The Olfactory System as a Puzzle: Playing With Its Pieces

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Abstract

The mammalian olfactory bulb (OB) has all the features of a whole mammalian brain but in a more reduced space: neuronal lamination, sensory inputs, afferences, or efferences to other centers of the central nervous system, or a contribution of new neural elements. Therefore, it is widely considered as "a brain inside the brain." Although this rostral region has the same origin and general layering as the other cerebral cortices, some distinctive features make it very profitable in experimentation in neurobiology: the sensory inputs are driven directly on its surface, the main output can be accessed anatomically, and new elements appear in it throughout adult life. These three morphological characteristics have been manipulated to analyze further the response of the whole OB. The present review offers a general outlook into the consequences of such experimentation in the anatomy, connectivity and neurochemistry of the OB after (a) sensory deprivation, mainly by naris occlusion; (b) olfactory deinnervation by means of olfactory epithelium damage, olfactory nerve interruption, or even olfactory tract disruption; (c) the removal of the principal neurons of the OB; and (d) management of the arrival of newborn interneurons from the rostral migratory stream. These experiments were performed using surgical or chemical methods, but also by means of the analysis of genetic models, some of whose olfactory components are missing, colorless or mismatching within the wild-type scenario of odor processing. Anat Rec, 296:1383-1400, 2013. © 2013 Wiley Periodicals, Inc.

Key words: olfaction; olfactory bulb; neuronal lamination; nervous system

Abbreviations used: AON = accessory olfactory nucleus; BDNF = brain-derived neurotrophic factor; EGF = epidermal growth factor; FGF = fibroblast growth factor; LOT = lateral olfactory tract; MC = mitral cells; NCAM = neural cell adhesion molecule; OB = olfactory bulb; OMP = olfactory marker protein; ORN = olfactory receptor neuron; PCD = Purkinje cell degeneration; PSA-NCAM = polysialylated form of NCAM; RMS = rostral migratory stream; SVZ = subventricular zone; TGF = transforming growth factor.

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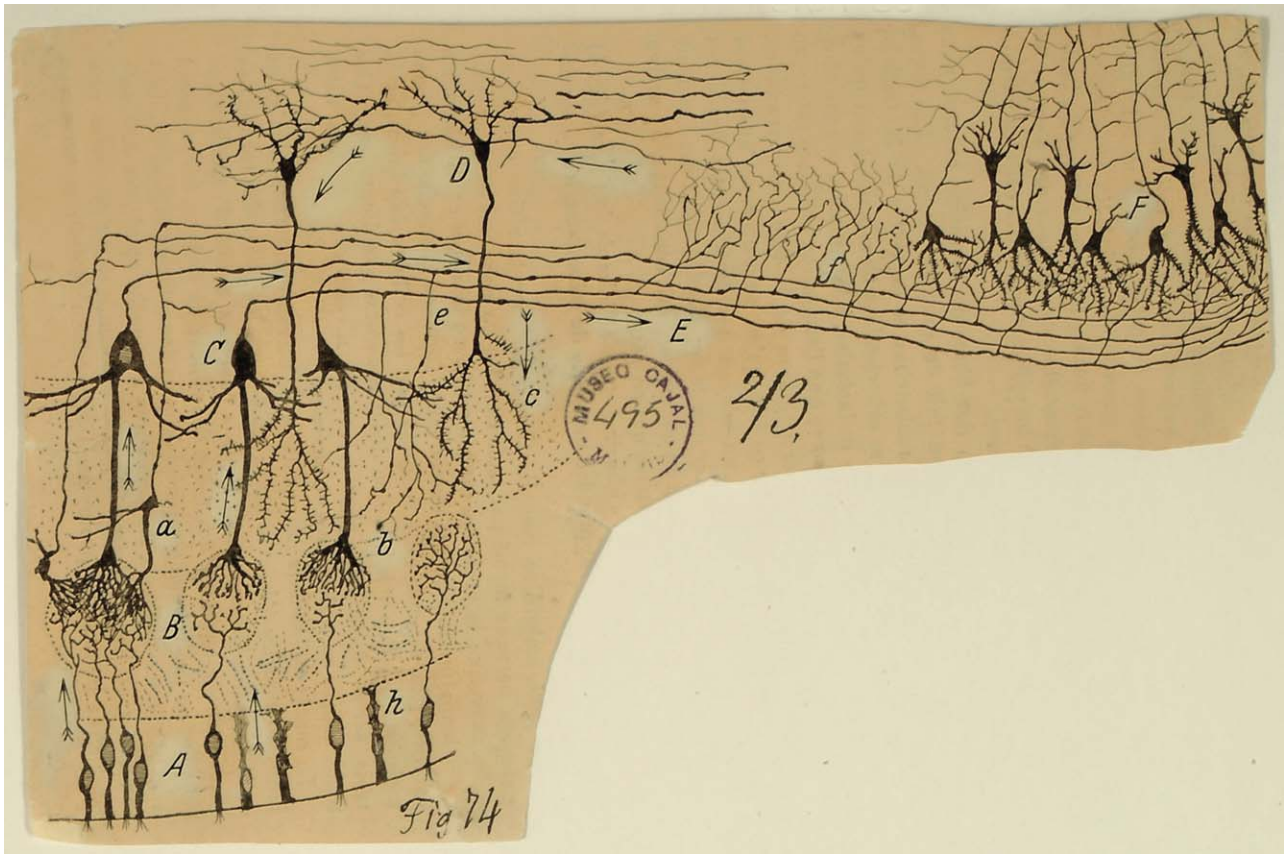

Fig. 1. Ramón y Cajal's drawing published in 1894. **A**: bipolar cells of the olfactory mucosa. **B**: olfactory glomeruli. **C**: MCs. **D**: granular cells. **E**: external root (lateral olfactory tract). **F**: sphenoidal cortex. (**a**) small tufted cell; (**b**) main dendrite of a MC; (**c**) terminal branching of a granular cell; (**e**), recurrent collateral of a MC; (**g**) superficial triangular cells of the cortex; (**h**) epithelial cells of the nasal mucosa. From the Cajal Legacy, Instituto Cajal, CSIC, Madrid, Spain.

The nervous system is able to make functional, biochemical and structural changes aimed at reducing the effects of normal or pathological alterations that can occur at any moment during life (Zilles, 1992). Thus, brain plasticity can be considered as the capacity for developing a new structural and functional reorganization of the central nervous system to adapt its organization to new situations. The input of sensory information plays an important role in the formation and in the reorganization of the brain. Once their finite dynamic range has been assumed, there is enough plasticity in sensory systems to adjust continuously their output in order to maximize useful information between the environment and the brain (Stemmler and Koch, 1999). In addition, by experimentally modifying the quantity or type of sensory experience, a deep impact on target structures and on the general function of the brain can emerge (Cummings and Brunjes, 1997), thus forcing adaptation and reorganization of the neural sensory elements. In fact, sensory deprivation is one of the first -and preferred- approaches to the study of brain plasticity and development (Gómez-Pinilla et al., 1989; Coppola, 2012). The mammalian olfactory pathway has an intrinsic, natural plasticity: the olfactory bulb (OB) receives a continuous replacement of olfactory axons from the olfactory epithelium, together with a continuous contribution of newly generated neurons coming from the subventricular zone (SVZ). In addition, the olfactory system not only governs this basic chemoreception, which is a primary sense in mammals; its role has also been extended recently to more common cues, such as learning and memory (Yamamoto, 1991; Wiedenmayer et al., 2000; Deng et al., 2010).

