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Plasticity in olfactory bulb circuits

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Olfaction is crucial for animal survival and human well-being. The olfactory bulb is the obligatory input station for olfactory information. In contrast to the traditional view as a static relay station, recent evidence indicates that the olfactory bulb dynamically processes olfactory information in an experience-dependent and context-dependent manner. Here, we review recent studies on experience-dependent plasticity of the main circuit components within the olfactory bulb of rodents. We argue that the olfactory bulb plasticity allows optimal representations of behaviorally-relevant odors in the continuously changing olfactory environment.

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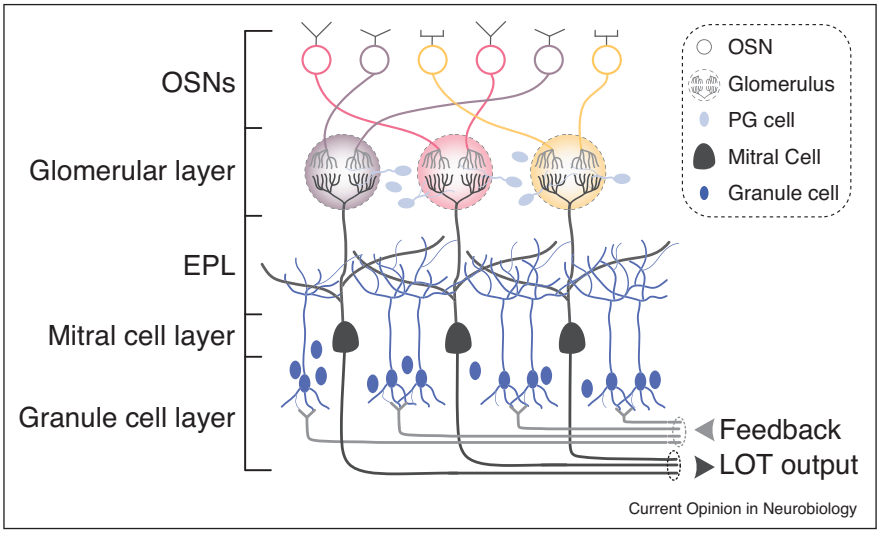
Introduction

The ability to navigate a complex olfactory environment adaptively is crucial in various behavioral contexts, such as foraging for food and avoiding predators. Olfaction is particularly crucial for rodents that rely heavily on their sense of smell and accordingly are equipped with a highly evolved olfactory system. Even in humans that are often considered to depend mainly on other senses such as vision, anosmic patients report fear due to their inability to detect a gas leak and identify rotten food and often suffer from depression [1]. The olfactory bulb is the obligatory input station of olfactory information, receiving direct sensory inputs from the nose and transmitting the information to the rest of the brain. The olfactory bulb comprises a relatively simple feedforward pathway, and thus it has been tempting to speculate that the olfactory bulb is a simple relay station while significant information processing occurs in downstream brain centers. This conventional dogma has been, however, challenged by recent findings that showed that the olfactory bulb dynamically processes odorant information in a state-dependent and experience-dependent manner. Moreover, the olfactory bulb is one of the two loci in the rodent brain where new neurons are incorporated every day to the existing circuit throughout life. These adult-born neurons migrate from the subventricular zone in the central brain and differentiate into local inhibitory neurons in the bulb, providing an additional level of plasticity. In this review, we will summarize recent literature on experience-dependent plasticity of the olfactory bulb circuit (Figure 1) in rodents. We propose that the principal function of the olfactory bulb is to optimally represent the behaviorally relevant odorants by continuously updating its circuits based on the ongoing statistical structure of the olfactory environment.

OSN inputs and glomeruli

Odorants are detected by olfactory sensory neurons (OSNs) in the olfactory epithelium inside the nasal cavity, each of which expresses one of ~1000 odorant receptor genes. OSNs expressing the same odorant receptor extend their axons to two of ~2000 glomeruli in the glomerular layer of the olfactory bulb [2]. At glomeruli, OSN axons make glutamatergic synapses on the projection neurons (mitral/tufted cells) and local interneurons. Several studies have found that OSN inputs to the bulb show a degree of experience-dependent plasticity. A recent study showed that OSN axon terminals demonstrate an activity-dependent turnover, and naris occlusion reduces the turnover rate [3]. This structural plasticity of OSN terminals provides a potential basis for functional plasticity of OSN inputs to the olfactory bulb. For instance, olfactory fear conditioning can enhance the size of the glomeruli responsive to associated odors and the OSN inputs to these glomeruli [4,5]. Furthermore, another report based on intrinsic signal imaging, which is thought to be dominated by OSN axon activity, demonstrated that associative learning can enhance OSN responses to the associated odors [6]. However, other studies failed to detect experience-dependent changes in OSN inputs, even in paradigms that drive changes in mitral cell activity. For example, OSN synaptic release monitored with synapto-pHluorin was stable during repeated passive odor experience [7] and perceptual learning [8] over days. Importantly, the degree of correlation of OSN inputs to the olfactory bulb is not a good predictor of olfactory discrimination learning [9]. Collectively, it appears that OSN inputs can be plastic, but the olfactory bulb probably possesses additional mechanisms

