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Olfactory Computation in Glomerular Microcircuits

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Definition

The first, superficial computational layer of the vertebrate olfactory bulb consists of discrete spheroid clusters of neuropil known as glomeruli. Within these glomerular microcircuits, primary olfactory sensory neuron axonal arbors interact with the dendrites of olfactory bulb principal neurons and multiple classes of local interneurons. The computations within and among these glomerular microcircuits determine how the primary sensory information arriving in the olfactory bulb is transformed prior to subsequent computations in the deep olfactory bulb and other regions of the brain. Among the important computations in the glomerular layer are a high-dimensional form of contrast enhancement and a competitive global normalization of activity levels across a population of second-order sensory neurons.

Detailed Description

The Olfactory Bulb

The olfactory bulb (OB) is the target of primary olfactory sensory neuron (OSN) axons that project across the blood-brain barrier at the cribriform plate (Fig. 1). Each OSN expresses, canonically, one type of odorant receptor protein from a family of hundreds (depending on species), and the specific receptor protein expressed determines the chemoreceptive field of that OSN. Critically, the axons of "sister" OSNs that express the same receptor converge together and arborize in the same location, forming a spheroid tangle of neuropil that is visible at the light microscopic level and known as a *glomerulus*. Inhaled odorants will bind to multiple odorant receptors with different affinities and hence will activate multiple glomeruli to differing degrees in patterns characteristic of that odor. These odor-specific patterns of glomerular activation are the basis for odor recognition.

Odor information is exported from the OB and propagated into the rest of the brain via mitral cells (Mi) and middle/deep tufted cells, the principal neurons of the OB. Importantly, while mitral cells can be activated directly by OSN input to glomeruli, the majority of their afferent excitation appears to be indirect, mediated via external tufted (ET) cell interneurons (Fig. 1). Mitral cell output also is strongly regulated by interactions with local interneurons within the glomerular-layer microcircuit (as well as a deeper layer of OB

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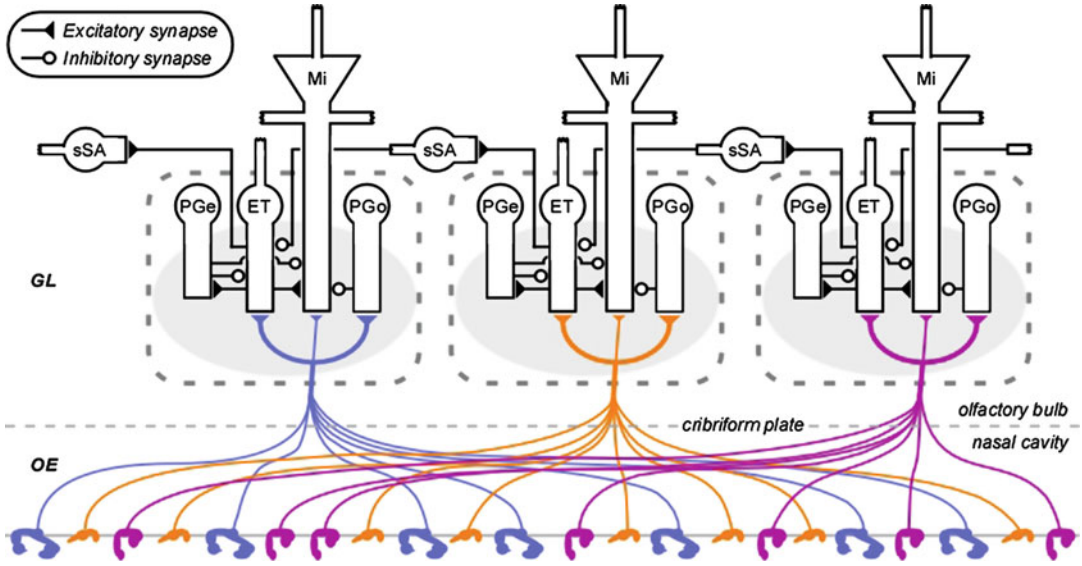