THE PUZZLE

The structure of the main olfactory system is composed of well-differentiated parts, which when put together conform a balanced landscape: the main forwards path begins in the olfactory epithelium with the olfactory receptor neurons (ORN), which synapse onto the main projecting neurons within the glomeruli of the OB: mitral cells (MC) and tufted cells (medium and internal). The information from both mitral and tufted cells emerges from the OB to higher cortices without stopping in the thalamus, which is unusual among the sensory systems. This direction of olfactory communication has been known since the earliest studies of Cajal, even though the father of neuroscience himself was somehow wrong (Fig. 1; see the interesting review of López-Mascaraque, 2006). Physiological and molecular

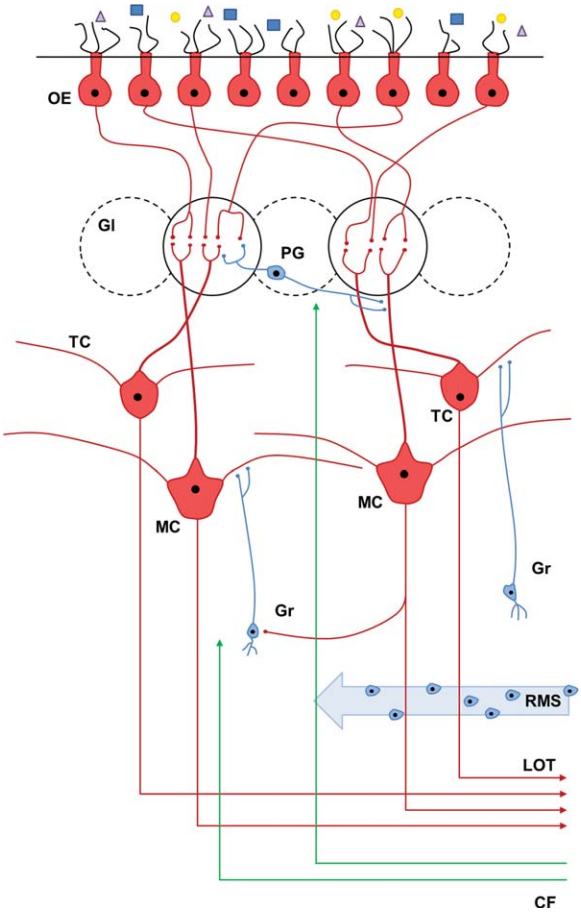

Fig. 2. Schematic view of an intact OB. CF, centrifugal fiber; Gl, glomerulus; Gr, granular cell; LOT, lateral olfactory tract; MC, mitral cell; OE, olfactory epithelium; PG, periglomerular cell; RMS, rostral migratory stream; TC, tufted cell.

studies have strengthened this scheme (i.e., Mori et al., 1999): the pieces of the olfactory puzzle are the same for any odor information, but they are placed in parallel, depicting a similar architecture for each scent.

This puzzle is made up by more pieces: those that provide backwards information from higher brain centers, the centrifugal fibers, as well as groups of interneurons, mainly the inner ones (granule cells) and the outer ones (juxtaglomerular cells; for a review of the complexity of these elements, see (Gutièrrez-Mecinas et al., 2005; Kosaka and Kosaka, 2005; Baltanás et al., 2007, 2011. By simplifying the scenario, both groups of interneurons refine the information flowing through the projecting cells by keeping the glomeruli/MC columns "secluded" from the neighboring ones, similar to standard bearers defending their lords (Fig. 2). Thus, there are two main ways to refine specific odor information: lateral inhibition of the interneurons around the olfactory units (glomeruli/MC) and feedback information carried by centrifugal fibers.

The olfactory map may change if some of the pieces are lost, multiplying some of them, or regulating the input forwards or backwards. However, not all the elements in this system can be changed easily. It is possible to divide the experimental paradigms into two main groups: functional models, in which the circuit is intact but odorant information is weakened and those in which some of the pieces are lacking, due to surgical or genetic depletion of certain neurons.

We now analyze the most important models used to study neural plasticity in the olfactory system: (i) sensory deprivation, where the cellular elements exist but the odorants themselves cannot reach the source of the information stream; (ii) olfactory deinnervation, whereby different relay stations lose their communication due to damage to the connecting tracts; (iii) removal of projecting neurons, which currently can only be achieved by using specific genetic models, and (iv) variations in the cell turnover of the interneuron system, which are more complex to deal with.

THE SENSORY DELETION PARADIGM

The essential role of sensory experience in the development and maintenance of nervous systems has been firmly established by many studies performed in recent decades, in which sensory activity has been eliminated or reduced experimentally. Analysis of the changes in the experimental condition in comparison to the normal one has provided valuable information about the structure, development and reorganizational capacity of sensory systems (Brunjes, 1994).

Different methods can be used to manipulate specific sensory information. These methods can be divided into two large groups. The first is deprivation methods, which cause a drastic reduction in the quantity or quality of the information that reaches the sensory system, but preserve the structure. Deprivation can be physical (dark-rearing for the visual system, ear-plugs for hearing), pharmacological (modifying the ability of transmission and/or discrimination of the circuitry, i.e., treatment of a nerve with tetrodotoxin), or surgical (suturing of the eyelids or the naris; Fig. 3A). The other group of procedures involves deafferentation methods, in which the sensory pathway is physically interrupted (partially or completely) by means of lesions: that is, the removal or elimination of an element of the sensory circuitry. Different paradigms have been developed: elimination of the ORNs (treatment of the olfactory mucosa with detergents or other toxic agents; Fig. 3B; McBride et al., 2003); sectioning of the olfactory nerve (Anders and Johnson, 1990; Suzuki and Takeda, 1991); sectioning of the lateral olfactory tract (Fig. 3C; Weiler and Farbman, 1999), or—the most aggressive procedure—elimination of a relay station, such as the OB (surgical bulbectomy; Fig. 3D; Kelly et al., 1997).

OLFACTORY DEPRIVATION: THE PIECES OF THE EDGES ARE FADED

Most animals have bilateral access to odorants through olfactory sensory epithelia. Olfactory deprivation consists of unilaterally or bilaterally preventing the interaction of the odorants with their molecular receptors located on the ORNs. In this model, the olfactory system cannot be stimulated by peripheral olfactory inputs, but the nervous pathway is physically unharmed (Baker et al., 1993; Brunjes, 1994; Briñón et al., 2001).

