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Neural and behavioral mechanisms of olfactory perception

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Abstract

Recent *in vivo* and *in vitro* studies have challenged existing models of olfactory processing in the vertebrate olfactory bulb and insect antennal lobe. Whereas lateral connectivity between olfactory glomeruli was previously thought to form a dense, topographically-organized inhibitory surround, new evidence suggests that lateral connections may be sparse, non-topographic, and partly excitatory. Other recent studies highlight the role of active sensing (sniffing) in shaping odor-evoked neural activity and perception.

Introduction

Sensory perception depends on the way sensory signals are transformed by neural circuits in the central nervous system. Moreover, our earliest perceptions of a stimulus often modify the way we interact with that stimulus, and this behavioral reaction in turn modifies central representations and ultimately our perceptions.

These events are relatively well-understood for some sensory modalities—especially vision—and much less well-understood in olfaction. Olfaction is an important topic in its own right because it has a critical importance in the lives of many organisms. Moreover, by comparing olfactory processing with processing in other sensory modalities, we are more likely to grasp which principles are fundamental to sensory processing in general, and which are peculiar to a specific modality.

This review will discuss recent advances in central olfactory processing. The first part of the review will focus on circuits and computations in the first brain region in the olfactory system. The second part will examine how odors are actively sampled by organisms, and how odor-evoked changes in sampling behavior affect the way the brain responds to odors.

Circuits and computations in the olfactory bulb and antennal lobe

The vertebrate olfactory bulb—and its insect analog, the antennal lobe—is the first brain region in the olfactory system. In most species, this region is divided into discrete glomeruli, each corresponding to a distinct type of olfactory receptor neuron (ORN) [1]. Glomeruli are also laterally interconnected by local interneurons.

In the classical view, an olfactory bulb mitral/tufted (M/T) cell is excited by direct ORN input to the glomerulus innervated by its apical dendrite, and indirectly inhibited by input to neighboring glomeruli [2,3]. If we treat the glomerular array as the “input space” of a M/T cell,

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then the classical M/T receptive field would comprise a small excitatory center surrounded by a much larger inhibitory annulus [4]. Nearby glomeruli are thought to have similar odor tuning, and so lateral interactions would thus occur preferentially between neurons receiving correlated ORN input.

In the last several years, new results have challenged this model. In addition, new data from the insect antennal lobe have revealed surprising similarities and differences between these brain regions.

Lateral inhibition may be sparse

One prediction of the classical model is that, on average, the number of stimuli that inhibit an olfactory bulb M/T cell should be larger than the number of stimuli that excite it. This would be expected if the inhibitory surround is dense, and if it occupies a larger region than the excitatory center [4]. However, when M/T cell receptive fields were mapped much more systematically than in previous studies, using odor concentrations that activate only sparse excitatory responses in M/T cells, the inhibitory input evoked by these stimuli was also sparse [5]. This result suggests that a M/T cell does not receive lateral inhibition from a large number of glomeruli—in other words, lateral inhibitory networks are unlikely to be very dense. In future, a combination of functional imaging and electrophysiological recording should resolve this apparent discrepancy with earlier studies.

Lateral connections are not limited to nearest neighbors

In the classical view, only nearest-neighbor glomeruli inhibit each other. However, the concept of strictly “topographic” lateral inhibition has been challenged by a new anatomical study [6]. A retrograde transsynaptic viral tracer was injected focally into a small region of the rat olfactory bulb comprising a handful of glomeruli. The classical model would predict that the connections onto these glomeruli should arise from a dense annulus that falls off with distance from the injection site. Contrary to this prediction, the retrograde tracer was transported into a sparse population of glomeruli distributed widely throughout the entire olfactory bulb. This result is consistent with the idea that lateral connectivity is sparse, and also implies that lateral connectivity does not vary in a graded fashion with distance.

Challenging the importance of chemotopic lateral connectivity

In the classical model, glomeruli are arranged on the surface of the bulb so that glomeruli with similar odor selectivity are located near each other. Currently, there is evidence in favor of this type of “chemotopy”, but there is also evidence against it [reviewed in 7]. What is needed is a systematic mapping of the odor selectivity of many spatially-localized glomeruli using a large set of chemically diverse odors.

If the spatial position of glomeruli is not strongly chemotopic, what alternative rules might govern these connections? Glomeruli with similar odor tuning might still be preferentially connected, but these networks would have to be long-range and sparse rather than local and dense [6]. Alternatively, lateral connections might be specific, but governed by a different logic (e.g., connected glomeruli might be tuned to chemically dissimilar odors that tend to co-occur in natural environments). Finally, lateral connections could be rather non-specific, perhaps even global. In this scenario, each glomerulus would receive an inhibitory signal which reflects the total level of activity in all glomeruli. The consequences of uniform, global inter-glomerular inhibition have been explored in a recent theoretical study [7]. It was found that this type of network can act as a form of gain control, tending to keep M/T cell activity within a limited dynamic range. Moreover, it tends to decorrelate the output of different glomeruli. Thus, even non-specific connectivity can still be computationally useful.