Figure 1



Schematic of the olfactory bulb circuit. OSN: olfactory sensory neuron; PG cell: periglomerular cell; LOT: lateral olfactory tract; EPL: external plexiform layer.

of plasticity that further shapes the circuit output in an experience-dependent manner.

A majority of interneurons in the glomerular layer are GABAergic periglomerular (PG) cells. PG cells regulate glomerular activity through their synapses on mitral/tufted cell dendrites and OSN axon terminals. A subset of adult-born neurons differentiate into PG cells and replace old PG cells [10]. Each mature PG cell typically connects with a single glomerulus [11]. Recent work demonstrated that this uniglomerular connectivity is a result of refinement, as young adult-born PG cells tend to connect with multiple glomeruli and are more broadly tuned to odorants than mature PG cells [12]. Odor experience influences this refinement, and young adult-born PG cells increase their responsiveness to the experienced odors [12]. Mature PG cell synapses are also dynamic within the target glomerulus, while odor enrichment can reduce the structural dynamics of PG cell synapses [13]. Thus, PG cells contribute to olfactory bulb plasticity. However, because of their uniglomerular nature, PG cells are unlikely to contribute to lateral inhibition, which is probably crucial for pattern separation in the olfactory bulb.

Mitral and tufted cells

Mitral cells and tufted cells are the two types of projection neurons in the olfactory bulb located in the mitral cell layer and the external plexiform layer (EPL), respectively. Each mitral/tufted cell projects their single primary apical dendrite to only one glomerulus where they receive inputs from the axons of OSNs expressing the same receptor [11]. Mitral/tufted cells directly project their axons to higher structures in the brain and are the sole source of olfactory information for the rest of the brain. Thus, mitral/tufted cell activity is synonymous with the olfactory bulb output. Mitral/tufted cells extend their lateral dendrites in the EPL where they interact with local inhibitory neurons, providing an anatomical substrate for lateral inhibition in the olfactory bulb.

Odorants evoke temporally dynamic ensemble activity of mitral/tufted cells within single sniff cycles [14]. Much of the previous knowledge on odor coding by mitral/tufted cells came from recording in anesthetized rodents. However, recent results have revealed that odor responses of mitral/tufted cells in awake animals are markedly different from those under anesthesia [7,15–17]. Odor responses of mitral/tufted cells in awake animals are sparser, weaker, and more transient. Furthermore, during wakefulness, passive and repeated experience of the same odorants leads to a gradual and odor-specific reduction of mitral cell responses [7,8,19•]. This selective reduction of odor responses is long-lasting and slowly recovers over months [7]. Such an experience-dependent reduction in mitral cell responses makes the representations of familiar odors more efficient.

Mitral/tufted cell responses to similar odorants can be more distinct than overlapping OSN representations, and the degree of separation of mitral/tufted cell responses correlates with the success in discrimination learning [9]. An important question is whether olfactory perceptual learning, which is learning to discriminate initially indistinguishable odorants, further decorrelates mitral/tufted cell representations of similar odorants. Such a neural correlate of perceptual learning is often considered to be restricted to higher brain centers such as the cortex.

However, recent studies have challenged this traditional view and shown that olfactory perceptual learning enhances pattern separation of mitral cell ensemble activity to the learned odors [18••,19•]. Improved pattern separation during perceptual learning was more prominent in mitral cells compared to tufted cells [19•], raising the possibility that discrimination of similar odorants may rely largely on mitral cell response patterns. Another study showed that during rapid associative learning (as opposed to slower perceptual learning to discriminate similar odorants), mice modulated their sniffing patterns, which could contribute to changes in mitral/tufted cell responses. However, this study also pointed out that changes in sniffing patterns were insufficient to explain the entirety of the response changes of mitral/tufted cells [20], indicating that either rapid top-down modulation and/or plasticity of the circuits within the olfactory bulb are critical in regulating mitral/tufted cells. Indeed, rapid noradrenergic modulation has been proposed to improve the signal-to-noise of mitral cells [21].

