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Odor representations in mammalian cortical circuits

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Summary

Spatial and temporal activity patterns of olfactory bulb projection neurons underlie the initial representations of odors in the brain. However, olfactory perception ultimately requires the integration of olfactory bulb output in higher cortical brain regions. Recent studies reveal that odor representations are sparse and highly distributed in the rodent primary olfactory (piriform) cortex. Furthermore, odor-evoked inhibition is far more widespread and broadly tuned than excitation in piriform cortex pyramidal cells. Other recent studies highlight how olfactory sensory inputs are integrated within pyramidal cell dendrites and that feedback projections from piriform cortex to olfactory bulb interneurons are a source of synaptic plasticity.

Introduction

Considerable effort has focused on exploring the features of circuits in the neocortex that contribute to visual, auditory, and somatosensory perception. Indeed, studies of sensory regions of neocortex underlying these three modalities have revealed a wealth of fundamental principles. Despite the uniqueness of the stimuli underlying these different sensory modalities, features ranging from the large-scale topographical arrangement of cortical sensory representations to the cellular mechanisms governing stimulus-specific activity often appear remarkably conserved.

In addition to light, sound, and touch the sense of smell plays a vital role in the ability of all animals to experience the external world. Whether it is the scent of a lover or the aroma of our morning coffee, olfactory perception is an important factor in our quality of life. Olfaction is evolutionary primitive and critical for the survival of many animal species—finding food, searching for mates, and avoiding predators are just a few behaviors that rely on odor detection and discrimination.

The molecular logic of the odorant receptors (ORs) expressed by olfactory sensory neurons (OSNs) has provided remarkable insight into the initial steps of odor coding [1]. Recent studies have also revealed how activity from OSNs is transformed into odor representations within the olfactory bulb [2,3], the first site in the brain that processes olfactory stimuli. However, the mechanisms governing the representation of olfactory information in higher brain regions have been much less explored. This review will highlight recent studies of the primary olfactory

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(piriform) cortex, a region that plays a critical role in odor discrimination and recognition [4, 5].

Initial odor coding in the brain

In rodents, olfactory information is first processed in the olfactory bulb, where OSNs expressing one of ~1000 different types of ORs map onto ~1800 glomeruli [6]. OSNs that express the same receptor converge onto one or two glomeruli and imaging experiments have shown that different odorants elicit distinct spatial patterns of glomerular activity [7–9]. A recent imaging study of mice and rats revealed great precision across animals (and species) in the spatial layout of glomeruli in relation to their odor sensitivity [10]. Imaging studies consistently find evidence for a coarse “chemotopic” map: glomeruli responsive to chemically related odorants are clustered within large domains of the bulb, but neighboring glomeruli can be as diverse in their odor sensitivity as distant ones. Within each glomerulus, 50–100 mitral and tufted (M/T) cells receive input from OSNs expressing a unique type of odorant receptor and thus M/T cell activity is thought to represent particular odorant molecular features. Recent studies also suggest that temporal patterns of M/T cell activity contribute to the initial representations of odor identity in the brain [11–14].

The axons of M/T cells coalesce to form the lateral olfactory tract (LOT) and make direct projections to the cortex. Thus, unlike other sensory systems, olfactory signaling is not passed to higher brain regions via a thalamic relay. A number of cortical areas (the olfactory tubercle and peduncle, entorhinal cortex, and amygdala) receive direct synaptic input from M/T cells, but the largest olfactory area is the piriform cortex [4]. In contrast to the six-layered structure of sensory neocortex, the phylogenetically older piriform cortex has a simpler three-layered architecture. Intriguingly, the expression of a single transcription factor (Lhx2) during a critical period of embryonic development regulates whether telencephalic progenitors generate piriform or neocortex [15].

Olfactory input to piriform cortex

Layer 2/3 pyramidal cells, the major principal cells in piriform cortex, receive glutamatergic input from LOT fibers onto their distal apical dendrites in layer 1. In slices of piriform cortex, pyramidal cells are driven to fire spikes by coincident activation of multiple LOT inputs [16]. Thus, pyramidal cells integrate information from multiple M/T cells and one simple presumption is that individual pyramidal cells pool input from M/T cells belonging to different glomeruli. Consistent with this idea, in vivo extracellular recording in piriform cortex has found that individual neurons fire spikes in response to multiple odorants [5,17,18]. However, exactly how many glomeruli project to single pyramidal cells and whether those glomerular combinations are deterministic or simply random are unknown. The development of single cell transsynaptic tracing techniques [19] could be used to answer these fundamental wiring questions.