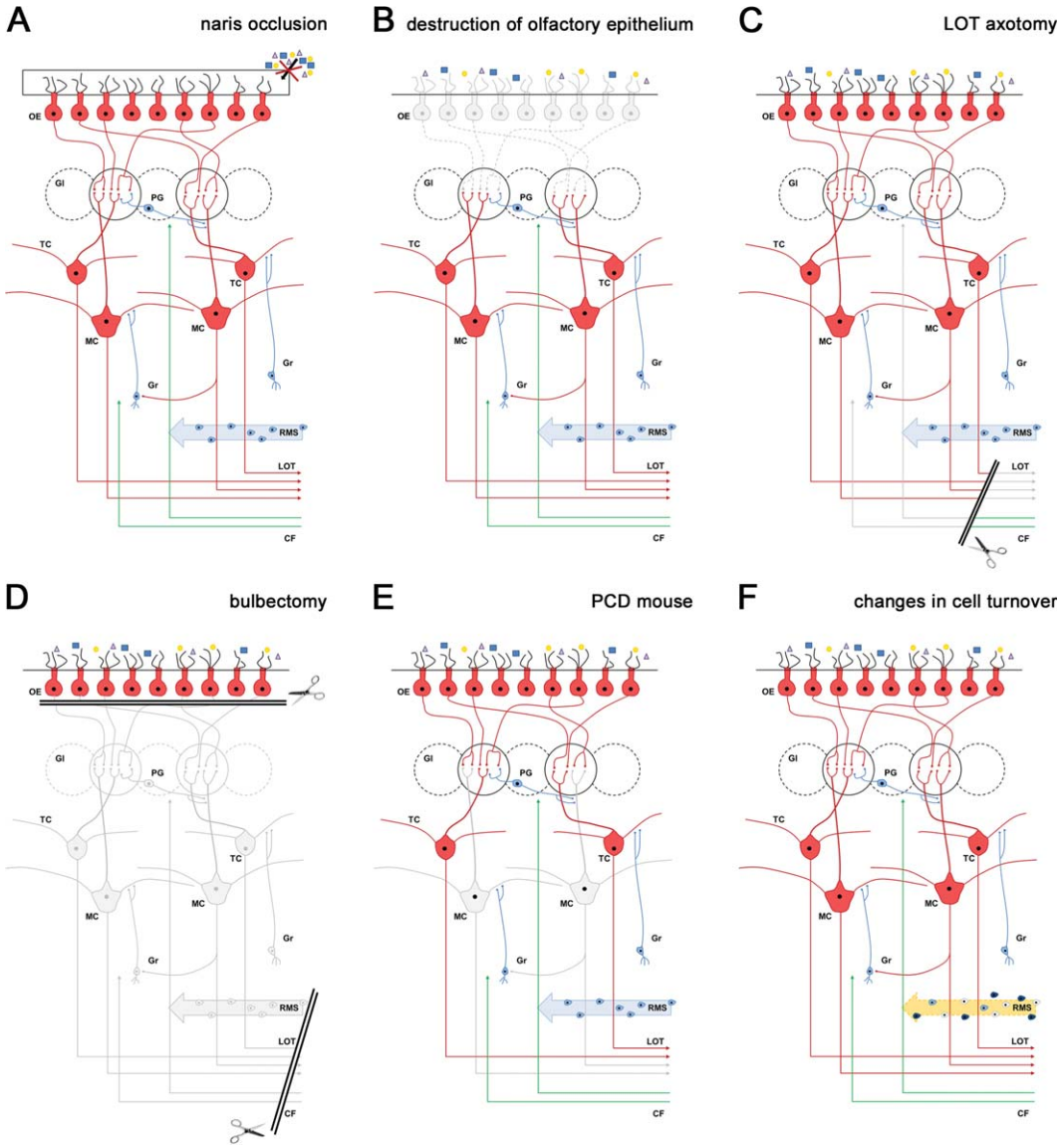

Fig. 3. Schematic view of the main modifications of the OB anatomy/circuitry employed for the study of neural plasticity. **A:** naris occlusion; odorants cannot reach the olfactory epithelium, but the OB structure remains intact. **B**: destruction of the olfactory epithelium; the ORNs are removed, losing the olfactory afferences to the glomeruli. **C**: Lateral Olfactory Tract axotomy; both afferences to and efferences from the OB are interrupted. **D**: bulbectomy; removal of the whole OB. **E**: PCD mutant mouse; degeneration of MCs (one type of the projecting neurons). **F**: modifications of cell turnover; different factors are capable of changing the proliferation, migration, or differentiation rates of neuroblasts that arrive to the olfactory bulb. CF, centrifugal fibers; Gl, glomerulus; Gr, granular cell; LOT, lateral olfactory tract; MC, mitral cell; OE, olfactory epithelium; PG, periglomerular cell; RMS, rostral migratory stream; TC, tufted cell.

While molecular biology has provided novel ways to interrupt the olfactory processes at different points (see below), most of our current knowledge concerning the effects of stimulus deprivation stems from the use of the unilateral olfactory deprivation technique (Fig. 3A; Meisami, 1976; Brunjes, 1994; Coppola et al., 2006). This technique has formed the mainstay of olfactory neuroplasticity studies and remains in active use (Coppola, 2012). Unilateral naris occlusion can be performed by introducing polyethylene tubes into the naris (Cummings and Brunjes, 1997; Cummings et al., 1997) or by a surgical procedure, consisting in a brief cauterization of the external naris of the animals (Brown and Brunjes, 1990; Brunjes, 1994). The evidence shows that a lack of olfactory inputs causes several alterations in the olfactory system, including a generalized decrease in neuronal activity (Pedersen et al., 1987). These initial changes are followed by later modifications, especially evident in the OB but also present in several structures distributed along the olfactory sensory pathway.

Olfactory Epithelium

The olfactory epithelium of vertebrates is one of the regions with the highest rates of neurogenesis, a balance existing between cell death and proliferation in the ORN

population (Graziadei and Monti-Graziadei, 1985; Crews and Hunter, 1994). Sensory deprivation causes a 40% reduction in neurogenesis in the ipsilateral olfactory mucosa (Farbman et al., 1988; Brunjes, 1994; Mirich and Brunjes, 2001). This is translated to a reduction in the number of ORNs (Stahl et al., 1990), which leads to a considerable reduction in the thickness of the olfactory epithelium ipsilateral to the deprivation side (Farbman et al., 1988; Cummings and Brunjes, 1994; Mirich and Brunjes, 2001).

When only one naris is occluded (as in most of the studies published), both the ipsi- and contralateral structures respond differently. Thus, while the olfactory marker protein (OMP) content is reduced in the ORNs of the nonoccluded side (contralateral to deprivation), an increase in OMP expression is detected in the ORNs on the occluded side of the nasal cavity (ipsilateral to deprivation). This suggests that the OMP concentration is up- or down-regulated, depending on the amount of odor stimulation that the ORNs receive (Waguespack et al., 2005). This apparent change in protein concentrations may be part of a more general compensatory response of the olfactory neurons to odor levels in the environment. Recently, He et al. (2012), using patch-clamp recordings of genetically tagged ORNs with defined olfactory receptors, addressed how early experience shapes the functional properties of an individual ORN. They found that sensory deprivation increased the sensitivity of particular ORNs (those expressing MOR23) in the ipsilateral epithelium, whereas in the open one over-stimulation caused the opposite effect due to increased airflow and odorant influx. Recent experiments have examined the transcriptomes of the olfactory epithelia from both the occluded and the nonoccluded sides of deprived animals and from control, non-deprived mice. Comparison of these three data sets revealed that the key genes involved in olfactory reception, transduction, and transmission were up-regulated in the deprived-side mucosa, with opposite effects in the nondeprived-side mucosa, as compared with controls (Coppola and Waggener, 2012). Taking these data together, it is plausible to suggest that ORNs have evolved by maintaining a sufficient degree of plasticity to continuously adjust their responses to maximize the useful information that can be derived from the odor environment (Stemmler and Koch, 1999; Coppola, 2012).

Olfactory Bulb

Size modification. The most dramatic change after neonatal olfactory deprivation is observed in the ipsilateral OB, which fails to reach its normal adult size (Meisami, 1976; Benson et al., 1984; Cummings et al., 1997). Thirty days after neonatal closure of the naris, the volume of the ipsilateral OB undergoes a reduction of 25% in comparison with control animals (Brunjes, 1994). In part, this decrease is due to a reduction in the volumes of the external plexiform and glomerular layers (Frazier and Brunjes, 1988), but the most dramatic decline after unilateral deprivation is observed in the granule cell layer of the ipsilateral OB (Frazier and Brunjes, 1988). This shrinkage is essentially due to apoptotic cell death, mainly in the granule cell layer (Fiske and Brunjes, 2001; Najbauer et al., 2002; Petreanu and Álvarez-Buylla, 2002; Mandairon et al., 2003; Lemasson et al., 2005). A singular feature of the olfactory system is its continuous supply of new interneurons (mainly granule cells and juxtaglomerular cells) to the OB from the rostral migratory stream (RMS). A large body of recent studies has established that some of these adult newborn neurons survive and become functionally integrated in an activity-dependent manner (Lledo and Saghatelyan, 2005; Lazarini and Lledo, 2011). This integration is dependent on the olfactory environment and thus unilateral olfactory deprivation affects this continuous neurogenic process. In fact, 45 days of odor deprivation decreases the survival of adult-born neurons in the bulb, the complexity of their dendritic arborization and their spine density (Saghatelyan et al., 2005).

Interestingly, olfactory enrichment and olfactory learning cause the opposite effect, eliciting an increase in newborn cell survival (Rochefort et al., 2002; Lledo and Saghatelyan, 2005; Mandairon et al., 2006; Lazarini and Lledo, 2011). In addition to cell death, olfactory deprivation also yields an accumulation of cells in the RMS just before they reach the OB (Saghatelyan et al., 2004) that can also be responsible for the lower number of cells observed within the OB ipsilateral to the deprivation side. Contrary to migration and survival processes, the proliferation rate does not seem to be affected by olfactory sensory experience (Yamaguchi and Mori, 2005). In humans, OB size also correlates with olfactory function (Yousem et al., 1999; Buschhuter et al., 2008; Veyseller et al., 2012). Furthermore, the OB seems to be plastic throughout our life spans: patients with the most severe chronic rhino-sinusitis tend to have the smallest OB volumes and poorer olfactory performance (Rombaux et al., 2008). These findings suggest that the levels of peripheral input in humans may affect cell survival in the OB and other olfactory processes as they do in rodents (Coppola, 2012).

