining a pattern of sustained discharge of output neurons (Carlson et al., 2000).

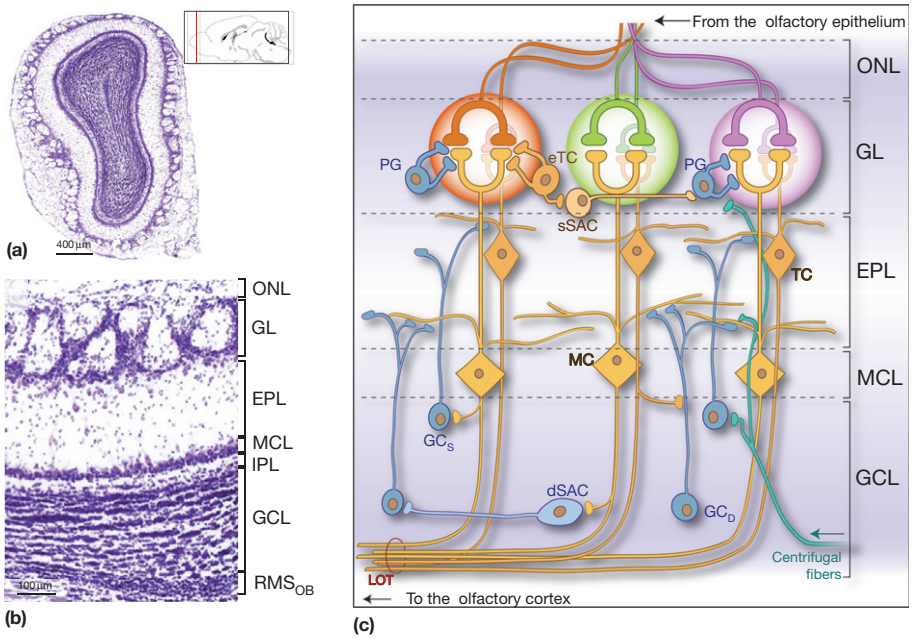

FIGURE 1.3 Anatomical organization of the main olfactory bulb. (a) Nissl-stained coronal section of the mouse olfactory bulb showing the different concentric layers. Inset, a sagittal section showing the rostrocaudal level of the coronal section. (b) Higher magnification view. ONL, olfactory nerve layer; GL, glomerular layer; EPL, external plexiform layer; MCL, mitral cell layer; IPL, internal plexiform layer; GCL, granule cell layer; RMS OB, rostral migratory stream of the olfactory bulb. (a) Olfactory sensory neurons (OSNs) in the olfactory epithelium (OE) that express the same odorant receptors project their axons to the main olfactory bulb into one of the glomeruli that form the glomerular layer (GL). In the GL, sensory neuron terminals synapse onto the apical dendrites of output neurons, namely the mitral cell (MC) and the tufted cells (TC). In addition, periglomerular cells (PGC), superficial short-axon cells (sSAC) and external tufted cells (eTC) act on glomerular synaptic transmission exerting diverse functional effects. In the external plexiform layer (EPL), the lateral dendrites of mitral and tufted cells interact with the dendrites of granule cells (GC). Granule cells can also be subdivided into distinct subpopulations: superficial granule cells (GC_S), which target the superficial lamina of the external plexiform layer and synapse with tufted cells, and deep granule cells (GC_D), which target the deep lamina of the external plexiform layer are connected to mitral cells. The somas of mitral cells are aligned and delineate the mitral cell layer (MCL), and the somas of tufted cells are scattered in the EPL. Granule cell somas and also some deep short-axon cells (dSAC) compose the granule cell layer (GCL). Centrifugal fibers from other brains regions innervate specific layers of the olfactory bulb depending on their brain origin. Lastly, output neuron axons fasciculate to form the lateral olfactory tract (LOT). All of the cell types colored in orange are glutamatergic; GABAergic cells are in blue. ONL, olfactory nerve layer.

Juxtaglomerular cells have dendrites restricted to one glomerulus and impinge onto olfactory nerve terminals or primary dendrites of mitral/tufted cells. Juxtaglomerular cells can be subdivided into three categories (Figure 1.3). The first category is comprised by periglomerular cells, small axonless interneurons that are the main source of γ-aminobutyric acid (GABA) in the glomerular layer and which provide feedback and feedforward inhibition to output neurons (Wachowiak and Shipley, 2006). It is noteworthy that a subpopulation of these GABAergic cells is also dopaminergic (Kosaka and Kosaka, 2005). Their inhibitory action alters the strength of sensory signals as they pass out of the bulb, and it is thought to provide a mechanism of filtering of weak sensory inputs (Gire and Schoppa, 2009). In addition, periglomerular cells also exert a presynaptic regulation of sensory inputs thanks to the expression of $GABA_B$ and D_2 dopamine receptors on olfactory sensory terminals (Aroniadou-Anderjaska et al., 2000; Hsia et al., 1999). The second category concerns the superficial short-axon cells. This heterogeneous cell population, comprising GABAergic and glutamatergic neurons, displays dendritic and axonal branching in several glomeruli and is thought to mediate lateral inhibition between glomeruli (Aungst et al., 2003; Kiyokage et al., 2010). The third group is composed of external tufted cells. These local glutamatergic cells, distinct from the output tufted cells, innervate periglomerular cells, short-axon cells, and mitral cells. Their spontaneous intrinsic rhythmic activity, synchronized by gap junctions and with the breathing rhythm, coordinates the activity of the cells located within each glomerulus (De Saint Jan et al., 2009; Hayar et al., 2004). In addition to direct fast excitation from OSN, external tufted cells provide a significant slow feed-forward excitation onto mitral cells (Najac et al., 2011). Moreover, activation of external tufted cells and glutamatergic superficial short-axon cells triggers lateral excitation of distant periglomerular cells, thus providing feedforward inhibition onto mitral/tufted cells of remote glomeruli (Aungst et al., 2003; Wachowiak and Shipley, 2006). This distributed inhibition mediates a globally averaged level of feedforward inhibition onto

distant mitral/tufted cells and contributes to normalization of the intensity of sensory input, a key function for constructing intensity-independent representations of stimulus quality (Linster and Cleland, 2009). It is also known that several major classes of periglomerular cells are generated in the adult through the subventricular zone (SVZ) and the rostral migratory stream (RMS) and that their respective proportions remain constant throughout life (Lledo et al., 2008).