Odors are represented by distributed cell ensembles in piriform cortex

A natural question is whether the exquisite spatial arrangement of OR input to olfactory bulb glomeruli extends to higher brain regions. Immunohistochemical studies have taken advantage of odor-evoked immediate early gene expression to examine how individual odorants are spatially represented in piriform cortex [20,21]. Individual odorants induced Fos expression in subsets of pyramidal cells that were sparsely distributed throughout piriform cortex. The distinct, yet partially overlapping patterns of labeled cells generated by different odorants did not reveal a precise chemotopic map in piriform cortex. However, Fos imaging is limited to the detection of responses of cells to only a single odorant and the mechanisms underlying Fos induction are unclear.

In vivo 2-photon calcium imaging has recently been used to explore how large populations of pyramidal cells in mouse piriform cortex represent odorants [22]. The advantages of this approach for mapping odorant representations are the ability to survey responses to a variety of odorants within the same populations of cells and the idea that somatic calcium signals can be interpreted as readout of cell spiking. A key finding was that different odorants each activated 3–15% of the imaged pyramidal cell population. Each odorant activated distinct cell ensembles that were spatially dispersed across the cortex and individual cells within each ensemble could respond to different odorants. The unique but overlapping cell ensembles activated by different odorants did not reveal any "patchiness" or spatial preference. Together, these findings indicate that individual cells possess discontinuous receptive fields and that cells with widely differing receptive fields are interspersed across piriform cortex. Apparently, unlike sensory regions of neocortex where cells responsive to similar stimulus features are spatially clustered, piriform cortex uses a completely different organizational principle.

In vivo patch clamp recordings provide further evidence for the distributed nature of odorant representations in rat piriform cortex [23]. Cell-attached recordings of spikes from a large set of individually sampled layer 2/3 cells were used to infer the distribution of odor-evoked firing activity across the cortical population. Despite their structural diversity, application of unique odorants each activated ~10% of tested cells—remarkably similar to the population response derived from calcium imaging [22]. Odorant responses typically consisted of weak increases in firing rate, while only a small fraction of cells fired strongly. Together, these features suggest that odorant representations are "sparse" in mammalian olfactory cortex. Sparse population coding has also been described in the higher olfactory centers of insects [24,25], suggesting that this coding strategy may be highly conserved across diverse species.

Local inhibitory circuits shape odor representations in piriform cortex

What mechanisms contribute to the sparse odorant-evoked firing of pyramidal cells in piriform cortex? In vivo intracellular voltage-clamp recordings of odorant-evoked excitatory and inhibitory postsynaptic currents (EPSCs, IPSCs) provided some clues [23]. Across the cortical population, odorant-evoked GABAergic inhibition appeared widespread while excitation was less common. In individual pyramidal cells, excitation was odorant-specific and inhibition was nonselective. Recordings from interneurons suggested a basis for "global" inhibition in piriform cortex: in contrast to pyramidal cells, odorant-evoked excitation in local interneurons was ubiquitous and individual interneurons were excited by many different odorants. Global inhibition is likely to contribute to sparse odorant representations by ensuring that only pyramidal cells receiving strong and preferred excitation are driven to spike.

In visual, auditory, and somatosensory cortex synaptic excitation and inhibition are largely co-tuned to the same stimuli [26–29]. While pyramidal cells in sensory neocortex receive "balanced" excitation and inhibition, excitation precedes inhibition in response to brief impulse-like stimuli and the relative timing between excitation and inhibition shapes stimulus selectivity and precisely timed spike output. GABAergic inhibitory circuits also regulate the integration of LOT input and spike timing in piriform cortex [23,30]. In slice recordings of pyramidal cells, LOT stimulation evokes EPSCs that are followed ~10 ms later by IPSCs [30]. This inhibition targets the soma, appears to arise from interneurons recruited in a feedforward manner, and generates a narrow time window in which pyramidal cells can integrate EPSCs and reach spike threshold. Thus, local inhibition may also enforce coincidence detection in pyramidal cells and promote the representation of sensory inputs from the olfactory bulb that are closely time locked.

