Odor Perception and Olfactory Bulb Plasticity in Adult Mammals

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INTRODUCTION

Sensory processing involves a hierarchy of interconnected sensory, cortical, and subcortical areas. When discussing these hierarchies and interactions, olfactory processing is often set apart due to the lack of direct thalamic pathways between sensory and cortical processing areas. Indeed, olfactory signals, after being received and transformed by sensory neurons, are projected directly to an anatomically well-studied cortical structure—the olfactory bulb (OB)—with projections to the thalamus established further downstream of the pathway. A recent review has compared the OB to the thalamus in its functional signal processing properties (Kay and Sherman 2007) and discussed how both structures act as early processing stages in which cortical and modulatory feedback can substantially shape sensory representations. Here, we review recent evidence showing that, indeed, the OB is more than a relay station or a feedforward filter but rather actively shapes, and is actively shaped by, olfactory perception—a notion introduced >20 yr ago by Freeman and Schneider (1982). A crucial component of this function constitutes the central projections to the OB, including cortical, subcortical, and modulatory projections (reviewed in Shipley and Ennis 1996) (Fig. 1). We discuss data showing how olfactory experience changes the OB network and how manipulations of the OB network change odor perception on several timescales. We finally review in more detail a few experiments showing a tight correlation between the modulation of OB neural activity and odor perception. Literature pertaining to neonatal olfactory learning has been intensely and clearly reviewed elsewhere (McLean and Harley 2004; Sullivan and Dryer 1996); thus this review will focus on adult odor perception.

ODORANT IN THE GRANULE CELL LAYER, BUT ALSO MODULATES ACTIVATION OF OB NEURAL NETWORK

The olfactory bulb—the first cortical relay of the olfactory pathway—presents a high level of plasticity in response to olfactory experience including short-term exposure, enrichment, and associative learning (Fig. 2A). Indeed, a simple manipulation of olfactory experience, such as exposure to odorants, can modify the bulbar neural network and, more specifically, the odor response patterns of bulbar output neurons (Buonviso and Chaput 2000). For example, a short-term (20-min) exposure of adult rats to an odorant, in the absence of any paired reinforcement, reduced the subsequently recorded proportion of mitral cells responding to odorants with increased firing rates, while increasing the proportion of mitral cells that were inhibited in response to odors (Buonviso and Chaput 2000). Surprisingly, the proportion of excitatory responses to odors was decreased not only to the exposure odor but also to other novel odors. Moreover, it has been shown that even in the anesthetized rat, less than a minute exposure to an odorant can fine-tune the receptive field of mitral cells (Fletcher and Wilson 2003) and that a simple odor exposure modifies the OB circuit and mitral cell single-unit responses to subsequent odor presentation (Kay and Laurent 1999; Spors and Grinvald 2002). In response to associative learning, it has been observed that after giving birth, female sheep develop a selective recognition for their lamb accompanied by an increase of the number of mitral cells in the OB that respond to lamb odor (Kendrick et al. 1992). Early work by Freeman and colleagues showed that the dynamics of bulbar odor responses are modulated by associative learning and that partially distributed OB activity correlates with odor-specific behavioral responding (see, e.g., Freeman and Schneider 1982; Grajski and Freeman 1989). Aversive conditioning of odor stimuli in adult rabbits induced changes in their bulbar electroencephalogram (EEG) map (Gray et al. 1986) and, in rats, odor–reward conditioning modulates local field potential oscillations (Beshel et al. 2007; Kay et al. 1996; Martin et al. 2004, 2006). Modifications of the bulbar network following exposure or experience can also be observed using an immediate-early gene (IEG), such as c-fos, arg 3.1, or Zif268 (expression modulated by sensory input and plasticity) mapping. Odor exposure induces a specific increase in c-fos and arg 3.1 expressions in some particular OB quadrants. Previous familiarization with the test odor results in a decreased expression of both IEGs in these quadrants, leading to an alteration of the odor-specific pattern of c-fos and arg 3.1 expression (Montag-Sallaz and Buonviso 2002), whereas enrichment for a period of 10 days not only increases an increase in the number of Zif268-positive cells in response to an odorant in the granule cell layer, but also modulates activation patterns in the glomerular cell layer (Mandairon et al. 2008a; Woo et al. 2007).