An increase in pattern separation improves the robustness of representations such that the downstream readout mechanism can reliably distinguish the representations of similar odorants. However, considering that the capacity of the activity space (i.e. all possible population activity patterns) for mitral cells is limited, increased pattern separation comes with the cost of efficiency because an unnecessary separation would decrease the total number of stimuli that can be discriminated. Recent studies found that the robustness and efficiency of mitral cell representations may be balanced depending on the context of learning. As described above, perceptual learning to discriminate very similar odorants leads to a gradual increase in pattern separation of mitral cell responses, increasing the robustness of representations [18••,19•]. However, learning to discriminate quite different odorants results in a decreased separation of mitral cell responses, enhancing the efficiency of representations [18••]. As a result, after learning, the degree of separation becomes less dependent on how similar the odorant chemicals are. These results suggest that mitral cells attempt to compromise between robustness and efficiency of representations of behaviorally relevant odorants, perhaps to approach towards an optimal balance, depending on the statistical structure of their olfactory environment. This balancing process may involve online feedback control, as it can manifest quickly during task switching [22].

Granule cells

As summarized above, olfactory perceptual learning induces an improved pattern separation of odor representations by mitral cell ensembles. Such a pattern decorrelation is likely mediated by plasticity to generate circuits for selective inhibition that can amplify the difference between similar patterns of mitral cell activity [23].

Granule cells (GCs) are the main source of lateral inhibition in the olfactory bulb, extending dendrites in the EPL and forming reciprocal, dendrodendritic synapses with lateral dendrites of mitral cells. Mitral cell dendrites in the EPL secrete glutamate to excite GC dendrites, which in turn secrete GABA to inhibit mitral cells [24]. Consistent with the notion that GCs are essential for the increased pattern separation of mitral cells during perceptual learning, artificial activation of GCs can enhance pattern separation and improve odor discrimination [9,25], while inactivation of GCs decreases pattern separation and impairs odor discrimination [9]. Furthermore, associative olfactory learning can modify the GC-mitral cell connectivity, such that the strength of excitatory synaptic inputs from mitral cells to GCs increases in the rewarded-odor-responding regions of the olfactory bulb [26].

In addition to the apical input from mitral cells, GCs are the main cell type in the olfactory bulb that receives centrifugal feedback inputs from various brain areas including the anterior olfactory cortex, the piriform cortex, and neuromodulatory centers [27]. Mitral cells send outputs to the cortical regions that project back to the olfactory bulb, so cortical glutamatergic feedback projections to GCs effectively form multisynaptic feedback and lateral inhibition to mitral cells. These cortical feedback projections can exhibit long-term potentiation in slice experiments [28,29]. Furthermore, disruption of inhibitory feedback inputs onto GCs can affect olfactory discrimination [30,31], suggesting that these feedback pathways are essential for olfactory discrimination. Future work should further illuminate the underlying mechanism.

Perhaps due to their small size, standard extracellular recording of GCs has proven difficult, and thus little was known about their activity pattern *in vivo*. Recent studies with *in vivo* two-photon calcium imaging [7] and juxtacellular loose-patch recording [32] found that both spontaneous and odor-evoked activity of GCs is substantially enhanced during wakefulness compared to anesthesia. This is the opposite of mitral cells whose activity is sparser during wakefulness, suggesting that mitral cell activity in awake animals is more strongly influenced by GC inhibition than previously appreciated in anesthetized recordings. The state dependence of GC activity probably involves the centrifugal inputs from higher brain areas that are sensitive to brain state [33,34]. It is tempting to speculate that the main excitatory drive of GC activity may originate from the cortex rather than mitral cells [35].

~95% of adult-born neurons in the olfactory bulb differentiate into GCs. Young (within eight weeks after birth) adult-born GCs are particularly plastic [28] and therefore adult neurogenesis provides the GC population with a unique potential to contribute to the experience-