Since extremely faint signals can be detected by the olfactory system, there may be some mechanisms that promote reliable information transmission from olfactory sensory neurons to the brain. In the absence of any presynaptic specialization such as the synaptic ribbons in the retina or the cochlea, the sustained and reliable synaptic transmission of odor information benefits from the high convergence of sensory neurons and also from a very high probability of glutamate release, reflected by a marked paired-pulse depression (Hsia et al., 1999; Murphy et al., 2004). In addition to the synaptic mechanisms described above, glutamate spillover within glomeruli and the presence of gap junctions between output neurons connected to the same glomerulus would help in increasing the signal-to-noise ratio and normalizing the activity of output neurons (Christie et al., 2005; Linster and Cleland, 2009).

1.2.2.2 *The Dendrodendritic Synapse Provides the Major Source of Inhibitory Contact to Output Neurons*

In contrast to the primary dendrite, mitral/tufted cell secondary (or basal) dendrites radiate up to 1000 μm horizontally, spanning almost the entire olfactory bulb. In the EPL, mitral/tufted cell dendrites interact with the dendrites of granule cells and both contain synaptic vesicles (Figure 1.4; Price and Powell, 1970). As granule cells are the largest group of bulbar interneurons (there are about 100 granule cells for one output neuron), and

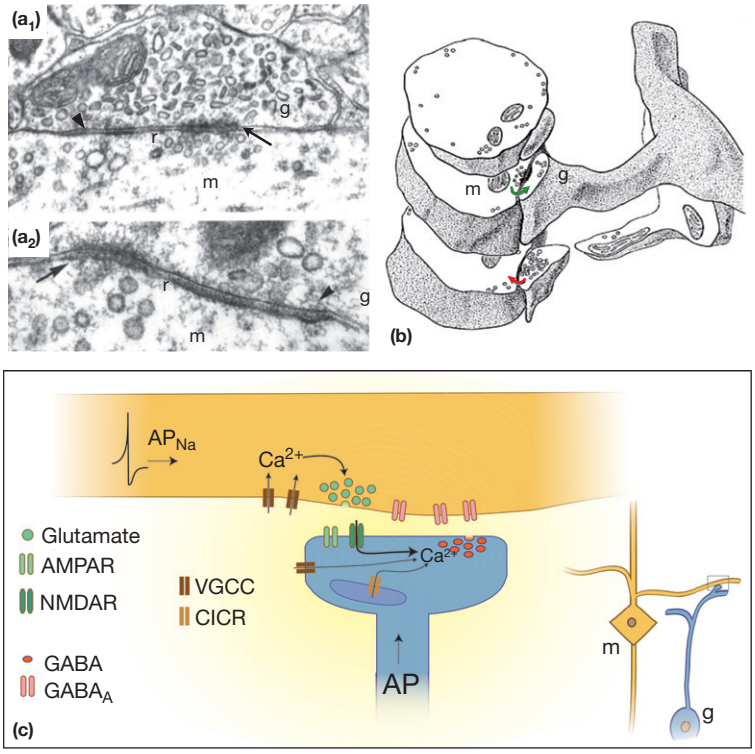

FIGURE 1.4 The dendrodendritic reciprocal synapse in the main olfactory bulb. (a) Two electron micrographs of a mitral cell dendrite (m) making a mitral-to-granule asymmetric synapse (arrow) onto a granule cell spine (g), which in turn makes a granule-to-mitral symmetric synapse (arrowhead) back onto the same mitral cell dendrite (adapted from Price JL and Powell TP (1970). The synaptology of the granule cells of the olfactory bulb. *Journal of Cell Science* 7: 125–155, with permission). (b) Serial section reconstitution of a reciprocal synapse between a lateral dendrite of mitral cell (m) and a granule cell spine (g). Green arrow, glutamatergic synapse; red arrow, GABAergic synapse (adapted from Rall W, Shepherd GM, Reese TS, and Brightman MW (1966) Dendrodendritic synaptic pathway for inhibition in the olfactory bulb. *Experimental Neurology* 14: 44–56, with permission). (c) Schematic representation of the dendrodendritic synapse. Action potentials (AP) propagating in mitral cell secondary dendrites (m, represented in orange) activate voltage-gated calcium channels (VGCC), which trigger the release of glutamate at reciprocal synapses. This glutamate locally depolarizes granule cell spines (g, represented in blue) via AMPA receptors (AMPAR) and NMDA receptors (NMDAR), which triggers calcium entry from NMDA receptors and also from voltage-gated calcium channels and calcium-induced calcium release from internal stores (CICR). This in turn causes GABA release back onto the mitral cell dendrite that activates $GABA_A$ receptors ($GABA_A$). In addition, action potentials generated in the soma of the granule cell can propagate in the dendritic tree and trigger a global release of GABA.

as they are axonless neurons, synaptic transmission between dendrites remains the dominant mode of neuronal interaction in the olfactory bulb (Schoppa and Urban, 2003; Shepherd et al., 2007).

Granule cells can also be subdivided into distinct subpopulations: superficial granule cells that target the superficial lamina of the EPL and are believed to establish synapses mostly with tufted cells and deep granule cells targeting the deep lamina of the EPL which are connected to the mitral cells (Figure 1.3; Mori et al., 1983; Shepherd et al., 2007). These two microcircuits (tufted/superficial granule cells versus mitral/deep granule cells) are thought to maintain different functions in odor processing. Because of their short lateral dendrites and the intrabulbar connections between mirror-symmetric glomeruli they support, tufted cells may be important for intensity perception of odorants (Lodovichi et al., 2003; Nagayama et al., 2004). By contrast, the mitral-granule cell circuit is thought to mediate complex inhibitory functions that are important for odor discrimination (Lledo and Lagier, 2006).