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The inhibitory neurons in the OB, which regulate the activity of mitral cells, are continuously generated in adulthood. Precursors proliferate in the subventricular zone of lateral ventricles and then newly generated cells migrate along the rostral migratory stream to reach the OB (Temple and Alvarez-Buylla 1999). Once in the OB, they migrate radially toward more OSN Mi GC PG ET SA

Activating nicotinic receptors modulates perception
Activation of NMDA receptors enhances perceptual discrimination
Noradrenergic modulation of odor discrimination
NA receptors support short term habituation memory
Cortical feedback modulates dynamics and supports odor-reward learning

Glomerular activation patterns are modulated by experience
Mitrail cell odor responses sparsen in response to experience
Granule cell odor responses increase in response to experience
Dynamics are modulated through learning
New born cell survival is modulated

FIG. 2. A: schematic illustration of network modulation by experience (left) and perceptual modulation by network manipulations (right). See text for details and citations. B: modulation of newborn cell survival is an example for network modulations induced by olfactory experience. The graphs show a color-coded map of bromodeoxyuridine (BrdU)-positive cell density in the OB in pseudoconditioned group exposed to $\pm$ limonene (left) and conditioned group to $\pm$ limonene (right). BrdU-positive cells were counted in the granule cell layer on every 5th section of the OB (14-μm thickness; sampling interval = 70 μm). The granule cell layer was divided into 36 sectors of 10° with the reference axis drawn on the ventral aspect of the subependymal layer of the OB. The volume of the granule cell layer was represented by an array in which each bin has the value of BrdU-positive cells density in one 10° sector and each column corresponds to one section (for details, see Mandairon et al. 2006b). C: manipulation of the bulbar network via daily injections of $N$-methyl-$d$-aspartate (NMDA) modulates behavioral perception. The 2 enantiomers of limonene and terpinene were not discriminated before NMDA infusion (left). After the 10 days of NMDA administration directly in the OBs, animals were able to discriminate between $\pm$ limonene and $\pm$ terpinene (for details, see Mandairon et al. 2006d).
external layers and acquire characteristics of mature granule and periglomerular interneurons (Lois and Alvarez-Buylla 1994; Petreanu and Alvarez-Buylla 2002). These newborn cells integrate into the neuronal network and modulate olfactory processing (Carleton et al. 2003). Current experiments show that sensory deprivation decreases the survival of newborn cells in the OB (Mandairon et al. 2003, 2006c), whereas odor enrichment enhances the survival of newborn cells (Rochefort et al. 2002) and modifies the responses of adult-born neurons to odors (Magavi et al. 2005). Similarly, the acquisition of an olfactory-discrimination task also modulates the survival of newborn granule cells in an odor- and task-specific manner (Alonso et al. 2006; Mandairon et al. 2006b) (Fig. 2B).

In summary, the most recent data on OB network changes due to olfactory experience suggest that experience modulates bulbar networks by modulating the effect of inhibition. This modulation of inhibition is evidenced by changes in mitral cell responses to odorants (Buonviso and Chaput 2000), activation patterns of inhibitory interneurons in response to odor stimulation (Mandairon et al. 2008a), changes in inhibitory neuron survival in the glomerular and granule cell layers (Alonso et al. 2006; Mandairon et al. 2006b; Mouret et al. 2008), and changes in oscillatory dynamics (Beshel et al. 2007; Martin et al. 2004).