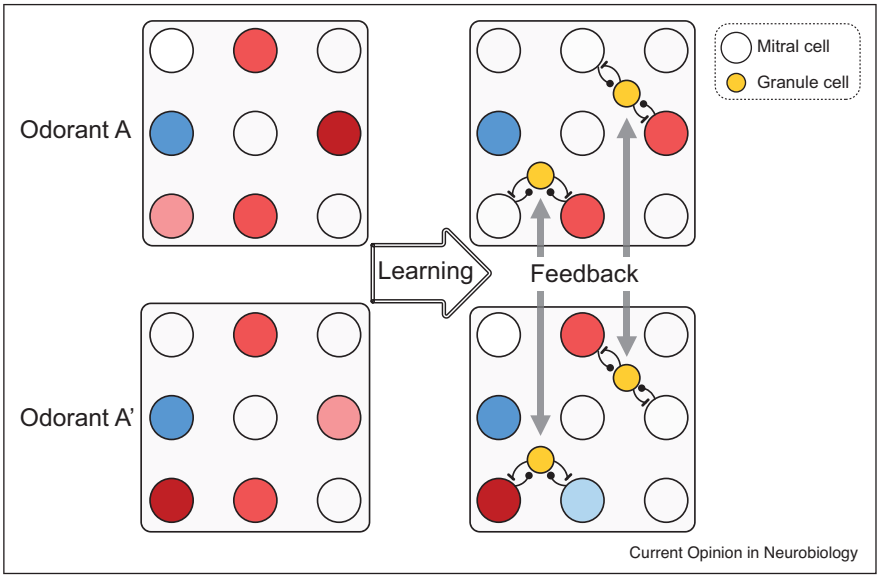
dependent modulation of the olfactory bulb output. Indeed, the maturation and connectivity of adult-born GCs is regulated by olfactory experience and learning. Olfactory learning enhances the survival of adult-born GCs, and this effect is dependent on noradrenergic feedback [36]. The spines of apical dendrites of GCs which synapse on mitral cells go through constant remodeling throughout life in both young and mature adult-born GCs [37] and these dynamics are reduced by odor enrichment [13]. Olfactory experience and learning increase the density of spines in the apical dendrites of adult-born GCs and thus their connectivity with mitral cells [38,39••,40], as well as induce LTP in the inhibitory GC-mitral cell synapses [41]. Apical dendritic spines of adult-born GCs are guided by BDNF released by mitral cells [42]. Similarly to the plasticity of apical synapses, learning strengthens the glutamatergic inputs from anterior olfactory nucleus to the basal dendrites of adult-born GCs [43]. Consistent with these findings, a recent study that compared the response properties of two genetically defined GC populations, one enriched with young adult-born GCs and the other enriched with mature GCs, found that mature GCs show broader responses than young adult-born GCs. Furthermore, associative learning selectively enhanced the responses of adult-born GCs to task-related odors [39••]. Another recent study performed longitudinal calcium imaging of the apical dendrites of adult-born GCs and found that individual dendrites narrow their odor tuning within the first weeks of the GC's birth. With odor enrichment (i.e. passive odor experience without explicit learning), the odor tuning of young adult-born GCs changed more dynamically but maintained its broadness [44•]. It will be interesting in the future to examine how this plasticity during the early maturation period relates to further integration of adult-born GCs during learning.

Taking together the results above, it seems that young adult-born GCs are selectively incorporated into the bulbar circuit to sculpt the olfactory bulb representations of familiar and behaviorally relevant odorants. A prediction of this idea is that ablation or inactivation of adult-born neurons would impair olfactory behaviors. However, previous studies that interfered with the functions of adult-born neurons have been conflicting, with some studies showing minor behavioral effects and others showing no effect. The weak to no effects are surprising given that the olfactory bulb receives thousands of adult-born neurons every day throughout adulthood, and it is difficult to imagine that such a costly process is maintained during evolution without important behavioral functions. A recent study provided a potential explanation for this discrepancy [45•]. In this study, it was found that genetic ablation of adult-born neurons reduces mitral cell pattern separation and impairs the learning of a very difficult discrimination task that involved eight very similar odor mixtures. However, the same mice were able to perform as well as wild-type mice in a standard, easy discrimination task. Importantly, ablation of a similar number of mature GCs did not have a strong behavioral effect [45•]. Complementing this observation from loss-of-function experiments, 40 Hz optogenetic activation of adult-born neurons can facilitate the learning of a difficult go/no-go olfactory discrimination task, but has little effect on an easy discrimination task [46]. Similarly, genetically enhancing adult neurogenesis by conditional expression of the cell cycle regulators Cdk4/cyclinD1 does not affect the performance in easy tasks, but it can facilitate the learning of a difficult go/no-go olfactory discrimination task [47].

