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Behavioral analysis of olfactory coding and computation in rodents

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Behavioral analysis is essential to understand how the olfactory system transforms chemosensory signals into information that can be used to guide actions. Recent studies in rodents have begun to address the behavioral relevance of putative olfactory codes and computations including spatial maps, oscillatory synchrony, and evolving temporal codes. To date, these studies have failed to find support for a role of any of these mechanisms in odor discrimination. Progress calls for experiments using precise psychophysical methods in conjunction with neural recording or perturbation, in addition to ethologically minded exploration of more complex forms of odor-guided behavior.

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Introduction

How does the brain encode and process odors? Ideas about olfactory sensory function have been driven by advances in cellular and synaptic neurophysiology [1], molecular biology [2], theory [3,4], *in vivo* electrophysiology [5–7], and imaging [8,9]. Common to these diverse approaches has been a sensory perspective. That is, chemosensory information is seen as being encoded into an array of activity that is transformed through a series of computations from the olfactory bulb to the olfactory cortex and beyond. A central goal of olfactory research is to understand these codes and computations [10]. Yet, although much has been learnt about mechanisms in olfactory processing, there is still substantial debate over their significance to olfactory function.

A putative odor code expressed at some locus in the olfactory system must be read out by downstream neurons [11], which in turn must be read out by further downstream neurons. Ultimately, what starts as an odor

representation must end with the selection of an appropriate behavioral response. Quantitative studies of such olfactory-guided behavior can, therefore, provide important constraints on possible olfactory codes and insights into the nature of olfactory computations. Although behavioral studies have not historically been at the forefront of olfaction research, this situation has started to change. In this review I examine how recent behavioral studies in one important animal model, the rodent, have begun to contribute to our understanding of olfactory function.

At the outset, it is useful to divide behavioral studies of sensory function into two extremes of approach: psychophysical and ethological. Psychophysical studies aim to control and quantify all possible sensory and performance variables. Although psychophysics is by and large performed with humans, animals can be trained to perform similar tasks using operant conditioning, opening up the possibility of getting at the underlying neural mechanisms [12]. Ethological studies focus more on the natural behavior of animals rather than on conditioned behavior. The ethological approach typically loses some degree of experimental control, but can tap into functions that are less easily accessed through experimental conditioning.

Spatial coding: correlation and intervention

Since the discovery of a remarkable spatial map of receptors across the glomeruli in the olfactory bulb [2,13], the role of spatial maps in olfactory function has been debated [7,11]. Is the stereotypical spatial arrangement of receptors on the surface of the olfactory bulb intrinsic to the logic of olfaction, and hence important to the representation and processing of odors, or is it simply a result of developmental wiring or other constraints? Processing by inhibitory lateral interactions within the olfactory bulb would support a functional role for relative spatial positions insofar as these interactions are spatially localized [14–16].

A main strategy to support the idea of spatial coding (see glossary) has been to correlate glomerular activity maps for pairs of odors to the ability of animals to distinguish these same odor pairs. Measurements of spontaneous responses (habituation and dishabituation; see glossary) show that rats generalize (cross-habituate; see glossary) between odor pairs with very similar glomerular activity maps, but not between odor pairs with more distinct glomerular maps [17]. Through differential reinforcement (operant conditioning), rodents can be trained to discriminate with high accuracy these and all odor pairs tested to date, regardless of the similarity of their

Glossary

Cross-habituation: The tendency of two distinct but related stimuli to produce mutual habituation.

Dishabituation: Relief of habituation caused by the presentation of a distinct stimulus.

Habituation: The progressive decrease in behavioral response that accompanies repeated presentations of a stimulus.

Labeled line code: A code in which information is conveyed by the identity of the activated neurons.

Olfactometer: A device for delivery of odors

Spatial code: A code in which information is conveyed by the relative positions of activated neurons.

Temporal code: A code in which information is carried by the relative timing of action potentials in a population of neurons

glomerular maps [18,19]. However, although their discrimination performance is very good, rats still show a significant correlation between glomerular map similarity and discrimination accuracy [20].

Although these results are consistent with the possibility that the arrangement of the glomerular map is significant to odor representations, there are interpretational caveats. First, odor chemical structure, the independent variable in these studies, is a key determinant of glomerular activity patterns, but also determines other features of odor encoding. For instance, activity patterns across the olfactory epithelium also correlate well with discrimination performance [21,22]. In addition, the above analyses do not distinguish spatial position from the identity of glomeruli: a labeled line code (see glossary), in which the identities of neurons but not their spatial positions are relevant for computation, is sufficient to explain the available data.