The synaptic interactions that play a key role in the mitral/tufted-granule cell circuits have some simple yet unusual features. Output cells and granule cells communicate via reciprocal dendrodendritic synapses (Figure 1.4; Jahr and Nicoll, 1980; Price and Powell, 1970; Rall et al., 1966; review in Schoppa and Urban, 2003). This feature also extends to periglomerular cells that synapse with mitral/tufted apical dendrites in the glomerulus. The reciprocal circuit provides inhibition that forms the basis for a reliable, spatially localized, and recurrent inhibition. Synaptic depolarization in mitral/tufted cells driven by the long-lasting excitatory inputs from sensory neurons triggers the generation of an action potential. This action potential invades the lateral dendrites (Xiong and Chen, 2002) and triggers glutamate release from output neuron dendrites onto granule cell spines. The activation of AMPA and NMDA receptors present in the spines of granule cells leads to a depolarization and a local calcium entry in interneuron dendrites and spines. This, in turn, elicits the synchronous and asynchronous release of GABA directly back onto output neurons. The release of GABA from granule cell spines is driven by calcium entry, mainly from NMDA receptors, but also from voltage-gated calcium channels and internal stores (Figure 1.4; Egger et al., 2005; Isaacson and Strowbridge, 1998; Schoppa et al., 1998). Thus, dendritic GABA release from granule cell spines might occur (1) through an action potential-independent manner, providing a local and graded form of inhibition, or (2) through an action potential-dependent manner, triggered by somatic excitatory inputs and supporting a global form of inhibition (Lledo and Lagier, 2006). Additionally, interneurons of the olfactory bulb also receive GABAergic inputs, as classically reported in several other brain areas. Recent studies have revealed that this inhibition is mediated by inframitral interneurons called 'deep short-axon cells' (Figure 1.3), which represent an unexpectedly large and diversified population of interneurons in the olfactory bulb (Eyre et al., 2008; Pressler and Strowbridge, 2006). These deep short-axon cells receive inputs from output neurons and possibly from centrifugal fibers and provide a feedback inhibition onto granule cells (and to a lesser extent periglomerular cells) thanks to a large axonal arbor.

Since secondary dendrites have large projection fields and extensive reciprocal connections with interneurons, each local bulbar interneuron may contact the dendrites of numerous output neurons. This suggests not only that dendrodendritic interactions provide a fast and graded feedback inhibition, but that they also underlie lateral inhibition between output neurons that innervate different glomeruli. In this sense, granule cells would provide both local (recurrent) and integrated (lateral and global) inhibition to output neurons (Lledo and Lagier, 2006). How do inhibition and local microcircuits shape and encode the spatial representation of sensory inputs?

1.2.3 Sensory Processing in the Output Layer

The mitral/tufted-granule cell circuit is thought to perform three main functions: sharpening the tuning of output neurons, decorrelating sensory inputs into time-varying temporal patterns, and synchronizing activated output neuron activity. These computations are crucial for odor coding and especially for odor discrimination: reducing or facilitating inhibition between granule cells and output neurons impairs or improves odor-discrimination performance, respectively (Abraham et al., 2010).

First, olfactory 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 inhibition, originally introduced in the 1950s to explain visual contrast enhancement in the retina (see Shepherd, 2010) has been extensively characterized mathematically. Anatomical and functional characterizations of the olfactory bulb circuit have revealed the importance of lateral inhibition. Thanks to this inhibitory mechanism, activity in few stimulated output neurons may lead to the inhibition of other neighboring neurons innervating distinct glomeruli (Egger and Urban, 2006; Yokoi et al., 1995). This inhibition, which critically relies on dendrodendritic synapses, was proposed as a mechanism for sharpening the tuning of output cells compared to their inputs (e.g., Koulakov and Rinberg, 2011). For instance, examination of the responses of individual mitral cells to inhalation of aliphatic aldehydes

reveals that many individual cells are excited by one subset of these odorants, unaffected by a second subset, and inhibited by a third subset (Figure 1.5; Tan et al., 2010; Yokoi et al., 1995). Interestingly, the magnitude of lateral inhibition received by neighboring output neurons through the granule cell circuit is dynamically regulated, since it depends on the activity level of the postsynaptic output neuron (Arevian et al., 2008). Such interactions may underlie the limited mitral cell activation observed in animals that are awake (Koulakov and Rinberg, 2011). Because odor maps generated by different odors are extensive all over the surface of the olfactory bulb and often overlap, the propagation of action potentials into the lateral dendrites, and the possible spread of excitation through granule cell dendrites, contributes to a contrast enhancement mechanism that sharpens the tuning of widely dispersed output neuron odorant-receptive fields. Rather than a center-surround receptive field like that in the retina, mitral cells have a more distributed and sparse receptive field (Fantana et al., 2008). Lastly, the interglomerular lateral inhibition provided by superficial short-axon cells in the glomerular layer described above could, to a lesser extent, provide an additional form of lateral inhibition (Aungst et al., 2003; Linster and Cleland, 2009).

Second, the long-range projections of secondary dendrites underlie fundamental computations characteristic of the nonlinear dynamical system (Laurent, 2002). Indeed, output cells respond to a constant odor exposure with odor-specific temporal spike patterns that may constitute a "temporal code" of odor identity for downstream regions (Figure 1.6(a)). The spatially distributed pattern of activated output neurons – sometimes ambiguous for similar odorants – evolves progressively over time and diverges from the initial pattern, following a trajectory in the coding space that is characteristic of a given odorant and a given intensity (Figure 1.6(b); Bathellier et al., 2008; Laurent, 2002; Mazor and Laurent, 2005; Stopfer et al., 2003). Within this framework, the main function of bulbar microcircuits would be to decorrelate similar input patterns into divergent odor-specific temporal dynamics of output cell activity. This computation, called decorrelation, would reformat combinatorial representations by reducing the overlap between clustered input activity patterns, thus making odor representation more distinct and facilitating their discrimination by downstream olfactory centers (Friedrich and Laurent, 2001). This temporal coding scheme may also be generalized in the case of terrestrial mammals, in which active breathing introduces an additional temporal dynamic to the stimulus (Wachowiak, 2011; see respiratory traces in Figure 1.5). Odor inhalation triggers precise and reliable cell- and odor-specific temporal spike patterns, which are tightly time-locked to the sniff phase and carry sufficient information for the discrimination of odors (Cury and Uchida, 2010; Dhawale et al., 2010; Shusterman et al., 2011). The timing of mitral cell activation relative to the sniff phase has been recently highlighted as another possible mechanism for the rapid encoding of odor (Smear et al., 2011). This additional extrinsic rhythmicity imposed by the breathing cycle provides an external "clock" for the entire olfactory system that may promote spike-timing dependent coding relative to the phase of the underlying respiratory cycle (Wachowiak, 2011).

