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Mechanisms of odor discrimination: neurophysiological and behavioral approaches

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Understanding how complex neuronal circuits in the brain perform advanced computations is a central question in neuroscience that can only be addressed using a combination of approaches, including neurophysiology and behavioral analyses. In the olfactory bulb, neurophysiological studies have revealed that neuronal interactions reorganize odor-evoked activity patterns so that their discriminability is enhanced. Recent behavioral studies have examined the role of this computation in odor discrimination tasks and generated working models of behavioral odor discrimination strategies. The results appear consistent with a role of pattern reorganization in odor discrimination behavior but further studies are necessary to resolve this issue. These studies advance the understanding of neuronal circuit function in the olfactory bulb and illustrate benefits and caveats of comparing behavioral and neurophysiological results.

Introduction

Neuronal circuits in the brain consist of many interacting neurons that accomplish computations by processing activity patterns. The sheer complexity of such circuits poses an enormous challenge to neuroscientists and calls for a combination of experimental approaches to study their function. An increasingly popular model circuit is the olfactory bulb (OB). Sensory input is conveyed to the OB directly from the nose through an array of discrete input channels, the glomeruli. Each glomerulus is innervated by convergent axons of olfactory receptor neurons expressing the same odorant receptor [1] so that each odor evokes a specific activation pattern across the glomerular array [2–5]. The neuronal circuits within the OB that process these input activity patterns are characterized by interneuron-mediated inhibition between the principal neurons, the mitral cells [5–9] (Figure 1). Inhibitory interactions occur over a wide range of spatial scales and can be subdivided into two layers [5,10] (Figure 1). OB output is conveyed to multiple higher forebrain areas [11]. The functional architecture of the OB is similar to that of the primary olfactory center in insects, the antennal lobe, and shares basic features with other brain structures. It is, however, impossible to predict how glomerular activity patterns are processed in the OB solely on the basis of the circuit layout.

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Neurophysiological computations in the olfactory bulb

Neuronal computations have been studied using optical and electrophysiological techniques in the intact OB and antennal lobe. One computation that might support odor discrimination was first discovered in zebrafish [12] and subsequently in insects [13–15]: during the first few hundred milliseconds of an odor response, firing-rate patterns across the mitral cell population become reorganized until they approach odor-specific steady states [12,16,17]. This process makes initially similar activity patterns, evoked by chemically related stimuli, progressively more distinct and enhances their discriminability [16] (Figure 2a). Hence, mitral cell activity patterns, when analyzed as firing rates, become more informative about the properties that are unique to each odor. Mathematically, activity patterns across multiple neurons are described as points in a high-dimensional 'neural space' where each dimension represents the firing rate of one neuron. Similar patterns form clusters in this space, whereas dissimilar patterns are more evenly distributed. The divergence of initially similar activity patterns during the early phase of an odor response is therefore referred to as 'declustering' or 'decorrelation'.

During an odor response, stimulus-specific subsets of mitral cells rhythmically synchronize their action potentials with near-zero time lag and a precision of a few milliseconds [6,17–20]. This synchronization is mediated by interneurons [21] and detectable as a fast oscillation in the local field potential. However, a substantial fraction of mitral cells change their firing rates without synchronizing. In zebrafish, synchronized and residual spikes convey complementary stimulus information [19]: patterns of residual (non-synchronized) spikes diverge over time and become declustered, similar to firing-rate patterns analyzed regardless of synchronization, indicating that they are informative about unique features of each odor. Patterns of synchronized spikes evoked by related stimuli converge and, thus, convey information about features that are common to a chemical category of odors (Figure 2b,c). The synchronization of odor-specific mitral cell subsets can therefore enhance the bandwidth of information transmission to higher brain areas.

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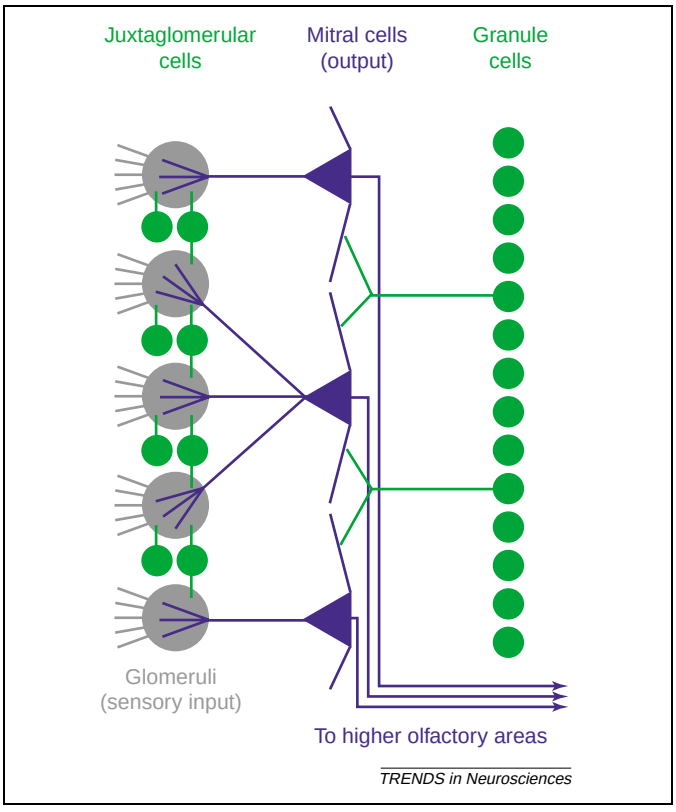