These results support the notion that adult-born GCs have a privileged role to facilitate a fine discrimination of similar odorants. During their highly plastic period, adult-born GCs may establish stronger connections with mitral cells that are responsive to behaviorally relevant odorants. Such a specific connectivity could underlie selective inhibition that would decorrelate mitral cell responses to similar odorants (Figure 2). Even though the observation that non-selective activation of adult-born GCs can facilitate discrimination [46] may seem at odds with this model, we argue that non-selective activation could enhance selective plasticity. For example, the non-selective activation may enhance the selective integration of adult-born GCs that connect with task-relevant mitral cells through Hebbian plasticity. A larger decorrelation could also facilitate a more rapid discrimination at each odorant encounter, which may be important for certain behaviors. Even though it may seem that adult-born GCs have limited contributions to discrimination when the behavioral effects are apparent only in very difficult tasks, we speculate that these difficult tasks in simple lab settings uncover circuit functions that are frequently engaged in complex environments in which wild animals survive. Future studies tracking the activity of young adult-born GCs longitudinally during learning of a difficult discrimination task that requires adult-born GCs would provide additional insights into how adult-born GCs contribute to fine pattern separation of the olfactory bulb. Furthermore, a single cell transcriptomic analysis of GCs of different ages is beginning to uncover potential molecular mechanisms of plasticity of young adult-born GCs [48]. There is also evidence that GCs may contain molecularly and functionally distinct subtypes [49,50], which is an interesting topic for future investigations.

Motherhood has been studied as a special condition that drives olfactory bulb plasticity. For instance, motherhood induces enhanced mitral cell representations of natural and behaviorally relevant odors while weakening the representations for pure odors [51]. Such plasticity may be related to the mother's ability to identify and care for their pups. Furthermore, maternal behaviors are impaired in mothers that experienced stress during pregnancy, which limits the dendritic growth of young adult-born

Figure 2



A model of perceptual learning-related plasticity in the olfactory bulb. Similar odorants (A and A') evoke similar response patterns in mitral cells before learning (left). Perceptual learning induces pattern decorrelation of mitral cell representations of the learned odorants (right). The enhanced pattern separation is mediated by adaptive and selective lateral inhibition from granule cells, particularly adult-born granule cells. In addition to mitral cell inputs, granule cells also receive feedback innervation from higher brain centers, which enables context-dependent odor processing. Red circles: mitral cells with excitatory odor responses; blue circles: mitral cells with suppressive odor responses. The intensity of colors represents the strength of the responses. Yellow circles: granule cells.

GCs [52]. Although a direct link has not been established, it is possible that plasticity of young adult-born GCs drives the functional plasticity of mitral cells during motherhood and supports maternal behaviors.

Another interesting topic is whether learned valence information is represented in GCs. The increase of excitatory synaptic inputs onto GCs during associative olfactory learning may be stronger in the olfactory bulb regions that respond to the rewarded odor compared with GCs in unrewarded-odor-responding regions [26]. A recent study examined the expression of the immediate early gene cFos and suggested that young adult-born GCs, but not mature GCs, respond preferentially to odors associated with a reward [53]. However, another study using a similar go/no go task found that both rewarded and unrewarded odors are equally represented in adult-born GCs [39••]. There are also suggestions that the mitral/tufted cells encode valence information [54,55]. It remains unclear how strongly the olfactory bulb output is influenced by the associated value of odorants, and whether the learned valence representations in the olfactory bulb can directly drive reward-motivated behaviors.

Concluding remarks

Here, we reviewed the recent advances on plasticity of the rodent olfactory bulb. An emerging view is that the olfactory bulb is not a passive relay station but a dynamic signal processing unit that facilitates the encoding of behaviorally relevant odorants. An intriguing question is why the olfactory bulb evolved to be such a dynamic system that takes advantage of highly plastic adult-born neurons to constantly adjust the way it processes incoming sensory information, a strategy not utilized in other sensory systems. We propose that the answer to this question lies in a unique statistical feature of the olfactory world. Compared to other sensory systems that process stimuli correlated within the stimulus space (e.g. spatiotemporal correlation in vision and spectrotemporal correlation in audition), olfaction is uniquely combinatorial, where the inputs are combinatorial activation of ~1000 discrete and semi-independent channels. Even when assuming simple binary codes, 1000 channels can generate $\sim 10^{301}$ distinct combinations. In many cases, there is no prior knowledge about which of these astronomical number of combinations are behaviorally relevant, or which combinations should be generalized versus discriminated. We propose that olfactory bulb plasticity allows the olfactory system to adaptively allocate its limited resources to optimally represent relevant odorants, so that downstream areas can use these representations and associate them with behavioral outputs through learning. This is in contrast to other systems that have developmentally restricted crucial periods of high-level plasticity. The reason for the lifelong plasticity of the olfactory bulb may be hinted by the observation that the median survival duration of adult-born neurons is about a couple months, and at least one form of mitral cell

functional plasticity lasts for about this period [7]. A couple months is roughly the duration of individual seasons, each of which has a unique combination of odorants in the environment. The olfactory bulb may have evolved lifelong plasticity with a time constant to match the seasonal changes in the olfactory environment, from spring flowers to summer fruits to fallen leaves in the autumn.

Conflict of interest statement

Nothing declared.

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