Third, the long-range projection of secondary dendrites and recurrent inhibition provided by granule cells shape the temporal patterns of output neuron activity and lead to the synchronization of the network. This synchronization gives rise to oscillations of the local field potentials (LFP) in the gamma frequency band (30–100 Hz; see LFP traces in Figure 1.6(a)), a phenomenon already described by Sir Adrian in 1942 (Adrian, 1942; see also Shepherd, 2010). Since the pioneering theoretical work of Rall and Shepherd (Rall and Shepherd, 1968; Rall et al., 1966), experimental and computational studies have confirmed that recurrent inhibition provided by the dendrodendritic reciprocal synapse is

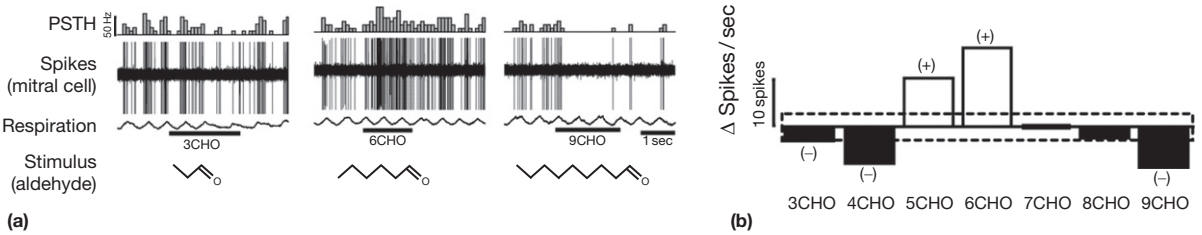

FIGURE 1.5 Molecular receptive field property of mitral cell. (a) *In vivo* recording of mitral cell spiking activity in anesthetized rat exposed to a homologous series of aliphatic aldehydes. Top, peristimulus time histogram (PSTH), which represents the average of five single-trial responses. The bottom traces indicate the respiratory cycle. The black bar marks the period of odor presentation. Note the respiratory-driven spiking activity of mitral cell. (b) Histogram of the change in spike rates (white column = increase; black column = decrease) during odorant-stimulation compared with the spike rate during prestimulation period. Stimulus odorants are propylaldehyde (3CHO), butylaldehyde (4CHO), valeraldehyde (5CHO), hexylaldehyde (6CHO), heptylaldehyde (7CHO), octylaldehyde (8CHO), and nonylaldehyde (9CHO). *Adapted from Nagayama S, Takahashi YK, Yoshihara Y, et al. (2004) Mitral and tufted cells differ with respect to the manner in which odor maps are decoded in the rat olfactory bulb.* Journal of Neurophysiology *91: 2532–2540, with permission.*

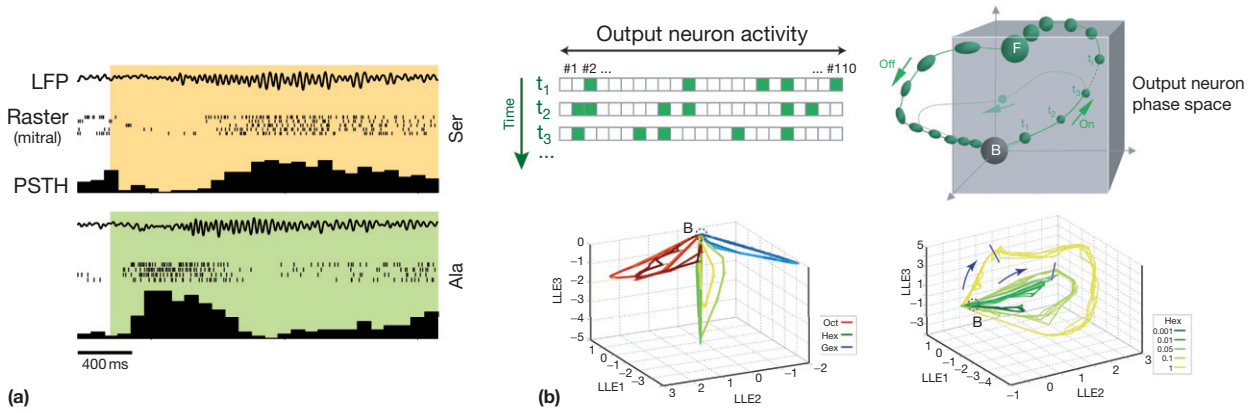

FIGURE 1.6 Temporal pattern and population coding of odor responses. (a) Five single-trial responses of one zebrafish mitral cell to two odor stimuli (Ala, alanine; Ser, serine). LFP, local field potential (bandpass filtered 5–50 Hz); middle, spike raster in which each tick represents the timing of one action potential from the mitral cell; bottom, peristimulus time histogram (PSTH), which represents the average of ten single-trial responses. Color shading indicates odor presentation. Note the odor-specific slow temporal response patterns. (b) The activity of the population of 99 recorded output neurons at a given time is represented as a point in a 110-dimensional space, in which each dimension represents the firing rate of one of the 110 PNs in the corresponding time bin. Each odor representation is thus represented by a multidimensional vector of output neuron states that evolves with time in a stimulus-specific manner and represents odor-evoked trajectories. Then the 110-dimensional data were analyzed with a dimensionality reduction method (namely principal component analysis) and projected in the space of the first three principal components to allow visualization. From an initial resting state (origin of the coordinate system, b), the population vector evolves through an extended trajectory to an odor-specific fixed point (F). When the pulse terminates, the population vector returns from the fixed point back to baseline via a different trajectory. Different odors evoke different trajectories for the population vector. These trajectories are highly reproducible and specific of the odor and of the odor concentration. *Adapted from Friedrich RW and Stopfer M (2001) Recent dynamics in olfactory population coding.* Current Opinion in Neurobiology *11: 468–474; Stopfer M, Jayaraman V, and Laurent G (2003) Intensity versus identity coding in an olfactory system.* Neuron *39: 991–1004; Mazor O and Laurent G (2005) Transient dynamics versus fixed points in odor representations by locust antennal lobe projection neurons.* Neuron *48: 661–673, with permission.*