Olfactory Computation in Glomerular Microcircuits, Fig. 1 Schematic diagram of glomerular microcircuitry in the olfactory bulb. Three different classes of olfactory sensory neuron in the olfactory epithelium (OE) of the nasal cavity project to three corresponding glomeruli (gray ovals) in the olfactory bulb glomerular layer (GL). Within each glomerulus, the sensory neurons activate principal neurons including mitral cells (Mi) and middle/deep tufted cells (not shown) as well as local interneurons including the excitatory external tufted (ET) cells and the inhibitory periglomerular (PG) and superficial short-axon (sSA) cells. Some PG cells receive direct afferent input from olfactory sensory neurons (PGo), whereas the majority receive their afferent input indirectly via external tufted cells (PGe). PG and sSA neurons – particularly the latter – interconnect glomeruli nonspecifically, ultimately delivering broadly sourced feedback inhibition onto mitral cells (Banerjee et al. 2015) via intermediary ET cells (Whitesell et al. 2013). Deep bulbar circuitry (the interconnectivity of mitral cell lateral dendrites with granule cells) is not depicted

circuitry not discussed here) that transform these raw afferent representations; these local interactions also appear to act on mitral cells predominantly via ET cells (Whitesell et al. 2013). Specifically, as in other sensory systems, these early transformations of olfactory inputs include (1) the dynamic sharpening of primary sensory representations (Cleland 2010), (2) mitigation of the confounding effects of stimulus intensity (i.e., odorant concentration; Cleland et al. 2011), and (3) the constraining of absolute input intensity to levels that can be managed by follower circuitry. Unlike other sensory systems, however, the similarity space in which olfactory representations are embedded is computationally high-dimensional. Hence, similarity-dependent computations such as contrast enhancement (aka sharpening of the representation, a form of signal decorrelation) require algorithmic solutions capable of computing in high-dimensional spaces. These solutions are implemented in the microcircuitry of the OB glomerular layer.

High Dimensionality

The high dimensionality of the system arises from the diversity of primary odorant receptors and the lack of a common physical basis function by which to organize their receptive fields. The chromatic receptive fields of the three types of cones in the human retina share the common basis of wavelength, and the diverse receptive fields of auditory hair cells all can be mapped along a one-dimensional basis of auditory frequency, but the receptive fields of olfactory receptors are essentially arbitrary with respect to one another. Given that, for any pair of odorant receptors, a ligand exists that will activate one and not the other, each odorant receptor type must be treated as independent. The similarity space that can contain all possible odorant inputs therefore has the same

dimensionality as the number of different odorant receptor types expressed – over 1000 in mice, roughly 350–400 in humans.

Critically, of course, not all possible odorant inputs or combinations thereof are equally likely. In any given, finite universe of odorants, the dimensionality of odor space can be reduced, often substantially. (Indeed, the putative dimensionality of olfactory similarity space has been measured in some studies, though the results obtained in these studies have more to do with the particular, limited set of odorants selected than with the nature of the olfactory system per se). A corollary of this principle is that any quantitative description of olfactory similarity space depends on the statistical structure of the olfactory environment – that is, how likely is it that any given odorant from this environment will differentially activate any given pair of odorant receptors? If the olfactory system is to be able to interpret any possible combination of receptor inputs received, then the high dimensionality of the input space is unavoidable.

Glomerular Microcircuitry

In general, each half of each OB in mice contains one glomerulus for each olfactory receptor type, to which the converging axons of that family of OSNs project (Mombaerts 2006). Because the high dimensionality of the olfactory similarity space cannot be continuously projected onto the two-dimensional surface of the OB, physical proximity cannot serve as a proxy for receptive field similarity as it can, for example, in the retina or the cochlear nucleus. The classical algorithm, nearest-neighbor lateral inhibition, therefore can be ruled out as an effective solution for olfactory contrast enhancement.