Neurochemical changes. Odor deprivation in animals induces specific neurochemical plasticity. The best-known example is the down-regulation of dopamine synthesis in the juxtaglomerular neurons of the ipsilateral OB (Brunjes et al., 1985; Stone et al., 1990; Brunjes, 1994; Cho et al., 1996). This decrease in dopamine content is so evident and consistent that tyrosine hydroxylase expression (the rate-limiting enzyme of dopamine synthesis) is currently used as an indicator of the integrity of olfactory sensory input to the OB (Baker and Greer, 1990; Briñón et al., 2001; Gómez et al., 2007a,b). Neurotrophic factors, neuromodulators and their receptors in the bulb are also affected by unilateral olfactory deprivation. The levels of the neurotrophin brain-derived neurotrophic factor (BDNF) are initially increased and thereafter decrease in the ipsilateral OB (McLean et al., 2001).However, nerve growth factor receptors are increased in the glomerular layer of deprived OBs (Gómez-Pinilla et al., 1989). In addition, a decrease occurs in some early expression genes. The expression of c-Fos (Jin et al., 1996; Liu et al., 1999), Fos-B (Liu et al., 1999) and the activity of the kinase ERK are down-regulated after olfactory deprivation (Mirich et al., 2004). Neonatal naris occlusion reduces the number of neuronal cell bodies immunoreactive for GluR1 in the external plexiform layer of the adult mouse OB (Hamilton and Coppola, 2003). Moreover, the expressions of several calcium-binding proteins, such as calbindin D-28k and

parvalbumin are also reduced after naris closure (Philpot et al., 1997a,b), whereas neurogranin (a calmodulin-binding protein) increases after early, but not adult, olfactory deprivation (Gribaudo et al., 2012). All these data highlight the involvement of all the OB layers and neurochemical systems after poor olfactory stimulation.

Electrophysiological adaptation. In addition to neuroanatomical and neurochemical modifications, olfactory deprivation decreases both electrophysiological and metabolic neural activity (Wilson and Wood, 1992; Philpot et al., 1997a,b), also restraining protein synthesis (Philpot et al., 1997a,b; Korol and Brunjes, 1990). Electrophysiological studies have shown that both spontaneous and odor-induced electrical activities are decreased in the MC and tufted cells of the OB ipsilateral to the deprivation side (Wilson and Wood, 1992; Philpot et al., 1997a,b). In adult rats, in the ipsilateral bulb both short-term (1–2 months) and long-term (12 months) unilateral olfactory deprivation increases the proportion of mitral/tufted cells that respond to multiple odorants. This suggests decreased stimulus discrimination as a response to decreased stimulus input (Wilson and Sullivan, 1995). A more recent study has shown that early unilateral olfactory deprivation increases OB sensitivity to odorants and reduces the temporal synchrony between unitary activities to the gamma band (Aylwin et al., 2009). Not only neurons but also astroglial cells show plasticity under unilateral olfactory deprivation conditions. Recently, it has been demonstrated that the functional status of both neuronal as well as astroglial gap junctions in the glomerular layer is controlled by sensory inputs (Roux et al., 2011).

All these data indicate that the bulbar elements are severely affected by deprivation and that they undergo considerable changes during postnatal life, depending on the prevailing olfactory environmental conditions (Brunjes, 1994). However, local circuits do not only mediate the modulation and processing of olfactory information that occur in the bulb; the centrifugal systems innervating the OB are also crucial elements in these events (Moriizumi et al., 1994). The serotonergic, noradrenergic, and cholinergic pathways are centrifugal systems fully extrinsic to the main OB. Our laboratory has investigated the possible alterations of these centrifugal systems under olfactory deprivation conditions and we have observed that the centrifugal pathways also have a high degree of plastic adaptation (Briñón et al., 2001; Gómez et al., 2006, 2007a,b). Whereas the cholinergic system does not seem to undergo any morphological change after naris closure, our results point to higher noradrenergic and lower serotonergic activities in both the ipsilateral and contralateral OBs after sixty days of deprivation. This means that olfactory deprivation not only affects the primary olfactory pathways directly, but also other brain centers such as the locus coeruleus or raphe nuclei.

Anterior Olfactory Nucleus

Although the changes affecting the intrinsic neuronal population of the OB are fairly well established, we have previously demonstrated that alteration of the olfactory pathway is more widespread, involving other areas, such as the anterior olfactory nucleus (AON). After 60 days of olfactory deprivation, the AON undergoes a striking reduction in volume, affecting both ipsilateral and contralateral sides (Barbado et al., 2001). In addition, neurochemical analysis indicates that disruption of the normal afferent activity to one OB affects the expression of calcium-binding proteins in the AON. The most affected elements are the calbindin D-28k-immunopositive cells located in the rostral subdivisions of the AON (Barbado et al., 2002). Analysis of the responses of AON neurons under odor stimulation has revealed that deprivation of ipsilateral nasal inputs enhances the response to contralateral odor stimulation to a considerable extent, showing that olfactory deprivation also elicits functional alterations in this structure (Kikuta et al., 2008).

Piriform Cortex

Despite the large body of data about the effects of deprivation in the OB, few authors have analyzed how higher olfactory centers react to the reduction in peripheral stimulation. However, examination of the glutamatergic olfactory transmission underscored the key role of early olfactory experiences in the establishment of cortical circuits (Franks and Isaacson, 2005). In fact, 30 days of olfactory deprivation causes shrinkage of layer Ia of the ipsilateral piriform cortex and a decrease in the number of semilunar neurons as well as a reduction in the apical dendrite sprouting of these cells (Wilson et al., 2000). These data show that olfactory deprivation not only affects the most peripheral structures of the olfactory pathway, but also the central processing of the information.

Consequences of Unilateral Olfactory Deprivation in General Olfaction

A compensatory response. Many of the changes reported following unilateral olfactory deprivation appear to be compensatory processes to preserve olfactory function under the lack of stimulation (Leon, 1998; Coppola, 2012); that is, regulatory centrifugal systems seem to react by trying to decrease the impact of the loss of the arrival of olfactory information. In normal conditions, serotonin inhibits olfactory transmission at bulbar level, decreasing sensitivity and increasing olfactory discrimination (Aungst and Shipley, 2005). Moreover, noradrenalin increases the olfactory sensory response by enhancing the excitatory response of MCs (Hayar et al., 2001). After olfactory deprivation, a decrease in serotonergic action and an increase in noradrenaline bulbar levels are seen, probably aimed at facilitating olfactory transmission to higher olfactory centers. In fact, electrophysiological experiments have shown that naris occlusion increases olfactory sensitivity in the bulb (Philpot et al., 1997a,b), whereas olfactory enrichment causes the opposite effect (Mandairon et al., 2006). Exposure to specific odorants diminishes the number of projecting cells responding to those odors, resulting in a decrease in olfactory sensitivity and increased discrimination (Mandairon et al., 2006). Consistent with these findings, rats trained for an odorant detection task showed heightened responses and altered mucosal response patterns to the trained odors, as

compared with those in age-matched controls (Youngentob and Kent, 1995).

Both olfactory brains become different after unilateral deprivation. The regions of the olfactory pathway contralateral to the naris closure site are also affected by this surgery. Previous reports have indicated that the contralateral OB could be used as control for unilateral deprivation, since no changes are observed between the contralateral and control OBs (Brunjes et al., 1985; Frazier-Cierpial and Brunjes, 1989). However, several authors have shown that the contralateral OB is indeed affected by naris closure (Johnson et al., 1996; Mandairon et al., 2003; Gómez et al., 2007a,b). In animals with unilateral naris closure, the open side can represent a condition of over stimulation due to increased airflow (and thus more odorant influx), together with the absence of resting periods in normal conditions. In this sense, the "open" olfactory pathway structures are significantly different from the untreated controls in both morphology and in the gene/protein expression profile (Coppola et al., 2006; Coppola and Waggener, 2012; Gómez et al., 2006, 2007a,b; Tian and Ma, 2008; He et al., 2012), probably because they receive different levels of odor stimulation.

OLFACTORY DEAFFERENTATION: THE PIECES OF THE EDGES ARE MISSING

Deafferentation models comprise: (1) lesion of the ORN of the olfactory epithelium (Fig. 3B); (2) transection of the olfactory nerve (elimination of the afferences from the olfactory epithelium to the OB); (3) transection of the lateral olfactory tract (LOT), that is, the elimination of afferences from the OB to higher olfactory centers (Fig. 3C); (4) elimination of the OB (bulbectomy; Fig. 3D). We do not consider the elimination of pure centrifugal inputs as a sensory deprivation mechanism, since it does not eradicate sensory information, but only abolishes the modulation of the transmission along the olfactory structures. In addition, the selective elimination of some centrifugal afferences (i.e., serotonergic axons) with neurotoxins does not prevent the olfactory information transmission process.

