Encyclopedia of Computational Neuroscience
DOI 10.1007/978-1-4614-7320-6_611-1

Olfactory Computation and Adult Neurogenesis

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Definition

The initial processing of olfactory information ("olfactory computation") by the brain is performed in the olfactory bulb. Strikingly, even in adult animals the largest population of neurons in this network is undergoing persistent turnover through neurogenesis and apoptosis, i.e., through the addition of new neurons and the subsequent death of a large fraction of them. This endows the network with computational power that yet has to be fully explored.

Detailed Description

Anatomy of the Olfactory Bulb

Olfactory processing begins with millions of olfactory receptor neurons (ORN) in the nasal epithelium. Each ORN expresses exactly one receptor gene, which determines the ORN's sensitivity spectrum across all odorants. The number of different active receptor genes ranges from 50 in drosophila and 350 in humans to over 1,000 in mice and rats (Murthy 2011). All ORNs expressing a given receptor gene project to a small number of glomeruli in the outermost layer of the olfactory bulb. Taken together, the inputs to all the glomeruli form an activation pattern or "olfactory image" that constitutes the first representation of an odor in the olfactory bulb. An initial reshaping of these patterns is performed in the glomeruli through intra- and inter-glomerular inhibition involving various types of periglomerular cells, external tufted cells, and short-axon cells (Fig. 1). Each glomerulus drives multiple mitral and tufted cells, which represent the principal cells of the olfactory bulb and project to various cortical regions.

A second reshaping of the odor representation arises from the mutual inhibition of mitral/tufted cells via granule cells, which constitute the largest population of neurons in the olfactory bulb. This inhibition is mediated by reciprocal dendrodendritic connections between mitral/tufted cells and granule cells on the secondary dendrites of the mitral/tufted cells. Since these dendrites can span across large fractions of the olfactory bulb, this inhibition can be long range. The reciprocal connections are comprised of glutamatergic, excitatory synapses from the mitral/tufted cells to the granule cells that are colocalized with GABAergic, inhibitory synapses from the granule cells back onto the respective mitral/tufted cells. The granule cells also receive centrifugal excitatory input from cortical structures like piriform cortex.

Physiology of Adult Neurogenesis

The olfactory bulb and the dentate gyrus are the only major brain areas in mammals to which new neurons are added in a steady stream even in adult animals. This has been best studied in rodents where on the order of 30,000, new interneurons arrive in the olfactory bulb every day (Kelsch et al. 2010). The vast majority of them develops into granule cells and a small fraction into

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DOI 10.1007/978-1-4614-7320-6_611-1

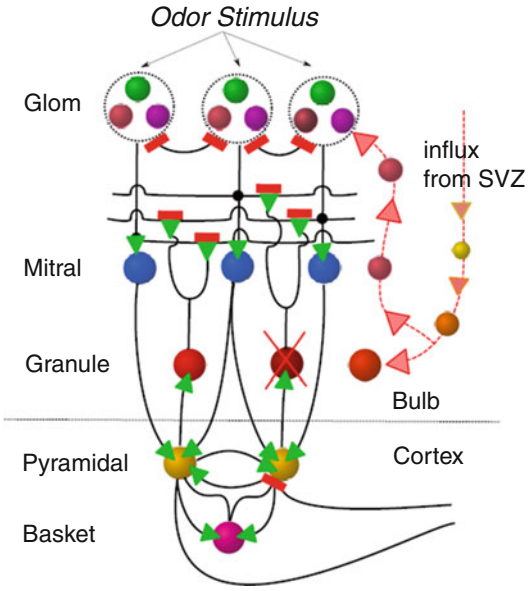

Fig. 1 Major cell types of the olfactory bulb and some of their connections with the cortex. The glomeruli (*glom*) are comprised of an ensemble of external tufted (*green*), periglomerular (*red*), and short-axon cells (*purple*). New adult-born periglomerular and granule cells arrive from the subventricular zone (*SVZ*). Excitatory (inhibitory) synapses are marked by *triangles* (*bars*)

periglomerular cells. Both cell types integrate functionally into the already established circuitry of the olfactory bulb. While a large fraction of the new neurons survives only for a brief period of 2–3 weeks, some new neurons survive for many months.

Adult-born periglomerular cells and granule cells differ in various aspects of their development (Lepousez et al. 2013). Periglomerular cells develop the ability to spike before their excitatory synaptic contacts appear and there is no strict order in which glutamatergic and GABAergic synapses are established (Kelsch et al. 2010). In contrast, in granule cells GABAergic inputs arise before glutamatergic ones, and the sodium currents that underlie action potentials develop only after synapses receiving excitatory inputs are formed. Moreover, the proximal synapses representing excitatory inputs from mitral cell axon collaterals and from cortical structures develop before the distal reciprocal synapses with mitral cells (Kelsch et al. 2010).

Even after their integration into the bulbar circuit, the adult-born cells undergo further development. Young adult-born periglomerular cells are more excitable than mature ones; this may also hold for granule cells (Lepousez et al. 2013). Proximal synapses of granule cells can undergo significant long-term potentiation, but only while the cells are young (Kelsch et al. 2010). Structurally, however, even in mature adult-born granule and periglomerular cells, the synapses exhibit substantial turnover, which is reduced in response to enriched odor exposure (Livneh and Mizrahi 2012).