A second class of approaches has been formed on the basis of intervention. If a spatial map is important to olfactory behavior, then disrupting the map (while leaving other aspects of function intact) ought to result in an impairment of one or more olfactory functions. Slotnick and colleagues [23–25], in a series of behavioral studies, used psychophysical measurements of discrimination ability and detection thresholds to test the impact of olfactory bulb lesions on olfactory acuity. The results of this series of studies are rather remarkable. Not only do ablations of large portions of the olfactory bulb or other destruction of olfactory inputs usually fail to produce significant impairments of odor discrimination and detection (even near psychophysical limits) but animals that are trained before such manipulations can often still recognize the same odors after the ablation [23–25]. Even rats with no olfactory bulbs are able to perform olfactory discriminations, supported by olfactory nerve input that reinnervates areas of olfactory cortex (anterior olfactory nucleus) [26]. These findings hint that odor discrimination tasks are not likely to be very sensitive to relatively subtle perturbations, such as scrambling the topography of the spatial map. Rather than concluding that spatial maps and lateral

inhibition have only a minor function in the olfactory bulb, it could be argued that discrimination and detection of odors are not the computations subserved by these mechanisms.

Synchrony and oscillations

A computational role for synchronous and oscillatory neuronal activity has long been sought in olfaction. There has for some time been evidence for these phenomena in electrophysiological recordings [5], but there is still very little evidence that these phenomena contribute to olfactory behavior in mammals. Synchrony is a mechanism for enhancing the impact of a population of neurons on downstream targets, whereas oscillations can be indicative of synchrony and in some cases causal. Although less direct than synchrony, oscillations are considerably easier to measure (e.g., through local field potentials). Ravel and co-workers [27,28] have recently shown that gamma (30–80 Hz) and beta (15–30 Hz) oscillations in the olfactory bulb and cortex change over the course of olfactory learning, with gamma oscillations weakening and beta oscillations strengthening with training. Although this study provides evidence that the oscillations are somehow linked to odor learning and/or processing, a stronger correlational argument could be made by relating, on a trial-by-trial basis, the strength of oscillations to behavioral performance. An even more rigorous test would be to decode spike data on the basis of synchrony or oscillation phase and show that this results in a more accurate odor classification than a code that omits this feature.

In insects, a canonical intervention experiment was performed by Stopfer *et al.* [29], who tested the role of oscillations using a classical conditioning assay in honeybees. The intervention was provided by the GABA_A receptor antagonist picrotoxin, which the authors found to block oscillations while leaving firing rates unchanged [29]. This treatment caused honeybees to generalize from trained to untrained odors. One of the key requirements of such an intervention experiment is specificity. Manipulations of inhibition will generally be tricky to interpret because inhibitory interactions are generally important not only to oscillations but also to various other potential bulbar functions, including lateral inhibition [14,30]. The selectivity in honeybees might be fortuitous in this respect. An equivalent experiment has not yet been performed in rodents. However, Fletcher *et al.* [31] showed that neonatal rats do not express gamma frequency oscillations, even though they show specific olfactory responses in a cross-habituation paradigm. This dissociation indicates that local field potential oscillations are not an essential mechanism for this kind of behavior, but these studies do not directly address the role of synchrony *per se*, which might still exist in young animals but fail to produce visible oscillations. Furthermore, it remains possible that there are differences in the neural

computations and behavioral capabilities of older and younger olfactory systems.

The speed of odor coding

A second kind of temporal code (see glossary) that has been proposed in olfaction involves the use of temporal patterns to encode odor quality. Thus, the neural mechanisms devoted to processing the dynamics of stimuli in other modalities would be utilized in the olfactory system to encode the properties of an odor [6]. Studies in the (immobilized, unanesthetized) zebrafish showed that olfactory responses evolved over the course of hundreds of milliseconds of constant odor presentation, becoming decorrelated in the process [32]. Evolving temporal codes on these time scales suggest direct behavioral correlates. If it is true that decorrelation of activity patterns in response to odors contributes to the olfactory acuity of an animal, then over hundreds of milliseconds you would expect odor discriminations to become more accurate.

Uchida and Mainen [20] tested this idea by training rats to classify different odors with responses to left or right choice ports (i.e., a two alternative choice task). The animals decided when to terminate odor sampling, in what is commonly called a 'reaction time' paradigm. Even for discrimination of closely related odors, rats sampled for only 250–350 ms before leaving the odor port. Given that this time includes any response preparation and motor initiation time, as little as 100–200 ms is often sufficient to form a fully detailed odor code. Similarly short response times were also found in mice [33^{*}]. Importantly, these studies tested rodents not only with easy stimuli but also at psychophysical thresholds using binary odor mixtures. These results demonstrate that well-trained animals need not rely on slowly evolving temporal codes to extract information to classify a known stimulus. They do not, however, rule out faster temporal codes.