Lesion of the Olfactory Epithelium and Deafferentation of the Olfactory Nerve

The mechanisms of adaptation subsequent to lesion of the ORNs in the epithelium (Fig. 3B) and the sectioning of ORN axons are very similar; therefore, the results of both methods are grouped in the same section. Transection of the olfactory nerve triggers the degeneration of axons in a retrograde manner, leading to ORN apoptosis (Graziadei and Graziadei, 1979; Zielinski and Hara, 1992; Holcomb et al., 1995), while other cell types, including immature neurons, remain unharmed and capable of reinnervation (Schwob, 2002). Chemical lesioning of the olfactory mucosa also results in temporary deafferentation of the OB by destroying ORNs and immature cells. The chemicals used to lesion the olfactory mucosa include copper (Moran et al., 1987; Bettini et al., 2006), methyl bromide (Schwob et al., 1995; Weruaga et al., 2000), zinc sulfate (Margolis et al., 1974; Matulionis, 1975; Cancalon, 1982; Burd, 1993), dichlobenil olfactotoxin (Alonso et al., 2008; Lazarini et al., 2012), and the detergent Triton X-100 (Kawano and Margolis, 1982; Cancalon, 1983; Cummings et al., 2000; Iqbal and Byrd-Jacobs, 2010; Paskin et al., 2011).

These processes cause the elimination of ORNs and, in some cases, also a reduction in some proliferating basal cells (Holcomb et al., 1995; Calof et al., 1996), decreasing the thickness of the epithelium (Harding et al., 1977; Nadi et al., 1981; Kawano and Margolis, 1982; Burd, 1993; Herzog and Otto, 1999, 2002). The loss of the synapses that these ORNs establish on the OB causes the degeneration of some neuronal types of the OB (Gozzo and Fulop, 1984). In addition to morphological changes, these lesions also elicit changes in the expression of some neurochemical markers of the OB, similar to those observed after olfactory deprivation. There is a decrease in the expression levels of tyrosine hydroxylase, dopamine, substance P, neuronal nitric oxide synthase—and its related NADPH-diaphorase activity—and calbindin D-28K (Nadi et al., 1981; Kawano and Margolis, 1982; Baker et al., 1983, 1984; Kream et al., 1984; Leo et al., 2000; Weruaga et al., 2000). The immunoreactivity of the mouse external plexiform layer interneurons for GluR1 is also dramatically reduced following olfactory deafferentation in adulthood (Hamilton et al., 2008). Recently, it has been demonstrated that both olfactory deprivation and olfactory deafferentation reduce GAD67 protein and the number of short-axon cells expressing GAD67 in the OB (Parrish-Aungst et al., 2011).

In addition, similar to olfactory deprivation, ORN loss causes a concomitant reduction in adult OB neurogenesis due to an increase in apoptosis (Villanueva and Byrd-Jacobs, 2009). In fact, a recent investigation has shown that the increase in apoptosis within the OB is related to the inflammation process and microglial activation that follow olfactory deinnervation (Lazarini et al., 2012).

The olfactory epithelium is continuously regenerated due to the activity of neuronal precursors, denominated basal cells (Crews and Hunter, 1994). These cells increase their proliferation rate after the loss of ORNs, the number of neurons and the thickness of the olfactory epithelium recovering (Graziadei and Graziadei, 1979; Samanen and Forbes, 1984; Herzog and Otto, 1999; Astic and Saucier, 2001). The nature of these basal cells has been widely analyzed and there are two recognized subpopulations: horizontal basal cells and globose basal cells (Graziadei and Monti Graziadei, 1979; Schwob, 2005). Apart from their morphological characteristics, different studies have demonstrated that the horizontal basal cells can give rise only to themselves, whereas globose basal cells are the true multipotent stem cells of the olfactory epithelium. Such studies included immunocytochemistry, viral lineage tracing, colony forming unit assays, thymidine labeling and both regeneration and transplantation analyses (for review see Schwob, 2005). To summarize, ORNs are renovated throughout the life of the animals and after an injury they are able to regenerate to increase the rate of neurogenesis (of basal cells) and to make functional synaptic connections on to the OB. Such phenomena make this model attractive not only for studies addressing neurogenesis and neuronal plasticity, but also to validate therapeutic strategies after an insult, by examining the brain's abilities to

regenerate and reestablish connections (Costanzo, 1991; Paskin et al., 2011). Indeed, these reversible deafferentation methods have been used in the olfactory system to examine the degeneration and subsequent regeneration of the OB. In rodents, regeneration of the neuroepithelium is evident at 6–12 days following surgical transection of olfactory axons, with the activation of basal cell proliferation (Harding et al., 1977). After 8–15 days, the number of mature olfactory neurons begins to increase and near-control levels are reached after around 30 days. Reinnervation of the OB by olfactory axons occurs simultaneously with mature ORN repopulation and, in ~4 weeks, olfactory axons are observed (Graziadei and Monti-Graziadei, 1980) and OB neuronal markers mimic control values even at 25 days post-lesion (Harding et al., 1977; Weruaga et al., 2000). Regeneration of the olfactory system following chemical lesioning of the epithelium with Triton X-100 follows a similar chain of events in mammals (Cummings et al., 2000). However, with this technique both mature and immature neurons are destroyed, resulting in a slower recovery. Studies performed in zebrafish have shown that application of Triton X-100 in the nasal cavity of this teleost results in a rapid degeneration/regeneration of the olfactory epithelium (Iqbal and Byrd-Jacobs, 2010; Paskin et al., 2011). Additionally, bilateral zinc sulfate irrigation of the nasal cavities causes a fast degeneration of the olfactory nerve and a loss of sensory input to the bulb. Indeed, anosmia occurs as soon as 1 h following irrigation of the nasal cavities (McBride et al., 2003) and persists for 14–60 days until regeneration occurs. This regeneration means a recovery to physiological values of the catecholamine markers and the recovery of the sense of smell (Baker et al., 1984). However, it is not yet clear whether the synaptic connection pattern is the same as the previous one existing before the deafferentation (Astic and Saucier, 2001). Studies combining methyl bromide lesions of the mucosa with mouse strains exhibiting glomerular synaptic differences point to a recovery of the injured circuitry (Weruaga et al., 2000).

However, all of these mechanisms of lesion of the olfactory epithelium/nerve lead to a complete or almost complete destruction of this structure. Thus, despite the regeneration of the olfactory epithelium and nerve afterwards, the projections of the new ORN to their correspondent glomeruli are aberrant (Costanzo, 2000). However, if only a small set of ORNs is destroyed, by genetically targeted ablation, the establishment of their connections is maintained and the olfactory topographic map is preserved (Gogos et al., 2000). The most likely mechanism to ensure the correct targeting of this circuitry, both during development and in its continuous regeneration through out life, is a bulbar signal in a normal environment (Gogos et al., 2000). Therefore, after the total destruction of the olfactory epithelium, the conditions for regeneration of the olfactory nerve are very different from the embryological ones, or during the physiological continuous repositioning of ORNs in adulthood.

Bulbectomy

Bulbectomy is a surgical procedure in which either one (unilateral bulbectomy) or both bulbs (bilateral bulbectomy) are eliminated (Fig. 3D). This technique has been used frequently since the end of the 19th century to look for the source of the afferences that reach the OB and to detect the regions where the OB projects (Löwenthal, 1897). This method causes the retrograde degeneration of neurons projecting to and from the main and accessory OBs, with the ensuing alterations in olfactory structures from the mucosa to secondary cortices.

Olfactory epithelium. Ablation of one or two OBs causes degeneration of the olfactory axons by means of the rapid death of ORNs (Schwartz et al., 1991; Carter et al., 2004). Similarly, to lesions made to the olfactory epithelium or olfactory nerve axotomy, an increase in the neurogenesis rate of the basal cells of the olfactory epithelium is also observed (Carr and Farbman, 1992; Suzuki et al., 1998). If OB ablation is partial, ORN axons travel to the residual bulb and form glomerular structures. Even if ablation is total, olfactory nerve axons grow to regions of the rostral brain and establish synapses with local neurons, forming ectopic glomerulus-like structures (Graziadei and Monti Graziadei, 1985). However, there are differences between the regeneration process of the olfactory epithelium after bulbectomy and after olfactory nerve axotomy: (i) the proliferation rate of basal cells is higher after bulbectomy (Carr and Farbman, 1992); (ii) the half-life of ORNs is lower in bulbectomized animals, since most of their axons do not make synaptic contacts and degenerate (Schwob et al., 1992; Carr and Farbman, 1993); (iii) regeneration of the olfactory epithelium after sectioning of ORN axons is completed at around 30 days after the lesion (Samanen and Forbes, 1984), whereas 1–9 months are needed for partial recovery of this structure after bulbectomy (Costanzo, 1984; Verhaagen et al., 1990; Schwob et al., 1992).