MANIPULATIONS OF THE OLFACTORY BULB NEURAL NETWORK MODULATE ODOR PERCEPTION

A crucial function of the OB is to integrate afferent information conveyed by olfactory sensory neurons with centrifugal neuromodulatory inputs (in particular the cholinergic, noradrenergic, and serotonergic systems) as well as other central (e.g., olfactory cortical) inputs (Halasz 1990; Luskin and Price 1982; Shipley et al. 1996). Both ascending (sensory) and centrifugal (modulatory and cortical) inputs can shape the bulbar network on various timescales and, consequently, mod-
ulate olfactory perception (Fig. 2A). For example, perceptual effects of ascending inputs can be mimicked by direct activation of the OB network via local N-methyl-D-aspartate injections, clarifying that local bulbar mechanisms are involved in perceptual changes due to sensory enrichment (Mandairon et al. 2006d) (Fig. 2C).

Centrifugal inputs include, for example, cholinergic projections from the nucleus of the horizontal limb of the diagonal band of Broca (Luskin and Price 1982; Macrides et al. 1981; Zaborszky et al. 1986). Manipulations of the bulbar network by changing cholinergic function have been shown to affect olfactory perception by changing rodents’ ability to differentiate between perceptually similar odorants (Linster et al. 2001; Mandairon et al. 2006a) and, in the case of muscarinic receptor modulation only, to affect the time span for olfactory short-term memory (Ravel et al. 1994).

The OB receives significant input from the noradrenergic pontine nucleus locus coeruleus (McLean et al. 1989; Shipley et al. 1996). Manipulation of the bulbar network by experimental interference with noradrenergic activity in the OB has resulted in changes in olfactory perception and memory formation. Doucette and collaborators (2007) found that local blockade of noradrenergic receptors in the OB decreases the ability of mice to learn a two-odor discrimination task in a go/no-go testing paradigm. The decreased ability to learn the discrimination is evident when chemically and perceptually highly similar odorant mixtures are presented as choice odors. Moreover, spontaneous discrimination between chemically related odorants is decreased when noradrenergic receptors and, in particular, α1 receptors are blocked; reward-motivated discrimination learning is not impaired, but is slowed in rats in which both α and β receptors are blocked (Mandairon et al. 2008b). Bulbar noradrenaline has also been implicated in the formation of olfactory habituation memory (Guéron et al. 2008) and has been shown to be important for the acquisition and/or formation of conditioned odor preferences or odor-specific memories (Kaba and Keverne 1988; Kendrick et al. 1992; McLean and Harley 2004; Sullivan and Dryer 1996).

In addition to neuromodulatory inputs, the OB receives projections in particular from pyramidal cells in secondary

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**FIG. 4.** Correlated network processing and perceptual changes due to manipulation of bulbar cholinergic inputs. A: enhanced cholinergic modulation in the OB affects glomerular computation by directly activating PG cells (Castillo et al. 1999; Ravel et al. 1990), depolarization of mitral cells (Castillo et al. 1999), and modulation of granule cell inhibitory effects onto mitral cells (Pressler et al. 2007). B: schematic depiction of setup for local infusion of neostigmine into the OB during in vivo experiments. C: during behavioral experiments, control and neostigmine-infused rats were habituated to a given odorant during 4 sequential trials and then presented with novel, chemically related test odors. Rats with increased bulbar ACh (neostigmine) discriminated between chemically highly similar odorants significantly better than saline-infused control rats (Chaudhury et al. 2009). D: OB mitral cell responses to chemically highly similar odorants differed significantly more in neostigmine-infused compared with saline-infused rats (Chaudhury et al. 2009).
olfactory cortical, frontal cortex, and hippocampal structures (Luskin and Price 1982; Macrides et al. 1981); these inputs have been shown to affect bulbar processing (Fig. 2A). Reversible blockade of central inputs to the OB in awake behaving rabbits showed that both bulbar EEG dynamics and unit firing are modulated by central feedback (Gray and Skinner 1988). Using electrical lesions of the olfactory peduncle, sparing output from the OB while decreasing feedback inputs to the OB, Kiselyczynk and colleagues (2006) demonstrated that manipulation of the bulbar efferent inputs change the formation of odor–reward associations, but not primary bulbar odor representations. A separate study by Martin and colleagues (2004, 2006) showed that decreased efferent inputs to the OB result in dramatic changes of bulbar dynamics, presumably affecting odor–reward association learning by desynchronizing bulbar and cortical networks.