The most striking feature of periglomerular cells and granule cells is the precise regulation of their survival and death. Their survival probability strongly depends on environmental factors. Odor enrichment during a critical period enhances their survival, while odor deprivation reduces it. In granule cells the critical period lasts from about 14 to 28 days after they are born (Lazarini and Lledo 2011); it begins therefore before the granule cells' distal synapses with the mitral cells are developed. The survival of periglomerular cells is sensitive to enrichment at least for 6 weeks. The detailed mechanisms controlling the survival are not yet understood. It is clear, however, that the apoptosis is the result of a precisely regulated program that removes the cells predominantly during postprandial

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slow-wave sleep (Lepousez and Lledo 2011). On the cell level, survival is enhanced if the excitability of granule cells is increased by genetic means and vice versa (Kelsch et al. 2010).

Impact of Adult Neurogenesis on Behavior

Adult neurogenesis has substantial impact on the ability of animals to discriminate similar odors and to retain odor memories. Spontaneous odor discrimination is often assessed using a habituation task that makes use of the fact that animals lose interest in an odor that is presented repeatedly. If after habituation to an odor an animal explores a new odor significantly longer, it is clear that it is able to discriminate between the two odors. It has been found that mice can learn to discriminate spontaneously between very similar test odors if they are presented repeatedly over the course of 5–10 days with odors that are related to the test odors. This perceptual learning is compromised if adult neurogenesis is suppressed (Lazarini and Lledo, 2011).

Adult neurogenesis plays also a role in memory. In the habituation task, mice with intact neurogenesis remember an odor after a single exposure for at least 120 min. With adult neurogenesis suppressed, however, they treat a repeated odor as a novel odor after as little as 60 min. Similarly, in a long-term memory task in which mice have to retrieve a reward from one of the two odorized holes, intact animals remember the correct odor association for 5 days, while animals without neurogenesis do not. Interestingly, even though animals with and without functional neurogenesis do not remember an odor any more after 30 days, the intact animals relearn the previously memorized odor faster than those with suppressed neurogenesis (Sultan et al. 2010). It is important to note that this enhancement of long-term memory through neurogenesis is only found when the animals are trained on an operant task, i.e., if the animals actively have to associate an odor with a decision. Tasks in which the relevant odor is only passively associated with a reward do not enhance neurogenesis and their memory is not compromised when neurogenesis is suppressed (Lazarini and Lledo 2011).

Computational Modeling

So far, adult neurogenesis in the olfactory bulb has been studied from a modeling perspective only to a limited extent. Motivated by the general notion of the importance of contrast enhancement in early sensory processing and by the observation that in zebra fish the olfactory bulb reshapes odor representations such that the correlation between the activity patterns representing similar odors is reduced (Friedrich and Laurent 2001), the focus has been on the decorrelating function of the olfactory bulb.

Due to the high dimension of odor space, the two-dimensional activity patterns evoked by odor stimuli in the input layer of the olfactory bulb are fractured. Thus, in contrast to the stimuli of the visual, auditory, and somatosensory system, these patterns are not characterized by a smooth map. Instead, the chemical response spectra of neighboring glomeruli are not much more similar than those of glomeruli that are far apart (Murthy 2011). A neuronal network that has to process such complex activation patterns is quite likely to reflect that complexity. Surprisingly, sparse random networks of thresholding neurons quite effectively decorrelate such patterns (Wiechert et al. 2010).

At the same time, it has been pointed out that many odors do not have an inherent meaning to animals and that the interpretation of these odors is learned by experience (Wilson and Stevenson 2006). This suggests that the olfactory networks adapt to their odor environment. From this perspective it is natural to assume that one role of the turnover of interneurons in the olfactory bulb is to restructure the network and to enable it to adapt to the demands of the animal's environment. Such processes could generate networks that reflect the complexity of the representations of the relevant odorants.

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In an early adaptive computational model, the effective mutual inhibition between pairs of mitral cells was taken to depend on the product of their activities, averaged across an odor ensemble (Cecchi et al. 2001). This simple evolution of the effective inhibition was sufficient to allow the network to learn to decorrelate the stimuli. In later work the granule cells were modeled explicitly with a steady stream of new cells connecting to randomly chosen mitral cells through reciprocal synapses (Chow et al. 2012). It was found that if the cells' survival required that their activity across an odor ensemble surpass a threshold, such networks learn to decorrelate even very similar stimuli. This process could underlie the neurogenesis-dependent perceptual learning observed experimentally. As had been found experimentally, new granule cells were found to be more likely to respond to novel odors in this model. The decorrelation achieved by this network can be understood to arise in part from a normalization in which the activities of different mitral cells – averaged across the odor ensemble – are evened out.

Possible consequences of the experimentally observed enhanced excitability and plasticity of young adult-born interneurons have not yet been explored theoretically.

Conclusion

Adult neurogenesis represents a fascinating aspect of olfactory computation. It plays an important role in the processes underlying odor discrimination and memory. Modeling has so far only elucidated its possible role in odor decorrelation, which may contribute to odor discrimination. Since the granule cells involved in the neurogenetic turnover receive substantial direct glutamatergic input from cortical areas, it seems likely that adult neurogenesis plays a much more refined role in odor processing than is apparent in experiments so far. What this role might be is yet unknown.

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DOI 10.1007/978-1-4614-7320-6_611-1

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