Piriform cortex. This structure is severely affected after bulbectomy. The most striking evidence is the loss of pyramidal cells due to the loss of afferences coming from the main olfactory component in the OB: namely, mitral/tufted cells (Heimer and Kalil, 1978). In addition, the neurochemical composition of the cortex is also altered after bulbectomy. In the deprived cortex, there is an increased number of neurons expressing calbindin, parvalbumin, and neuropeptide Y and a decrease in the population of neurons positive for glutamate metabotropic receptors (Kinzie et al., 1997; Holmes et al., 1998) and GAD67 (Gómez-Climent et al., 2011). Recently, it has been demonstrated that olfactory bulbectomy causes a dramatic decrease in the number of both PSA-NCAM and doublecortin-immunopositive cells in layer II of the piriform cortex, whereas the number of cells expressing NeuN (a mature neuronal marker) is increased. These data suggest that the absence of the whole set of the MC (olfactory bulbectomy) induces a [aberrant] maturation of immature neurons in the olfactory cortex (Gómez-Climent et al., 2011). Bulbectomy and later transplantation of the OB results in the regeneration of the afferences that connect the OB with the piriform cortex, even though these axons have first degenerated (Zigova et al., 1992).

Other structures. Other nonolfactory structures affected by bulbectomy are the locus coeruleus and the

raphe nuclei (Jancsar and Leonard, 1984). In addition, the hippocampus and the amygdala also undergo alterations, resulting in deficits in cognitive and memory processes (Carlsen et al., 1982). Bilateral olfactory bulbectomy results in changes in behavior and in the endocrine, immune, and neurotransmitter systems; such changes resemble the symptoms seen in patients with major depression. Accordingly, olfactory bulbectomy is frequently used as a model for this neuropsychiatric disorder (Song and Leonard, 2005; Carlini et al., 2012).

Transection of the Lateral Olfactory Tract

The LOT is the main fiber tract of the central olfactory system that connects the OB to the secondary olfactory cortices. It comprises the fibers of the OB projecting cells (MC and tufted cells). LOT transection (Fig. 3C) causes changes in the structure and functionality of all structures of the olfactory pathway. In the olfactory epithelium, this axotomy causes an increase of the proliferation rate of basal cells to produce a higher amount of mature ORNs, similar to what has been observed in the other deafferentation models (Weiler and Farbman, 1999). The OB undergoes a strong reduction in volume; the layers most affected being the external plexiform layer, the granule cell layer, and the periependymal white matter (Weiler and Farbman, 1999). Six weeks after lesion granular cells begin to die (Allison, 1953; Koyano et al., 2005) and MCs die after a few months (Allison, 1953; Verhaagen et al., 1993). In addition, reductions in the volume of both the piriform and enthorrinal cortices have also been detected, due to the loss of neuronal elements that make synaptic contacts with MC axons (Slotnick and Schoonover, 1993). Similar to what happens along the olfactory nerve, after such axotomy the LOT itself regenerates spontaneously and becomes functional when sectioning is neonatal (Munirathinam et al., 1997; Sakamoto et al., 2010).

REMOVING PROJECTING NEURONS: THE KEY PIECES OF THE PUZZLE ARE LOST

Two types of projecting neurons coexist in the OB: the MCs and both the inner and medial tufted cells. These elements constitute the efferences of this structure, innervating higher olfactory centers directly (de Olmos et al., 1978; Haberly, 2001; Cleland and Linster, 2003). Taking into account this connectivity, these cells could be considered the most important regarding olfactory input to the brain itself. Therefore, if all these neurons were removed, the OB would remain as a structure apart from the rest of the encephalon, almost as in bulbectomy. However, what happens if only one of these types of projecting neurons is removed?

Usually, to ablate a single cell type it is necessary to employ genetic models knocked-down for specific genes necessary for the survival of that cell type. However, a specific cell death (driven by the lack of one gene) usually takes place during embryonic development and different compensatory mechanisms may blur the real effects of the removal of that cell population. Thus, genetic models that lead to a specific postnatal cell degeneration avoid this problem. This is the case of the PCD (Purkinje cell degeneration) mutant mouse, which under goes a loss of MCs in the third month of life (Fig. 3E; Greer and Shepherd, 1982; Wang and Morgan, 2007). In addition, this model allows the specific olfactory role of mitral/tufted cells to be determined, an aspect that remains elusive even though differences between them have been demonstrated (Mori and Sakano, 2011; Griff et al., 2008a,b). Accordingly, in PCD animals it is possible to analyze the effect of MC loss both at the behavioral (olfaction) and the physiological (connections and neurogenesis) levels.

Effects on Olfaction

The histological changes caused by the *pcd* mutation are well known, but regarding olfactory function, the situation is not so clear: how does a PCD mouse smell without projecting neurons? In the early studies of this mutant mouse, degeneration of the axons in the LOT as well as a loss of MC were reported (Mullen et al., 1976; Landis and Mullen, 1978; Greer and Shepherd, 1982). In addition, the status of the OB after this degeneration was also analyzed the olfactory nerve and glomerular activity remaining unaffected (Greer and Shepherd, 1982). However, over 30 years of study the issue of the olfactory capacity of PCD mice has remained elusive, although recently, employing fine olfactometry (Bodyak and Slotnick, 1999), it has been demonstrated that PCD mice have impaired olfaction (Díaz et al., 2012). Thus, PCD mice are able to detect high concentrations of odorants and discriminate them in a coarse manner, but they are unable to detect them at low concentrations or perform fine discriminatory tasks (Díaz et al., 2012). Partial rescue of MCs also improves performance in odor detection and discrimination tasks (Díaz et al., 2012). Because of their differential morphology and structure, axonal projections to the olfactory cortex and odor responses, the information provided by MCs and tufted cells is thought to be transmitted through different channels, (Nagayama et al., 2004; Recio et al., 2007; Griff et al., 2008a,b; Mori and Sakano, 2011). However, each channel seems to be responsible for both odor discrimination and detection, since PCD mice are impaired in both olfactory capacities only losing MCs (Greer and Shepherd, 1982), these cells being related to the finest odor processing (Díaz et al., 2012).

Effects on Bulbar Connectivity and Neurogenesis

The death of MCs also affects the secondary olfactory structures (Greer and Halász, 1987; Bartolomei and Greer, 1998), especially their connectivity with the OB, as demonstrated with tracer injections into the OB (Recio et al., 2007). Since PCD animals lack mitral but not tufted cells, small tracer injections circumscribed to their "MC layer" label only the projections of the inner tufted cells, which could be compared with the projections of both types of neurons (tufted and mitral) labeled with the same tracer and using wild-type animals (Recio et al., 2007). That study showed that, as expected, the mutant animals exhibited a general decrease in the projections from the OB to the secondary olfactory structures and that MCs projected more caudally than tufted cells (Recio et al., 2007). In addition, the degeneration of MCs, and consequently of their axons, also causes

important compensatory plastic changes, such as the reinforcement of the ipsilateral inputs from the AON to the OB or the disappearance of contralateral connections (Recio et al., 2007).

Finally, the death of MCs also affects the cell turnover of the OB. On the one hand, the cell proliferation rate, the tangential migration of neuroblasts from the SVZ to the OB through the RMS and their differentiation are not changed (Valero et al., 2007). However, the radial migration and the survival of the newly generated interneurons are altered (Valero et al., 2007), probably due to a deficiency in reelin, a molecule present in MCs. The neuroblasts that reach an OB without MCs continue their radial migration further, reaching more superficial destinations than in a control OB. In addition, the absence of MCs causes a dramatic decrease in the number of synaptic targets available for the new interneurons and hence the survival of these neurons is reduced (Valero et al., 2007).

THE GAME OF CELL TURNOVER: WHAT ARE THE NEW PIECES LIKE?

