Context and chemistry in primary olfactory processing

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Recent studies have elucidated the apparent chemotopic organization of the olfactory bulb (OB), the most peripheral cortical structure in the vertebrate olfactory system[1-8]. Interpretations of these studies as regards olfactory perception focus almost entirely on feed forward processes from the sensory receptors to the OB, as the allure of chemotopy is its simplicity. It has long been known that the OB is not a passive sensory throughway, but that it receives input from many areas of the basal forebrain and elsewhere[9-12]. One of the problems in understanding the principles of olfactory coding in the mammalian brain is the inclusion of these centrifugal inputs to the OB and of meaning-based rather than passive odor exposure. The computational difficulty lies in integrating chemotopic input with meaning-driven centrifugal activity in the OB. We propose that OB physiology is modulated to a large degree by behavioral context, but that in special circumstances, the system may act as a feed-forward sensory throughway, with behavior predicted almost entirely by chemical structure. We support this with three studies.

Study 1) The principal neurons in the OB are the mitral cells (MCs), which receive direct sensory input from the nose and project their axons to much of the basal forebrain, particularly to the pyriform cortex (PC), the entorhinal cortex (EC) and the amygdala. All of these areas send input to the OB. We used a tightly controlled behavioral task to enable evaluation of MC firing rate during controlled odor exposure when animals sniff at 8 Hz or more[13]. Rats were required to make an odor discrimination in less than one second and respond immediately. We used a naturalistic odor-association task, which allowed us to change the association of an odor in as few as 5 trials. Thus, we were able to change odor associations several times in a single recording session while stably recording from individual MCs. Nearly all cells responded in a cell-specific fashion to the behavior, firing rate modulating with the phase of the task (waiting, light on, guillotine door opening, entering port, sniffing, drinking/waiting, light off, withdrawing, door closing, waiting). These patterns were stable as long as the behavioral requirements of the odor remained the same. When they were changed, the modulation patterns also changed, and when the behavior was returned to the original state, the original modulation pattern returned. This shows that while MCs receive odor input, they are modulated by much more than odor. The modulation patterns were not due to changes in respiratory frequency, as cells recorded simultaneously from different locations in the OB, showed markedly different slow temporal modulation patterns, under the same respiratory driving. Odor-specificity was seen in a subset of MCs. These cells fired more for one of the two odors used in a day's experiment. However, this odor-specificity was itself subject to behavioral context, as specificity suddenly disappeared or appeared when the behavioral requirements were changed. Previous studies found that odor identity could be predicted by respiratory phase firing of MCs during slow breathing[14-17] but were not able to evaluate firing patterns during fast breathing, due to MCs uncoupling from the respiratory rhythm during these periods.

Study 2) The source for MC behavioral modulation may come from more central brain areas, with one candidate being the EC. In this study, using well-isolated local field potential recordings from four brain areas (OB, PC, EC and hippocampus) we found that the EC sends input to the OB prior to the arrival of an odor[18,19]. Each of the structures in the set follows the behavior in a dynamic fashion; the frequency and amplitude structure of the local field potential and their interactions with each other change over the course of the 6-second behavior. The classic olfactory bursts described first by Adrian[20] were seen to disappear just prior to the arrival of the odor stimulus and to reappear only after the animal had made the behavioral discrimination. Coherence between the OB and PC is normally high, except just prior to and during odor processing, where it drops precipitously just as coherence between the OB and EC rises. Thus, the system as a whole changes its relationships and influences with the slow temporal structure of the behavior, where alterations in coherence patterns change on the order of 250 msec. The system can then be viewed as dynamic in its parts, if parts are viewed as those structures significantly coherent with the OB.

Study 3) Given the range and power of behavioral effects on the OB, it might be argued that objective stimuli do not exist in the system. However, in a recent set of experiments we show that in special circumstances, chemical structure can predict behavior[21]. Experiments from other groups have also shown that the chemical structure of monomolecular substances can determine behavior in some cases[22,23]. While experience with an odor set has a large effect on identification of monomolecular odorants in mice and rats[24], when the odor stimulus is a mixture, the story is sometimes simpler. We took advantage of the recent analysis of the rat I7 olfactory receptor to examine the psychophysical effects of two chemicals (octanal and citral) that appear bind to the receptor in an antagonistic fashion[25]. We found that the ability of rats to identify the components of a mixture of these two odorants depends directly on their relative concentrations, as they compete with each other in a very simple fashion. Other mixtures of chemicals, which do not both bind to the I7 receptor do not produce this effect and have a more complicated perceptual pattern over a large range of relative concentration values.

Thus, while meaning and expectation play a large role in determining OB activity, the chemotopy of receptor input and the biophysics of individual receptors do play some role in determining behavior. The next step in computational modeling will be to include both types of behavior in the same model.

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