There is new experimental evidence for this type of uniform, global lateral inhibition in the *Drosophila* antennal lobe [8]. Lateral inhibition onto two different glomeruli was measured in response to a variety of odors. The lateral inhibitory signals received by the two glomeruli were found to be quite similar, although the ORNs corresponding to these two glomeruli have rather different odor preferences. Moreover, the amount of lateral inhibition evoked by an odor was proportional to the total number of ORN spikes triggered by that odor. These results suggest that lateral inhibitory connections in the *Drosophila* antennal lobe are probably not highly specific.

Lateral connectivity is dynamic

Another twist to the classical model is that inter-glomerular connections in the olfactory bulb can be dynamic. A recent *in vitro* study in mouse olfactory bulb slices used calcium imaging to study how a subclass of GABAergic interneurons (granule cells) is recruited by feedforward excitatory stimuli. Simultaneous electrical stimulation of two glomeruli was found to recruit 50% more granule cells than the sum of the number of cells recruited by either glomerulus alone [9]. This finding predicts that the inhibitory coupling strength between two glomeruli should vary supra-linearly as a function of their combined activity, and this prediction was borne out in paired recordings from mitral cells. Taken together, these results emphasize the importance of viewing the olfactory bulb and antennal lobe as dynamical systems where small changes in the pattern of ORN input can produce disproportionately large changes in the activity of the network [10].

Lateral excitation

In the classical view, lateral connections between glomeruli are strictly inhibitory [e.g. 3, but see 11]. However, several laboratories have now demonstrated excitatory connections between glomeruli in the *Drosophila* antennal lobe [12-14]. Lateral excitatory connections are non-topographic, and even glomeruli on opposite sides of the antennal lobe can excite each other [12]. A novel class of excitatory local interneurons has been proposed to mediate lateral excitatory connections in the *Drosophila* antennal lobe [14]. In other insects, lateral excitation in the antennal lobe may be mediated by direct connections between the dendrites of multiglomerular projection neurons [11].

Although lateral excitatory connections between glomeruli have also been proposed in the vertebrate olfactory bulb, there is new evidence against this idea. Two *in vitro* studies recorded from pairs of mouse M/T cells and always failed to find excitatory connections between cells in different glomeruli. By contrast, excitatory connections were frequent between M/T cells in the same glomerulus [15,16]. This may be a fundamental difference between vertebrates and insects. Nevertheless, it appears that lateral excitation co-exists with lateral inhibition in some olfactory circuits, and suggests that the classical picture of a purely inhibitory surround is oversimplified.

Intra-glomerular processing

Lateral inter-glomerular connections are not the only circuits that produce a transformation of odor representations. Intra-glomerular circuits can also produce a substantial change in the way odors are represented as they pass from ORNs to second-order neurons.

An important feature of the glomerular microcircuit is the convergence of many ORNs onto each glomerulus. This convergence should allow second-order neurons to average signals across many independent inputs, and thus to improve the signal-to-noise ratio of their odor responses as compared to ORNs. This has now been demonstrated directly in the *Drosophila* antennal lobe [17]. Moreover, if ORN output synapses are strong, then this high convergence ratio could make individual postsynaptic neurons more sensitive to odors than a corresponding

individual ORN. Consistent with this idea, ORNs in the *Drosophila* antennal lobe make powerful synapses onto postsynaptic projection neurons [18]. As a result, weak ORN odor responses are amplified in postsynaptic cells [17,19]. Strong ORN responses are not amplified to the same degree, and this may be due in part to strong short-term depression at this synapse [18].

Each glomerulus contains the processes of many GABAergic interneurons. In the vertebrate olfactory bulb, these GABAergic interneurons are termed periglomerular (PG) cells. PG cells mediate intra-glomerular dendrodendritic inhibition of M/T cells and other PG cells, in addition to dendro-axonic inhibition of ORNs [20]. Pharmacologically blocking this circuit boosts both basal activity and odor-evoked activity in the mouse olfactory bulb [21,22]. This implies that intra-glomerular presynaptic inhibition tonically regulates the gain of ORN→M/T synapses.

Interestingly, presynaptic inhibition of ORN axon terminals in the mouse olfactory bulb is strictly intra-glomerular, and is not recruited by inter-glomerular cross-talk [21,22, but see 23]. Thus, presynaptic inhibition at ORN axon terminals represents form of gain control strictly limited to an individual glomerulus. Lateral cross-talk between glomeruli seems to occur only at a deeper layer of the olfactory bulb, via a separate class of GABAergic interneurons (granule cells) that are morphologically distinct from PG cells [24]. This contrasts with the situation in the *Drosophila* antennal lobe, where presynaptic inhibition at ORN axon terminals is a major pathway for lateral cross-talk between glomeruli [8].