crucial for establishing this network synchrony (Kay et al., 2009; Laurent, 2002; Lledo and Lagier, 2006). For example, specific modification of $GABA_A$ receptors expressed in the lateral dendrites of mitral cells disrupts the properties of gamma oscillations (Lagier et al., 2007). Such synchrony may play an important role in odor processing, especially for odor discrimination (Stopfer et al., 1997). As proposed in other brain regions, synchronization to a specific frequency would help in "binding together" remotely distributed mitral/tufted cells that participate in the encoding for the same odor, creating synchronized cell assemblies (Laurent, 2002). This synchronization also promotes temporal coincidence of spatially segregated inputs. Interestingly, downstream regions in the olfactory cortex can act as coincidence detectors (Franks and Isaacson, 2006; Franks et al., 2011).

Taking these data into account, it is clear that the interplay between local interneurons and output neurons provides a multidimensional device for the representation of olfactory information. Sparse and distributed connectivity between local interneurons and mitral output neurons may contribute to a global reformatting of odor representations in the form of an odor-specific spatiotemporal redistribution of activity across the olfactory bulb. Within this framework, two high-dimensional encoders involved in information coding within the bulbar network should be distinguished. The first is composed of the olfactory receptor repertoire expressed by the olfactory sensory neurons, which transduces receptor activation patterns into glomerular odor maps throughout a highly reliable synaptic transmission. The secondary encoder lies in the mitral-granule cell network that extracts higher-order features from the odor maps in order to process them into temporal spiking patterns across sparse ensembles of activated output neurons. Thus, spatiotemporal pattern coding of odors provides a large coding space that scales to the millions of discernible odors of our environment.

An important issue concerning odor coding theories relates to how downstream regions can read odor representations built in the olfactory bulb neuronal circuit. One important particularity of the olfactory system is that it is the only sensory pathway through which peripheral olfactory information can propagate towards cortical regions without any relay via the thalamus (Figure 1.1). The axons of bulbar output neurons project directly to different cerebral cortical structures that compose the so-called olfactory cortex (Wilson et al., 2006). The olfactory cortex includes the anterior olfactory cortex (also called the anterior olfactory nucleus), which connects the two olfactory bulbs through a portion of the anterior commissure (Kikuta et al., 2010), the piriform cortex (this region receives the major part of olfactory bulb projection and is considered to be the primary olfactory cortex), the olfactory tubercle, the cortical nucleus of the amygdala, and the entorhinal cortex, which

in turn projects to the hippocampus (Figure 1.1). From the olfactory cortex, olfactory information is ultimately relayed to the thalamus and to the neocortex, notably to the orbitofrontal cortex, the region of cortex thought to be involved in the conscious perception of smell (Gottfried, 2010). The general topographic organization of the olfactory bulb is not conserved in the downstream structures. Mitral cells from the same glomerulus project broadly in the entire piriform cortex without any apparent spatial correlation (Ghosh et al., 2011; Sosulski et al., 2011). Pyramidal cells of the piriform cortex receive convergent inputs from distinct glomeruli (Apicella et al., 2010; Davison and Ehlers, 2011; Miyamichi et al., 2011) and respond to multiple odorants (Poo and Isaacson, 2009; Stettler and Axel, 2009). This high degree of overlap between distributed bulbar projections to higher olfactory centers may constitute the anatomical basis for a combinatorial coding and a crosstalk between information strands emanating from different odorant receptors. This characteristic probably helps to integrate multiple modules of olfactory information into a synthetic representation of a particular scent made of numerous chemical compounds. Alternatively, the synaptic organization of olfactory bulb inputs to the olfactory cortex and the local inhibition within the olfactory cortex that enforces coincidence detection in pyramidal cells suggest that spike-timing-dependent coding of odor representation is an important element of the processing carried out by the olfactory cortex (Poo and Isaacson, 2009; Stokes and Isaacson, 2010).

1.2.4 Centrifugal Fibers from Higher Brain Structures Profusely Innervate the Olfactory Bulb

In addition to sensory inputs from the olfactory epithelium, the olfactory bulb receives a large number of centrifugal inputs from a variety of cortical and noncortical structures (Figure 1.3). Thus, rather than a simple bottom–up odor coding of olfactory signals, the olfactory bulb also deeply integrates top–down information, which modulates the odor representation depending on the internal state or experience of the animal. These direct centrifugal inputs include (1) glutamatergic fibers from olfactory cortex, mainly from the piriform cortex and the anterior olfactory cortex, and (2) modulatory projections from the locus coeruleus (noradrenaline), the horizontal limb of the diagonal band of Broca (acetylcholine and GABA), and the dorsal raphe nucleus (serotonin).

Most of the glutamatergic centrifugal fibers synapse onto granule cell somas, creating a trisynaptic loop between the olfactory cortex and the olfactory bulb. These excitatory inputs tune the excitability of granule cells, modulating the mitral cell–granule cell microcircuit and the associated processes mentioned above, such as synchronization (Mouret et al., 2009; Strowbridge, 2009). For instance, repetitive excitatory inputs can produce a large depolarization in the granule cell soma sufficient to relieve the Mg^{2+} blockade of NMDA receptors at distal dendrodendritic synapses, thereby promoting recurrent and lateral dendrodendritic inhibition in the olfactory bulb (Balu et al., 2007). The presence of these dense centrifugal inputs clearly suggests that olfaction processing does not involve simple feed-forward pathways. Rather, feedback loops involving long-range axonal projections from downstream regions of the olfactory cortex to the olfactory bulb continually reset the network and provide a dynamic processing of odor.