The OB is a neurogenic structure in which the formation of new neurons takes place throughout the lifespan of mammals (Altman, 1969). The cradle of these neurons is housed in the SVZ, lining the lateral ventricles in the forebrain (Lois and Álvarez-Buylla, 1993; Doetsch et al., 1997; Mirzadeh et al., 2008). Neural stem cells of the SVZ give rise to new neuroblasts that migrate tangentially (and proliferate) along the RMS, supported by glial tubes, until they reach the OB (Altman, 1969; Lois et al., 1996; Doetsch et al., 1997; Peretto et al., 1997; Carleton et al., 2003). In addition, the RMS also has proliferating cells that can act as stem cells (Gritti et al., 2002; Merkle et al., 2007). Once in the OB, neuroblasts begin to migrate radially from the rostralmost extension of the RMS towards outer layers, eventually differentiating into interneurons (Altman, 1969; Lois and Álvarez-Buylla, 1994; Carleton et al., 2003). The vast majority of these neuroblasts become granule cells in the granule cell layer, or periglomerular cells in the glomerular layer (Carleton et al., 2003; Imayoshi et al., 2008; Lledo et al., 2008; Mouret et al., 2009), but there is also differentiation into other interneurons in the external plexiform layer (EPL; Yang, 2008). This continuous cell turnover, which also takes place in humans (although controversy exists; Curtis et al., 2007; Bergmann et al., 2012), has not yet been fully elucidated. It is probable that the continuous arrival of cells in the OB would be necessary to replace the old interneurons that die during the life of the animals to maintain the homeostasis of the bulbar circuitry (Carleton et al., 2003; Imayoshi et al., 2008; Lledo et al., 2008), even though apoptosis is necessary for the establishment of these circuits (Yokoyama et al., 2011). Finally, through a transdifferentiation mechanism a small population of bulbar interneurons derives from the bone marrow (Recio et al., 2011).

It is relatively easy to address this part of the "olfactory puzzle" because a wide range of factors modifies cell proliferation and migration of the SVZ-OB axis (Fig. 3F). However, it should be taken into account that some of these factors affect the neurogenesis of both the SVZ and the RMS similarly, and at the same time, whereas others have different effects in these two regions (Díaz et al., 2009; Corona et al., 2011). This is easy to understand because the SVZ gives rise not only to new cells for the main OB, but also for the accessory OB (Bonfanti et al., 1997) and even the cortex (Goings et al., 2004; Sundholm-Peters et al., 2005). Thus, an initial regulation of neurogenesis in the SVZ may be modified or overlapped with other types of regulation in the migration pathway (Díaz et al., 2009; Corona et al., 2011).

The most frequent techniques used to explore the functions of the different regulation factors are the generation of knockdown animals or the administration of these factors (or agonists) through systemic, intraperitoneal or intraventricular routes. Below we offer a list of the most important regulation systems of neurogenesis.

Regulation of Proliferation

Growth factors. There are different growth factors whose effect on the SVZ proliferation has been studied in depth, mainly in the sense that they lead it to increase. This is the case of epidermal growth factor (EGF) or fibroblast growth factor (FGF). Both EGF and FGF promote the cell division of the neural precursors and, at high doses, can promote the migration towards adjacent regions (Doetsch et al., 2002; García-González et al., 2010). Sharing receptors with the EFG, transforming growth factor (TGF) also fosters cell proliferation. In addition, it has been demonstrated that the age-related decrease in TGF is one of the causes of the age-related decline in cell proliferation in the SVZ (Tropepe et al., 1997). Vascular endothelial growth factor, circulating tumor necrosis factor, stem cell factor, and erythropoietin also increase cell proliferation in a way closely related to angiogenic or hypoxic conditions (Shingo et al., 2001; Jin et al., 2002). Finally, Pax6 also promotes neurogenesis, since mutant mice lacking this transcription factor undergo a reduction in cell proliferation in the rostralmost part of the SVZ and the RMS, a decrease occurring in the number of new interneurons in the granular and glomerular layers (Curto, 2010). Pax6 also seems to stimulate neuroblast differentiation into interneurons and, although with some restrictions, the survival of these cells.

Cell surface molecules. Cell adhesion molecules, such as mCD24, also play an important role in the regulation of cell proliferation. mCD24 is a highly glycosylated molecule that is attached to glycosylphosphatidylinositol and that reduces cell proliferation (Belvindrah et al., 2002). Another cell adhesion molecule that promotes cell proliferation is LeX/SSEA, which has been proposed as a stem-cell marker and is also related to blood vessels (Capela and Temple, 2002). Ephrins and their tyrosine kinase receptors increase cell proliferation to the detriment of the organization of the RMS glial tubes that drive the migration of neuroblasts (Conover et al., 2000).

Morphogens. These are key molecules during development, but they can also have striking effects on cell proliferation in adults. The bone morphogenic proteins constitute one of the most important groups, reducing the proliferation of neural stem cells and hence the formation of new neuroblasts (Lim et al., 2000; Peretto

et al., 2004). By contrast, noggin, the antagonist of the former molecules, increases cell proliferation to the detriment of cell differentiation (Lim et al., 2000; Peretto et al., 2004). Sonic hedgehog also plays an important role in cell proliferation and progenitor cell maintenance, their absence causing severe morphological alteration and brain shrinkage (Machold et al., 2003). By contrast, the family of Notch receptors (and their ligands) maintains the quiescence of progenitors, decreasing proliferation and differentiation (Chambers et al., 2001).

Neurotransmitters. Depending on their receptors, neurotransmitters and neuropeptides can exert different effects on neurogenesis. These molecules play an important role as mediators of external conditions, such as different types of stimulus or pathological situations (Bovetti et al., 2011). For instance, monoamines such as dopamine and serotonin increase cell proliferation in the forebrain (Banasr et al., 2004; Hoglinger et al., 2004). The function of the former (dopamine) seems to be mediated in different steps by the D2 and D3 receptors through BDNF, EGF, or the ciliary neurotrophic factor (for a review, see Bovetti et al., 2011). Serotonin seems to be a mediator of estrogens (see below) and it regulates the SVZ and the RMS differently (Díaz et al., 2009). Its effects are mediated by different families of receptors—whose cellular localization in the SVZ-OB axis is not fully known—and by BDNF or dopamine itself (Bovetti et al., 2011). In contrast, nitric oxide has the opposite effect, reducing neurogenesis by blocking EGF receptors (Packer et al., 2003; Moreno-López et al., 2004; Matarredona et al., 2005; Torroglosa et al., 2007). Finally, amino acids such as GABA and glutamate have a complex effect. However, GABA is released by neuroblasts and reduces cell proliferation of SVZ astrocyte-like stem cells through their $GABA_A$ receptors, controlling and balancing cell proliferation and mobilization (Liu et al., 2005). However, glutamate is released by SVZ astrocytes and increases the proliferation of neuroblasts (Bovetti et al., 2011).

Hormones. Female hormones play an important role in the regulation of neurogenesis. This effect is complex: they not only depend on physiological stages, such as the oestral cycle or pregnancy (Shingo et al., 2003), but may also act directly on specific receptors or through different mediators (Banasr et al., 2001, 2004; Scharfman and Maclusky, 2005) and their action maybe restricted to different parts of the SVZ-OB axis (Smith et al., 2001; Díaz et al., 2009). Although with some differences among species, the general effect of prolactin and estrogens on this neurogenic region is an increase of cell proliferation (Smith et al., 2001; Shingo et al., 2003; Díaz et al., 2009), whereas progesterone decreases it (Shingo et al., 2003; Giachino et al., 2004).

Regulation of Migration

The regulation of migration is mainly focused on the RMS, the cell pathway from the SVZ to the OB. For this migration, the maintenance of the glial tubes that ensheath the migrating neuroblasts is essential (Peretto et al., 1997, 1999). One of the most important molecules involved in cell migration is the neural cell adhesion molecule (NCAM), in particular its polysialylated form (PSA-NCAM), which allows the correct migration of neuroblasts (Ono et al., 1994; Chazal et al., 2000). Indeed, the level of PSA of the NCAM also regulates the neuroblast differentiation. Thus, as these cells migrate along the RMS and lose PSA (+NCAM?), migration slows down and, once in the OB, they start to differentiate (Petridis et al., 2004).

Microtubule dynamics are also important for migration. There are two molecules with oppositefunctions that are key elements in these dynamics: doublecortin and stathmin (Camoletto et al., 1997; Brown et al., 2003; Yang et al., 2004). When these are phosphorylated, doublecortin is activated, whereas stathmin loses its function, the former increasing the stability and the polymerization of microtubules. Without phosphorylation, the inverse situation arises and the disorganization of the cytoskeleton increases due to the activity of stathmin (Belmont and Mitchison, 1996; Moores et al., 2004).