Figure 1. Olfactory bulb circuitry. Each glomerulus contains the convergent axons of receptor neurons expressing the same odorant receptor, axons and dendrites of juxtaglomerular neurons, and mitral cell dendrites. Mitral cells are the glutamatergic principal neurons that convey the output of the olfactory bulb (OB) to higher brain areas. Juxtaglomerular neurons comprise multiple cell types and mediate predominantly inhibitory interactions within and between glomeruli. In the deeper layers of the OB, numerous axonless inhibitory interneurons, the granule cells, make dendro-dendritic synapses with the basal dendrites or proximal primary dendrites of mitral cells. Many of these dendro-dendritic synapses are reciprocal. This basic circuitry is conserved throughout vertebrates, with small variations. For example, mitral cells typically have a few apical dendritic tufts innervating different glomeruli, except in mammals where apical dendrites are uniglomerular [9]. Basal dendrites of mitral cells are short or absent in fish and tend to increase in length from fish to mammals [9]. Nevertheless, the basic circuit diagram is highly conserved in all vertebrates and similar to the functional architecture of the antennal lobe in insects. In an abstracted view of OB circuits, inhibitory interactions between mitral cells can be subdivided into two layers, one mediated by juxtaglomerular cells and one mediated by granule cells. The reach of these inhibitory interactions ranges from very short (intraglomerular) to very long. Centrifugal connections from higher brain areas terminate on juxtaglomerular and granule cells but have been omitted for clarity.

These neuronal computations in the OB occur within the first few hundred milliseconds of an odor response. The time course of declustering can be assessed by following pair-wise correlation coefficients over time; however, it is best quantified by clustering indices based on multivariate analysis techniques [12,19,22,23] (Figure 2b; analysis methods are reviewed in [22,23]). When considering only firing rates, as in the initial study in zebrafish [12], declustering of mitral cell activity patterns took $\leq$800 ms to complete. However, when the fine temporal structure of activity (synchronization) was taken into account, declustering was observed by $\sim$400 ms [19] (Figure 2b). Hence, processing times derived from neurophysiological measurements depend on the readout procedure. Assuming that readout strategies by the brain are optimized, experimental measures of processing times should be regarded as upper limits for predictions of behavioral response times.

Because declustering increases the reliability of odor identification based on firing patterns across mitral cells [12,16], it could be important in odor discrimination. It is therefore interesting to examine whether this computation is indeed used by the brain in behavioral discrimination tasks. Three predictions can be derived from the physiological results to test this hypothesis:

(i) Initially similar activity patterns that do not decorrelate should be more difficult to discriminate than those that decorrelate. In zebrafish, the only odor pair for which mitral cell activity patterns did not decorrelate was Phe–Tyr [12,19] (Figure 2b).
(ii) Odor discrimination between chemically similar stimuli should require a minimum processing time sufficient at least for partial declustering.
(iii) Reaction times might increase with the difficulty of a discrimination task because simple discriminations should not require decorrelation. However, this is not a strict prediction because the reaction time could also be constrained by factors others than sensory processing.

Behavioral studies of odor discrimination

Behavioral experiments have started to address these predictions. Valentincic and Miklavc [24] examined odor discrimination behavior in adult zebrafish using a simple, well-established task [25]. After training zebrafish to associate one amino acid stimulus with a food reward, presentation of the rewarded odor (S^+) evokes an increase in swimming activity, whereas non-rewarded odors (S^-) have little effect. A significant difference in evoked swimming activity indicates that fish can discriminate between S^+ and S^-. Five groups of ten zebrafish were trained to associate one amino acid (S^+) with a reward before testing with a panel of 17 different amino acids (S^+ and 16 S^-), including those used previously in physiological studies [2,12,19]. Different groups of fish were trained on different S^+. Out of $\sim$80 amino acid pairs tested, only two could not be discriminated. One was Val–Ile, which is known to evoke the weakest and most variable mitral cell responses. The other was Phe–Tyr, which was the only pair for which activity patterns did not decorrelate [12,19] (Figure 2b). These results are consistent with the first prediction but should be substantiated by further experiments. For example, physiological and behavioral experiments should be performed in the same strains or individuals because similarity relationships between activity patterns could vary between individuals owing to polymorphisms in the olfactory receptor gene repertoire [26].

Testing the second and third predictions requires estimates of sensory processing times that might be derived from reaction-time measurements in discrimination tasks. Humans take 400–500 ms for simple odor discriminations and $\sim$2 s for more difficult discriminations [27,28]. Odor-induced 'reflexive' changes in sniffing behavior are already observed 160 ms after stimulus onset [29], suggesting that much of the time in discrimination tasks is needed for sensory processing. A median reaction time of 690 ms, with a large variance, was