In addition to the massive glutamatergic innervation from the olfactory cortex, the bulb receives diffuse inputs from neuromodulatory regions. It has been difficult to correlate cellular results and behavioral experiments, especially because these neuromodulators exert multiple and sometimes opposite effects on olfactory bulb neurons depending on the receptor and ligand concentration.

Acetylcholine is released in all the layers of the olfactory bulb by cholinergic fibers originating from the horizontal limb of the diagonal band of Broca and exerts multiple effects on the activity of both output neurons and local interneurons via the expression of different nicotinic and muscarinic receptors (Castillo et al., 1999). At the functional level, changes of behavioral state are partly mediated by changes in the level of acetylcholine tone (Tsuno et al., 2008). Disruption of this cholinergic tone affects output cell receptive fields, gamma oscillations, and olfactory discrimination (Chaudhury et al., 2009; Tsuno et al., 2008).

Serotoninergic fibers extend from the dorsal raphe nuclei and densely innervate the glomerular layer. Recently, serotonin has been shown to regulate sensory inputs to the olfactory bulb indirectly by promoting GABA release from periglomerular cells (Petzold et al., 2009). Noradrenergic fibers from the locus coeruleus are present in the deeper layers, in the granule cell layer, and also in the EPL. Noradrenaline exerts multiple effects on both partners of the dendrodendritic synapse, which may result in the modulation of output cell activity (Jahr and Nicoll, 1982; Nai et al., 2009). Both serotonin and noradrenaline levels increase after odor presentation, and both have been involved in odor preference in young animals and odor discrimination in adults (review in Mandairon and Linster, 2009).

Thus, neuromodulatory innervation is thought to promote flexible and context-dependent changes in the information-processing mode of local neuronal circuits. As will be discussed at greater length later in this chapter, neuromodulators play a major role in the plasticity of the olfactory bulb cells and circuits.

1.3 CIRCUIT DEVELOPMENT: A LESSON FROM ADULT NEUROGENESIS

In contrast to other sensory modalities, the olfactory system exhibits lifelong turnover of both peripheral sensory neurons and central interneurons of the olfactory bulb. In these two places, the addition of new neurons represents another means, in addition to molecular, synaptic or morphological alterations within individual cells, by which circuits can change their own functional organization. This cell-level renovation is neither static nor merely restorative. The process of neuron production during adulthood (called hereafter adult neurogenesis) constitutes an adaptive response to challenges imposed by an animal's environment and/or by its internal state (hormones, stress). Adult neurogenesis in the sensory organ and in the olfactory bulb also raises a number of important questions concerning the role of neurogenesis in olfaction.

1.3.1 Neurogenesis of Sensory Neurons in the Adult Olfactory Epithelium

Facing continuous environmental assaults due to their relatively unprotected position in the nasal cavity, olfactory sensory neurons of the olfactory epithelium are continuously renewed throughout adult life. This site of neurogenesis is made possible by the presence of multipotent progenitors found deep in the olfactory epithelium, near the basal lamina that separates the epithelium from the underlying lamina propria. This progenitor population is mainly composed of globose basal cells and, to a lesser extent, horizontal basal cells. Globose basal cells include transient amplifying precursors and immediate neuronal precursors that express specific markers such as Mash1 and neurogenin-1 and give rise to all the different cell types of the epithelium, including sensory neurons (Cau et al., 1997). During their journey towards the bulb, sensory neuron axons are enveloped by a class of glial cells called ensheathing glial cells, which may act as an extrinsic orientation cue (Sakano, 2010). The progressive generation of mature neurons is relatively rapid and takes only 8–10 days after lesion or toxin exposure. The turnover of sensory neurons, and by extension, the rate of neurogenesis in the olfactory epithelium, is normally regulated by environmental factors. Indeed, the mitotic rates of sensory neurons can be bidirectionally regulated: Naris occlusion reduces sensory neuron turnover and progenitor division, whereas naris reopening, chemical lesions of the epithelium, or olfactory bulb ablation stimulates progenitor activity, restoring the sensory neuron population (review in Schwob, 2002). It is noteworthy that 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 homeostasis. Thus, neurogenesis of sensory neurons depends on a proper balance of positive regulatory factors that stimulate proliferation and differentiation and negative regulatory molecules produced by mature sensory neurons to inhibit additional neuron production. There has been considerable interest in growth factors that control neurogenesis, differentiation, and apoptosis, such as transforming growth factor, fibroblast growth factor, and bone morphogenetic protein (Schwob, 2002). This adult neurogenesis in a peripheral organ, coupled with the fact that there are a limited number of cell classes in the olfactory epithelium, makes this area attractive for studying mechanisms that control the rate of formation of neurons and their death throughout adulthood.

What could be the functional meaning of this never-ending rejuvenation of the sensory organ? Mature sensory neurons that have been damaged by exposure or by pathogens and immature sensory neurons that cannot find adequate synaptic targets in the olfactory bulb are two obvious candidates to support the existence of this peripheral neurogenesis. 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 remain constant to a certain degree. Axon guiding through preexisting axons and guidance cues present in the olfactory bulb allow for correct targeting to the olfactory bulb (Sakano, 2010; Zou et al., 2009). Moreover, apoptotic cell death has been observed in cells throughout all stages of regeneration, implying apoptotic regulation of neuron numbers and targeting at all levels of the neuronal lineage. It remains to be determined whether the newly generated sensory neurons indeed bring unique features (such as high probability of glutamate release, lack of adaptation, etc.) to the targeted olfactory bulb circuits.