Wake up and sniff the coffee: interactions between behavior and perception

Most animals actively control the flow of air over their ORNs, generally via a repetitive sampling behavior [25-29]. Terrestrial vertebrates accomplish this by sniffing, insects and crustaceans by flicking their antennae, and snakes by flicking their tongues. Insects can also repetitively sample odors by wing-fanning air across their antennae, or by flying back and forth across an odor plume. There currently intense interest in how these periodic sampling behaviors affect the way that odors are represented in the brain, and conversely how odor perception modifies sampling behavior.

Perception and reaction can occur on the first odor sample

Odor detection can occur rapidly, on the timescale of a single odor sample. Conversely, odor detection can trigger a rapid modulation of sampling behavior. For example, a typical human subject can detect an odor in just one sniff, and can modify airflow through the nose within 160ms of sniff onset [30]. Free-flying *Drosophila* can rapidly detect an odor on its first encounter with a plume, and will rapidly reorient its flight trajectory within 250ms of the plume encounter [31]

Not only odor detection, but also some odor discrimination can be performed on this fast timescale. For example, trained rodents can discriminate between a pair of similar odors on the basis of a single sniff [32], although some discriminations can benefit from multiple sniffs [33,34]. Rats respond to a novel odor with faster sniffing, whereas a rat presented with a familiar odor will maintain its basal sniff rate. In some contexts, this difference in sniff rate can be detected within 140ms of the onset of the first sniff of the test odor [35].

Neural codes on the timescale of a sniff

Many M/T cells fire spikes with odor-specific temporal patterns that repeat once per sniff cycle [36]. These sniff-cycle patterns reflect both the staggered recruitment of ORN input to different glomeruli during each sniff [37] and also the dynamics of circuitry within the bulb [38]. Because these patterns are odor-specific, they potentially contain information that could be

used by downstream neurons. This raises the question of what timescales within these temporal patterns are most informative, and how this compares to the speed of behavioral reactions.

Recordings from large ensembles of M/T cells in the mouse olfactory bulb have shed new light on this question [36]. A single sniff-cycle was found to be sufficient to permit a computer algorithm to accurately discriminate between several test stimuli on the basis of the ensemble neural response. Moreover, there was a substantial amount of information in the latency to each cell's first spike after sniff onset. This type of "first-spike" code would be a particularly rapid form of temporal coding [39,40] that might help account for the rapid behavioral reactions observed in some tasks [30,32-35]. However, temporal information on this fine time timescale was not strictly necessary for accurate odor discrimination: good performance could also be obtained by averaging each cell's spike rate over the entire sniff cycle [36]. Thus, there is useful information present at a variety of timescales within the sniff cycle, including fast timescales that could support rapid behavioral responses.

Odor-evoked changes in sniffing affect central odor codes

When an animal adjusts its sampling behavior in response to an odor, this reaction has the potential to modify the way that odors are represented in the brain. A recent study addressed this issue at the very first stage of central processing, using calcium imaging of ORN axon terminals in awake behaving rats [41]. When a rat begins sniffing at high frequency in response to a novel odor, this was found to strongly attenuate ORN input to the bulb. Thus, the function of high-frequency sniffing is evidently not to increase the amount of ORN input to the brain. Rather, the function of high-frequency sniffing might be to promote adaptation to a background odor, thus readying the olfactory system to perceive new odors. Future experiments combining psychophysics with neurophysiology should shed more light on this issue.

Expectation and reward shape odor representations at an early stage

Odor sampling behavior reflects not only current perceptions, but also expectations. For example, rats expecting an odor increase their sniff rate in anticipation of that stimulus, and also in anticipation of a water reward [42]. This may be one reason why M/T cell activity is modulated by seemingly non-olfactory aspects of a behavioral task, such as the mere expectation of an odor and reward delivery [43,44]. Descending inputs from higher brain regions are another mechanism contributing to context-dependent modulation of odor responses in the olfactory bulb. These descending inputs synapse preferentially onto inhibitory granule cells, where they are likely to modulate the strength and/or spatial extent of lateral inhibition [45,46]. Consistent with this idea, behavioral context modulates the ratio of excitatory to inhibitory odor responses in rat M/T cells [47], as well as the strength of odor-evoked field potential oscillations in the rat olfactory bulb [48]. Pharmacological manipulations will help clarify which aspects of olfactory transformations arise from descending modulatory inputs, and when these inputs are active [49].

Conclusions

Taken together, these studies challenge—or at least complicate—the classical view of the olfactory bulb and antennal lobe. Lateral connections between glomeruli in the vertebrate bulb seem to be surprisingly sparse, and may be non-topographic. In the antennal lobe, lateral connections between glomeruli include excitatory as well as inhibitory connections. It is also increasingly clear that active sampling (sniffing, flicking) has a key role in shaping the brain's responses to odors. Olfactory perception rapidly modifies sampling behavior, and this in turn modulates neural activity in the brain in sometimes surprising ways.

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