In summary, experimental manipulations of the bulbar network, by changes in receptor function, efferent input, or neuro-modulation, always result in perceptual changes evidenced by changes in discrimination, odor–reward association learning, and memory formation. These data clearly implicate the OB in shaping olfactory representations, perception, and learning.

**CORRELATION BETWEEN ODOR PERCEPTION AND NEURAL NETWORK CHANGES**

Previous experiments by our group and others have provided evidence for a predictive relationship between OB neural activity and odor perception (Cleland et al. 2007; Kay and Laurent 1999; Youngentob et al. 2006). Recently, this predictive relationship has been further tested by manipulations affecting both bulbar network computations and odor perception, demonstrating that changes in bulbar computation are predictive of changes in perception.

As described earlier, olfactory experience changes odor perception in animals exposed to odors in a daily fashion: these animals subsequently tend to more easily discriminate between chemically similar odorants (Escamilla et al. 2008; Mandairon et al. 2006d,e) (Fig. 3A). We have recently shown that the perceptual changes are accompanied by an increase in inhibitory neuron responsiveness in the OB (Mandairon et al. 2008a), suggesting an increase in inhibitory processing (Fig. 3, B and C). Computational modeling clearly showed that the increase in inhibitory neuron responsiveness is predictive of the behaviorally observed, relative odor-nonspecific increase in perceptual discrimination (Mandairon et al. 2006d) (Fig. 3, Di and Dii).

In recent experiments, Beshel et al. (2007) showed that manipulations of OB dynamics can be correlated to manipulations of task difficulty when rats are asked to discriminate chemically very similar odorants to receive a food reward. Higher-power gamma oscillations, presumably reflecting higher synchrony among bulbar neurons, are observed for more difficult discrimination tasks (Beshel et al. 2007). Computational modeling has previously shown that better synchronization among neurons responding to sensory stimuli leads to higher discrimination ability within an olfactory network (Cleland and Linster 2002; Linster and Cleland 2001). These data strongly suggest an active modulation of bulbar dynamics as a function of task demands.

At the neural level, several recent experiments have shown a tight correlation between mitral cell odor responses and olfactory perception (Fig. 4A). An exhaustive study by Doucette et al. (2008), following up on earlier studies (Kay and Laurent 1999), showed that mitral cell responses to odors associated with reward or absence of reward diverge as the animal learns to associate one but not the other with the reward (Doucette and Restrepo 2008). Chaudhury et al. (2009) showed that manipulations of cholinergic activity in the OB lead to changes in mitral cell responsiveness to odors that are predictive of the changes observed in perceptual discriminations in response to the same manipulations (Chaudhury et al. 2009) (Fig. 4, B–D).

In summary, recent experiments clarify that odor representations are shaped in the OB in a manner predictive of perceptual odor qualities. Although not all types of behavioral tasks are equally affected, the results from a variety of experiments confirm that, indeed, olfactory experience shapes bulbar computations and, in return, bulbar computations shape olfactory perception.

**Conclusions**

The data and experiments reviewed here illustrate how perceptual events and olfactory bulb processing influence each other in a reciprocal manner. Olfactory experience, both passive and active, leads to changes in the OB neural network, which in turn changes how odors are processed and experienced. Observed behavioral and processing changes can be short-lasting or long-lasting, depending on the exact manipulations and behavioral demands used. Although it is clear that much olfactory processing—in particular the associations of olfactory stimuli—is located in downstream brain areas such as piriform cortex, orbitofrontal cortex, hippocampus, and amygdala, the representations conveyed to these areas are highly plastic and experience dependent and depend on the exact state of bulbar processing. Thus the state and plasticity of bulbar processing need to be taken into account when olfactory stimuli are used to study learning and memory.

**REFERENCES**


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