1.3.2 Adult-Born Interneurons in the Olfactory Bulb

The second adult region where ongoing neuronal addition/replacement takes place is the olfactory bulb (Figure 1.7). In this case, the ongoing neuronal production of olfactory bulb neurons occurs mainly in the SVZ under normal conditions. There, astrocytes in the adult SVZ, which line the border between the striatum and the lateral ventricle, act as slow-dividing adult primary neural stem cells, capable of generating a progeny of neuroblast precursors. Stem cell astrocytes (also called type-B cells) divide and generate rapidly dividing type-C transit-amplifying cells that in turn give rise to type-A migrating neuroblasts (reviewed in Doetsch, 2003; Figure 1.7). Once generated, these neuroblasts proceed

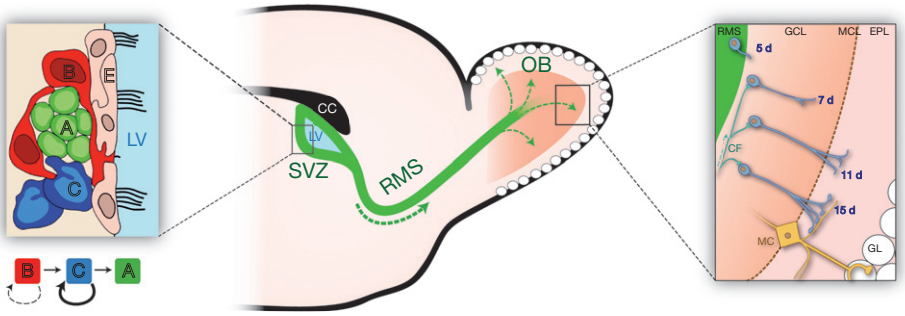

FIGURE 1.7 The subventricular zone – olfactory bulb neurogenic pathway in the adult rodent. The center panel is a schematic diagram of a sagittal section of the rodent forebrain. The subventricular zone (SVZ) lies in the walls of the lateral ventricle (LV), below the corpus calosum (CC). After their generation in the SVZ, neuroblasts migrate tangentially along the RMS to their final destination in the olfactory bulb (OB). Left panel shows the neurogenic niche. Separated from the lateral ventricle by a monolayer of ependymal cells (E), slow-dividing astrocytic stem cells (red, type-B cells) divide to generate transit-amplifying cells (blue, type-C cells), which in turn give rise to neuroblasts (in green, type-A cells) that start to migrate in chain to the rostral migratory stream (RMS). Right panel illustrates the sequence of morphological maturation, from the migrating neuroblast in the RMS (5 days after birth) to their final differentiation into interneurons (mainly granule cells, here represented in blue) and their integration into the network. Adult-born granule cells first receive somatic glutamatergic inputs from centrifugal fibers (CF) before establishing dendrodendritic synapse with mitral cells (MC).

towards the olfactory bulb along an intricate path of migration, up to 5 mm long in rodents, called the RMS (Lois and Alvarez-Buylla, 1994). Along the RMS, another population of astrocytes forms a glial tunnel that guides the chain migration of neuroblasts from the SVZ to the olfactory bulb. More than 30 000 neuroblasts exit the rodent SVZ for the RMS each day and reach the center of the olfactory bulb within 6 days (Doetsch, 2003). In the olfactory bulb, neuroblasts detach from these chains and migrate radially from the RMS. Finally, after 1–3 weeks, neuroblasts mature into olfactory inhibitory interneurons of two main types, granule cells (90% of the adult-born cells) and juxtaglomerular cells (5% of the adult-born cells), found in their respective olfactory bulb layers (Lledo et al., 2008; Petreanu and Alvarez-Buylla, 2002. Interneuron identity is specified at birth and is not specified within the olfactory bulb. Progenitors within the various domains of the SVZ are heterogeneous and are preprogrammed at birth to generate different subsets of olfactory bulb interneurons (Lledo et al., 2008; Merkle et al., 2007).

Using replication-incompetent viral vectors to transduce newly generated neurons in the SVZ and label them with GFP, the morphological and functional properties of these newborn bulbar neurons during their migration and differentiation have been characterized (Lledo et al., 2006). Morphologically, newly generated cells become more complex within the first week after their birth and they become fully mature morphologically as early as 4 weeks of age (Petreanu and Alvarez-Buylla, 2002; Whitman and Greer, 2007; Figure 1.7). After starting migration, neuroblasts express functional GABA and glutamate receptors (Platel et al., 2007). Upon reaching the olfactory bulb, they receive GABAergic and glutamatergic synaptic contacts, notably from centrifugal fibers (Figure 1.7). Then, as they progressively become excitable, they become spiking neurons and start to release GABA onto output cell dendrites (Bardy et al., 2010; Belluzzi et al., 2003; Carleton et al., 2003). Thus, the formation of synaptic contacts before their activation and GABA release would prevent any network perturbations due to aberrant contacts. Interestingly, of the neurons that successfully mature, only 50% survive to the first month (Petreanu and Alvarez-Buylla, 2002). Therefore, new neurons are intensively selected early in their life.

Although the ongoing bulbar neurogenesis has been extensively documented at the cellular level, the functional consequences are not yet clear. Ablation of adult neurogenesis using genetic, pharmacological, or radiation methods results in faint olfactory phenotype alterations, notably in short-term and long-term olfactory memory (reviewed in Lazarini and Lledo, 2010); however, all previous behavioral analysis has indicated that adult-born neurons might be recruited in short-term or long-term odor memory, two phenomena that may involve neural plasticity (see Section 1.4.2).

1.4 STRUCTURAL AND EXPERIENCE-INDUCED PLASTICITY IN THE OLFACTORY BULB

1.4.1 Activity-Dependent Plasticity in the Olfactory Bulb: Cell Properties and Transmitters

The mammalian olfactory system is known for undergoing experience-dependent plasticity. In the olfactory bulb, granule cells are the major sites of synaptic plasticity. In contrast to many axodendritic synapses described in the brain, the major synaptic interaction in the olfactory bulb, the dendrodendritic transmission between output

neurons and granule cells, does not exhibit a strong activity-dependent form of synaptic plasticity, but rather seems to be functionally hard-wired (although a form of short-term plasticity has been described, see Dietz and Murthy, 2005). On the contrary, plasticity at the dendrodendritic synapse is under the control of neuromodulatory inputs originating from brain regions known to be involved in attention and learning processes. As mentioned above, neuromodulators such as acetylcholine and noradrenaline are known to modulate the synaptic properties of the dendrodendritic synapse (Tsuno et al., 2008). From a general point of view, neuromodulators can have important and long-lasting effects on odor discrimination, learning, and memory, providing the olfactory system with a high degree of plasticity. The neuromodulators act at two distinct, yet complementary functional levels: cell excitability and synaptic activity. By acting on both inhibitory local interneurons and mitral/tufted output neurons (reviewed in Mandairon and Linster, 2009), they have profound effects on both odor processing at the first central relay and odor representation.