Instead, each intraglomerular microcircuit effectively generates its own inhibitory surround in olfactory similarity space by generating feedforward inhibition of its own mitral cells that successfully inhibits excitatory throughput when the glomerulus is weakly or moderately activated, but that is overcome by direct OSN-to-mitral excitation when the glomerulus is strongly activated. That is, stimulation in the center of the chemoreceptive field is propagated, whereas stimulation at the edge of the chemoreceptive field is inhibited below baseline. By eschewing competitive connections among different glomeruli, this non-topographical contrast enhancement algorithm is independent of olfactory dimensionality and will function irrespective of how many different olfactory receptors exist and irrespective of the comparative similarities of their receptive fields in any given environmental context (Cleland and Sethupathy 2006; Fukunaga et al. 2014). Moreover, the degree of sharpening produced by this microcircuit can be dynamically regulated by top-down inputs, such as cholinergic neuromodulation (Chaudhury et al. 2009; D'Souza and Vijayaraghavan 2012).

Non-topographical contrast enhancement uses relative levels of afferent excitation at each glomerulus as a proxy for ligand-receptor potency at the corresponding olfactory receptor and hence depends upon the global normalization of input activation levels across glomeruli to mitigate the confounding effects of concentration. Global feedback normalization preserves relational patterns of activity among glomeruli while also serving to constrain absolute afferent input levels within the relatively narrow dynamic ranges of follower neurons. In the OB, several mechanisms appear to contribute to the latter goal of matching absolute input activity levels to the needs of follower circuitry while preserving sensory information (Cleland et al. 2011); one of these in particular also underlies the competitive global normalization necessary to generate relational representations (Cleland et al. 2007; corrected implementation in Banerjee et al. 2015). Specifically, glomeruli across the OB are interconnected by a heterogeneous, laterally projecting network of GABAergic/dopaminergic periglomerular (PG) and superficial short-axon (sSA) cells.

Note that the nomenclature of these glomerular-layer inhibitory interneurons is evolving. The majority of these neurons express GAD67 and DAT and release both GABA and dopamine. This population is morphologically diverse and sometimes is treated as a single heterogeneous class (e.g., the DAT+ neurons of Banerjee et al. 2015), comprising most of the classically defined PG neurons and all of the classically defined sSA

neurons. More recent work has established a clearer class difference within this heterogeneous population that corresponds reasonably to distinct PG and sSA cell types; specifically, GAD67+/DAT+ neurons with large somata and axons correspond to the sSA class, while those with smaller somata and no axon initial segment correspond reasonably to the PG class (Galliano et al. 2018). The PG class can be subdivided further into PGe and PGo subtypes by virtue of whether or not they receive direct input from the olfactory nerve (Fig. 1). Finally, a separate, smaller class of GAD65+, non-dopaminergic interneurons also is often grouped into the PG cell category and may contribute to both PGe and PGo morphological subtypes (discussed in Sethupathy et al. 2013).

Activation of these neurons inhibits mitral cells broadly across the OB, thereby feeding back a globally averaged level of inhibition across the mitral cell population that can mediate gain control (Banerjee et al. 2015). This operation constrains the dynamic ranges of absolute MC activation levels, thereby fulfilling a necessary prerequisite for non-topographical contrast enhancement (Cleland et al. 2007).

Summary

Glomerular microcircuitry in the OB is able to regulate the sharpening of sensory representations and normalize absolute input intensities so as to deliver more consistent and reliable sensory information to the neural circuitry of the deep OB, as well as to extrabulbar follower regions such as the anterior olfactory nucleus, piriform cortex, and olfactory tubercle. Additionally, lateral projections by ET cells selectively connect "sister" glomeruli (associated with the same odorant receptor type) across the OB and modulate the response properties of associated mitral cells (Zhou and Belluscio 2008). External tufted cells also are intrinsically resonant at roughly respiratory frequencies, bursting rhythmically when activated (Hayar et al. 2004), and may serve to temporally coordinate strongly activated and weakly activated regions of the OB. Mitral cells also are intrinsically resonant, but at a faster beta-band frequency (Desmaisons et al. 1999); their resonance may govern the transformation of OB output into an energetically efficient metric based on spike timing that is relevant to computations within deep OB circuitry (Li and Cleland 2017) and potentially plastic. The essential function of glomerular layer microcircuitry appears to be to manage the physical complexities of odorant inputs, such as high dimensionality and uncontrollable stimulus intensities, thereby transforming afferent odor representations into a more manageable, diagnostic, and energetically efficient form.

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Further Reading

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