The diversity of interneuron networks in piriform cortex is just beginning to be characterized [31,32]. Future studies will likely establish that distinct classes of interneurons govern

particular features of information processing (i.e. gain control, noise suppression, odor-evoked oscillations) in piriform cortex.

Dendritic integration of sensory input in pyramidal cells

The intrinsic properties of pyramidal cell dendrites are also poised to influence the integration of sensory input in piriform cortex. Indeed, the anatomical segregation of LOT inputs onto the distal apical dendrites of pyramidal cells is ideal for studying dendritic integration. Recently, a study combining dual patch-clamp recordings along the soma-apical dendritic axis, calcium imaging, and computational modeling revealed that the properties of pyramidal cell dendrites in piriform cortex differ markedly from those in neocortex [33]. Although apical dendrites actively supported backpropagating action potentials (APs) and local calcium entry, distal dendritic excitation did not produce local spikes that influenced somatic AP output. Calcium imaging provided insight into the mechanism limiting the excitability of distal apical dendrites in piriform cortex [34]. In this study, high expression of A-type K^+ channels in distal apical dendrites was found to attenuate the ability of backpropagating APs to generate distal calcium signals. In contrast to the strong influence of local dendritic spikes on integrative processes in neocortical neurons [35], regenerative dendritic events do not appear to contribute to the processing of LOT input in piriform cortex. Rather, experiments and simulations suggest that pyramidal cell output follows the linear somatic summation of LOT inputs distributed diffusely across their distal apical dendrites [33].

Feedback from piriform cortex to olfactory bulb

In addition to conveying information to a large range of other cortical regions, the axons of pyramidal cells in piriform cortex also make dense projections back to the olfactory bulb [4]. These excitatory feedback connections target olfactory bulb granule cells, the main GABAergic interneurons that govern self and lateral dendrodendritic inhibition of M/T cells [3]. Activation of facilitating glutamatergic inputs from piriform cortex onto the proximal dendritic spines of granule cells has been shown to facilitate mitral cell self-inhibition [36, 37]. This excitatory feedback modulation of M/T cell inhibition may contribute to beta-frequency oscillations in odor-evoked activity observed in the olfactory bulb and piriform cortex [23,38].

Recent reports of synaptic plasticity at the contacts made by cortical feedback inputs onto granule cells suggest these synapses may also play a role in olfactory learning. Tetanic stimulation of proximal (presumably cortical) excitatory inputs onto granule cells in olfactory bulb slices produced a long-term potentiation (LTP) of synaptic strength [39,40]. The same tetanic stimulation that triggered granule cell LTP also produced a long-lasting enhancement of cortically-evoked, disynaptic inhibition onto mitral cells [39]. Granule cells are particularly intriguing since they are renewed throughout adult life from precursor cells in the subventricular zone [41]. This ongoing neurogenesis provides structural plasticity in the adult olfactory bulb and newborn granule cells are thought to enhance olfactory perception and memory [41]. Using viral labeling to distinguish adult-born granule cells, LTP was often found in cells shortly upon their arrival in the olfactory bulb but this property faded as the newborn neurons matured [40]. Thus, newborn granule cells may be particularly sensitive to synaptic plasticity. One could easily argue at this point that a role for this synaptic plasticity in olfactory learning remains far from certain. Nonetheless, LTP of cortical inputs to inhibitory granule cells provides an intriguing mechanism to regulate the spatial and temporal firing patterns of M/T cell activity.

Conclusions

Together, these studies indicate some notable differences in how sensory information is represented and processed in the piriform cortex compared to sensory regions of neocortex. Olfactory cortical representations are dispersed and overlapping rather than spatially clustered and there does not appear to be a chemotopic order in piriform cortex. Furthermore, unbalanced synaptic excitation and inhibition underlie firing activity that is sparse across the olfactory cortical population. Unlike the case in neocortex, the distal apical dendrites of pyramidal cells are only weakly excitable and local dendritic spikes do not contribute to somatic AP initiation. Many of these features may reflect specializations to accommodate the immensity of potential odorants animals may experience throughout life.

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