In addition to neuromodulatory top–down projections, feedback projections from the olfactory cortex to granule cells are the major source of synaptic plasticity in the olfactory bulb (Gao and Strowbridge, 2009; Nissant et al., 2009; Stripling and Patneau, 1999). In addition to different forms of short-term plasticity, tetanic stimulation of centrifugal excitatory inputs onto granule cells produces a long-term potentiation (LTP) of synaptic strength. Moreover, the same tetanic stimulation that triggers LTP in granule cells also produces a long-lasting enhancement of inhibition onto mitral cells (Gao and Strowbridge, 2009). This form of plasticity is thought to play a role in the long-term modification of the mitral–granule cell network and may shape the spatial and temporal firing patterns of output cell activity. Indeed, the activity of individual output cells can change dramatically depending on the odor context or during learning (Doucette and Restrepo, 2008; Fletcher and Wilson, 2003; Kay and Laurent, 1999; Pager, 1983).

The most thoroughly documented region of the olfactory system exhibiting synaptic plasticity is the olfactory cortex (Wilson et al., 2006). Synaptic contact between the olfactory bulb and the olfactory cortex occurs within the piriform cortex and through recurrent associative connections (Best and Wilson, 2004), as well as from distant and higher order areas, such as the orbitofrontal cortex (Cohen et al., 2008). In the piriform cortex, the massive recurrent connections as well as inputs from distant and high-order areas, such as the orbitofrontal cortex, provide the anatomical structure of an associative network (Best and Wilson, 2004; Cohen et al., 2008; Wilson and Sullivan, 2011).

Lastly, thanks to the accessibility of the olfactory epithelium, responses to naris closure or destruction of olfactory epithelium have highlighted how general decreases in sensory inputs can induce long-term activity-dependent structural plasticity in a sensory network. These experiments reveal how sensory deafferentation mainly affects interneuron populations, interneuron number and phenotype (notably dopamine expression) in particular, as well as the reorganization of the dendritic arbor and synapse density (Leo et al., 2000; Saghatelyan et al., 2005).

1.4.2 Adult-Born Neurons Are Substrates for Experience-Induced Plasticity

The continuous arrival of new interneurons provides another major source of plasticity in the bulbar network. In addition to bringing new building blocks and new connections into the network, adult-generated neurons have unique functional properties compared to neurons generated during early life. These attributes increase their functional impact in the network relative to more mature neurons. By using viral labeling approaches to distinguish adult-born granule cells from preexisting ones, LTP of glutamatergic synapses was found specifically in adult-born cells shortly after their arrival in the olfactory bulb, but this property progressively faded after several weeks (Nissant et al., 2009). Thus, adult-born granule cells may be particularly sensitive to synaptic plasticity but may also potentiate the LTP of cortical glutamatergic inputs to the olfactory bulb. LTP of cortical inputs – specifically to adult-born granule cells – provides an intriguing mechanism to regulate the spatial and temporal firing patterns of output neurons. A role for this synaptic plasticity in olfactory learning remains to be found. Interestingly, olfactory activity influences the maturation and the survival of newborn neurons. Anosmic mice exhibit a strong decrease in the survival of newly formed granule cells (Petreanu and Alvarez-Buylla, 2002), whereas enrichment of the olfactory environment potentiates the survival and accelerates the formation of glutamatergic synapses onto newborn cells (Kelsch et al., 2009; Mouret et al., 2008; Rochefort et al., 2002). Postprandial sleep has been recently shown to promote newborn cell death, possibly though the action of top–down inputs from the olfactory cortex (Yokoyama et al., 2011). Together, these results suggest that postnatal neurogenesis in the olfactory bulb is part of a plasticity mechanism coupled to sensory experience. Moreover, the link between the rate of neuronal survival and olfactory activity suggests that it constitutes a way for the system to adapt to the olfactory environment.

It takes about 2–3 weeks for an adult-generated neuron to become part of the existing olfactory bulb circuit

(Lledo et al., 2006). In this network, the presence of young evolving neurons brings special functions that the preexisting bulbar neurons cannot achieve. Since it takes time for new neurons to mature and become synaptically integrated, adult neurogenesis may contribute to slow, long-term adjustments of the olfactory bulb circuitry, rather than to fast and acute plastic changes. In contrast, the action of centrifugal fibers into the bulb may mediate the faster adaptive changes that adult neurogenesis cannot support. Interestingly, adult-born survival is also controlled by the concerted action of neuromodulators and feedback excitatory projections (Mouret et al., 2009). Therefore, the structural plasticity achieved through adult neurogenesis can be seen as a very long-term form of metaplasticity in the olfactory bulb network: Synaptic plasticity at centrifugal inputs facilitates further integration of long-lasting plastic elements provided by adult neurogenesis.

1.5 CONCLUDING REMARKS

Studies of architectural and functional organization of bulbar circuits have both revealed a wide range of distinct neuronal functioning. This diversity reflects the complex task that neuronal networks have to fulfill in order to process a high-dimensional sensory space. Obviously, information is encoded across neuron assemblies in the olfactory bulb that cannot be extracted by simply averaging the firing frequency. GABAergic inhibition is crucial for olfactory coding, but the functional architecture of dendrodendritic inhibitory microcircuits differ from conventional networks described in other sensory systems. In addition, odor representation is dynamic and highly complex, therefore requiring a unique mechanism of neuronal plasticity. Adult neurogenesis and the actions of centrifugal projections to the olfactory bulb are among the most prominent processes that allow for adaptive mechanisms of plasticity.

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