There are also molecules that can act as chemorepellents or chemo-attractants for such migration. Slit 1 and Slit 2 are two of the best-known chemo-repellents through Robo receptors, expressed in the neuroblasts along the RMS (Nguyen-Ba-Charvet et al., 2004). Mice knocked-out for at least one of these proteins show an abnormal pattern of neuroblast migration (even through the corpus callosum).These cells also leave the RMS prematurely (Nguyen-Ba-Charvet et al., 2004). Nevertheless, in these mutants migration towards the OB persists. However, this mechanism of repulsion is not the only one that leads neuroblasts to their final destiny. There are also molecules that can attract the migration of neuroblasts, but they are not essential and their effect is less well known because after bulbectomy cell migration as well as proliferation is maintained, although reduced (Kirschenbaum et al., 1999; Liu and Rao, 2003). Some of these attractants are the netrins, tenascin-R and reelin (Hack et al., 2002; Murase and Horwitz, 2002; Saghatelyan et al., 2004). Anosmin-1 also acts as a chemo-attractant (García-González et al., 2010), at least in development and postnatal bulbar neurogenesis. Reelin also seems to play a role in the radial migration of neuroblasts once they have reached the OB (Valero et al., 2007).

Neurotransmitters also affect the migration of neuroblasts, but their effect is much more restricted than in cell proliferation. Thus, only GABA and glutamate seem to visibly modify this cell migration, decreasing it and only through very specific receptors (Bovetti et al., 2011). Regarding nitric oxide, although this is present in the RMS, it does not seem to have any effect on cell migration (Moreno-López et al., 2004).

Finally, the movement of cerebrospinal flow also determines the capacity of neuroblasts to migrate. Thanks to the movement of the cilia of ependymal cells, this liquid flows from the dorso-caudal part to the ventro-rostral part of the lateral ventricles. Thus, mutant mice with an underdevelopment of these cilia undergo impairment inneuroblast migration (Sawamoto et al., 2006). It is not fully understood whether this movement acts directly on the migrating cells, or whether it can determine the distribution of chemo-repellent molecules such as Slit 1 and Slit 2.

Regulation of Cell Differentiation and Survival in the OB

Apart from PSA (see above), the differentiation and survival of neuroblasts in the OB are determined by

other factors. One of them is the activity of the OB itself (Petreanu and Álvarez-Buylla, 2002). Thus, mice with an odor-enriched environment have a higher survival of interneurons than those housed in standard conditions (Rochefort et al., 2002). Moreover, animals with naris occlusions (which causes sensory deprivation; see above) undergo a transient disruption of neurogenesis that can be restored after reopening the air flow (Cummings and Brunjes, 1997; Cummings et al., 1997). Molecules such as BDNF, whose levels decrease after sensory deprivation, mediate this effect. Thus, sensory deprivation diminishes the synaptic contacts of the new interneurons arriving at the OB as well as their survival in the new scenario (McLean et al., 2001). Sensory deprivation *per se* does not seem to affect the proliferation or migration of neuroblasts. However, it changes the release of other substances, such astenascin-R, which decrease, leading to a reduction in neurogenesis as a secondary effect (Saghatelyan et al., 2004).

Finally, the establishment of appropriate synapses to reach a correct physiology is necessary for the survival of new interneurons. The lack of connections with their target neurons (i.e. when MCs degenerate) can also produce an increase in the cell death rate of newly formed interneurons in the OB (Valero et al., 2007). Some physiological processes, such as sleep, also regulate the establishment of these adequate synapses in relation to correct apoptosis (Yokoyama et al., 2011). Neurotransmitters from the synapses of bulbar afferences can also modify the survival of interneurons: acetylcholine, through nicotine receptors, decreases survival (Mechawar et al., 2004), whereas noradrenaline reduces cell death (Bauer et al., 2003). GABA also enhances the maturation of interneurons indirectly through CREB activation, which increases the synthesis of BDNF or tenascin-R (Saghatelyan et al., 2004; Giachino et al., 2005). Regarding glutamate, this is critical for neuroblast survival only during their migration and after integration into the OB (Platel et al., 2010).

Destruction of Neurogenesis

Apart from the modification in neurogenesis, elimination of this "continuous piece support" causes severe alterations in OB morphology. However, it is not easy to completely eliminate the neurogenesis of the SVZ-OB axis because it is very resistant, even when subjected to different types of regulation (see above). Some chemicals can disrupt neurogenesis in the forebrain, but this alteration is only transient and the neurogenesis in the SVZ-OB axis is restored naturally. Accordingly, the most efficient tool for eliminating cell proliferation in the forebrain is ionizing radiation (Tada et al., 1999; Monje et al., 2002; Mizumatsu et al., 2003; Balentova et al., 2006; McGinn et al., 2008). The dose of such radiation is critical, because low doses may not only decrease cell proliferation, but also increase it (Shinohara et al., 1997; Tada et al., 1999; Balentova et al., 2007). In addition, the SVZ seems to be more resistant to ionizing radiation than the dentate gyrus of the hippocampal formation, since the former has more "true" stem cells, with slower division and greater resistance to radiation (Hellstrom et al., 2009). Therefore, relatively high doses of radiation are necessary to ablate neurogenesis in the SVZ-OB axis: at least 7.5 Gy (Tada et al., 1999; Díaz et al., 2011). Curiously, even with these procedures, proliferation is not completely eliminated, remaining very reduced (Lazarini et al., 2009; Díaz et al., 2011). However, this small number of proliferating cells does not increase with time and therefore it cannot restore the original rate of neurogenesis, which remains severely affected (Díaz et al., 2011).

The most remarkable consequence of the ablation of proliferation in the SVZ-OB axis is the virtual disappearance of the neurogenic niches and pathways (Díaz et al., 2011) as well as the presence of new neurons in the layers of the OB (Lazarini et al., 2009). This finally leads to a dramatic shrinkage of the size of the OB (Díaz et al., 2011). The striking alterations of this neurogenic ablation do not seem to change the olfactory capacities of mice dramatically. However, cranial irradiation of adult females disrupts their social behavior, possibly owing to impairments in olfaction (Feierstein et al., 2010). However, this same irradiation does not affect maternal behavior, suggesting compensatory mechanisms or different thresholds for different odorants (Feierstein et al., 2010). In addition, after irradiation that affects neurogenesis, the olfaction of irradiated mice remains as efficient as in control ones (Díaz et al., 2012), with slight impairments in long-term olfactory memory, thus demonstrating the high stability of this plastic system (Lazarini et al., 2009).

CONCLUSIONS

The olfactory system comprises subsequent, highly linear relay stations that are also composed of elements diverging in their functions: main projecting neurons (ORNs, MC/Tufted cells, pyramidal neurons, etc.), interneurons (which refine and survey the upstream information) and, finally, by centrifugal fibers and dispersing interneurons (which capture information from higher centers to feedback to the system). The normal, non-altered, olfactory system is built up by all of these elements forming a working complete neural circuit, like when the pieces of a puzzle offer, for example, a complete landscape. Moreover, this "landscape" changes continually—it is plastic—because of the natural replacement of ORNs and revival of the interneuron population by the RMS.

The olfactory system of rodents has been manipulated to outline the functionalities and chemical cues of the neurons integrating it. The most affordable method has been the deletion of olfactory inputs (sensory deprivation) and the elimination of some of the elements of the information flow: deinnervation/deafferentation, bulbectomy, and genetic models to remove MCs. These paradigms yield "logical" consequences: by injuring or eliminating neurons their corresponding axons disappear as well and this modifies the landscape in the next relay station. Further, depending on the time after the insult or inactivation, the subsequent olfactory centers are also affected: that is, the AON, the piriform cortex, etc. Because neurons are also the targets of other neurons (including interneurons), the disappearance itself of those pieces of the puzzle affects the surrounding scenario.

Despite these consequences, the most intriguing effect of sensory manipulation is the response of the entire brain towards the functioning of the whole system

affected. Here, we have discussed the changes in the olfactory mucosa, the OB and higher centers when olfaction is depleted by some means. In the OB, the region best analyzed, both gene expression and neural activity are adjusted to intensify the information travelling upstream, and the feedback inhibition is diminished downstream. The final result of these plastic changes is to allow the perception of any olfactory input, even though the resulting information might be blurred and coarse. The brain should always be aware of what is going on around it!

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