An important point to consider in psychophysical studies is that because differential reinforcement (reward or punishment) is what motivates the behavior, the experimenter must be aware of the potential impact of these 'instructions' on performance. In particular, it is commonly observed that response times in animals depend on the magnitude of expected reward [34]. In an asymmetrically rewarded task (go/no-go) [23,33^{*}], comparison of response times in 'go' and 'no-go' trials revealed such effects [35]. Symmetric task designs (e.g. two-alternative choice) are preferred in psychophysical studies in part because they can dissociate the effects of task difficulty from motivational effects.

A second important point with respect to these studies is that the time scale over which odor identity information can be read depends strongly on the algorithm used to extract it (compare the different methods used and time-

scales observed in [32,36,37]). This fact might hold not only for the analysis of neural data but also in the readout by the brain of olfactory information. Odor discrimination training might facilitate rapid behavioral responses by optimizing the readout of sensory information from the olfactory bulb by downstream areas in the cortex.

More complex olfactory computations

The above experiments focus on what is probably a very basic expression of olfactory function, that is, binary discriminations in well-trained animals. Although there is much to be learnt from such studies, animals almost certainly possess additional olfactory capabilities. Hopfield [4] postulated several olfactory computations that olfactory systems need to solve that are more sophisticated than simple discrimination. These include: first, concentration-invariant odor recognition, second, background-invariant odor recognition, and third, odor-mixture segmentation. Such computations could in turn support yet more complex behaviors. Consider homing behavior in salmon, one of the few examples that has been well studied ethologically. Although the mechanisms by which these fish navigate over hundreds or thousands of miles from their spawning grounds to the open ocean and back are not fully known, it has been proposed that they memorize and then retrace a series of sequential odor way-points [38]. We have comparatively little insight into the more complex ethological problems solved by rodents using olfaction, but it is known, for example, that rodents can follow scent trails of conspecifics [39]. In view of this potential complexity, it is reasonable to refer to frequently used binary discrimination tasks as fundamentally simple even if they are made extremely difficult by increasing the similarity of odors. It is possible that some coding mechanisms or computations might be crucial only for truly complex olfactory-guided tasks.

Although most investigations in this field have not strayed beyond the simple discrimination and detection behaviors exhibited by rodents, some groups have focused on the behavioral aspects of interactions among odors that will be relevant to understanding odor-guided behavior in more natural olfactory environments [40,41^{*}]. These studies make use of a relatively ethological paradigm in which rats dig through sand in cups for a food reward. The sand is scented with odorants that the rats learn to associate with the presence or absence of food. A distinct advantage of these paradigms is that they require little training. Sand-digging has thus been used to study not only odor coding but also more complex forms of olfactory memory [42,43], and even the relatively complex cognitive process of set-shifting [44]. Indeed, it has been argued that the olfactory system provides unique access to higher order cognitive mechanisms in rodents [45]. A challenge of more naturalistic paradigms is relatively poor experimental control and difficulty in quantifying all the relevant behavioral variables. For example, although the

concentration and time course of odor delivery from an olfactometer (see glossary) can be relayed with some accuracy [46], it is far more difficult to quantify the time course of a stimulus delivered from a sand cup to an approaching rat. Combining the control and quantification of psychophysical approaches with the advantages of ethologically relevant paradigms is an important challenge for future work.

Active sensation and olfactory scenes

The few computations described above extend beyond discrimination, but still probably only hint at the true breadth and intricacy of olfactory-guided behaviors in rodents. Interestingly, some insights into the potential precision and complexity of olfactory function in an ecological context have come from recent psychophysical studies.

In olfaction, the sniff is the essential motor process underlying active sensation. With respect to olfactory coding, the impact of the sniff cycle is of some interest [47]. First, the cycle provides a timing signal that could enable information to be encoded in spike latencies. Odor-specific spike latencies appear to be introduced during receptor transduction [48] and might be preserved as phase-specific firing patterns in the olfactory bulb and cortex [49]. Second, respiration at the theta frequency could play a role in coordinating olfactory sensory information with other sensory, cognitive or motor processes [47,50,51].

Sniffing can be measured by chronically implanting a temperature probe in the nose of an behaving animal, and in this way it is possible to monitor sniffing patterns during behavior. Trained rats sample odors at around 8 Hz (versus 1–2 Hz in the anesthetized animal) and can use just 1–2 sniffs to perform discrimination of even highly-similar odor stimuli [20]. Because a single sniff can evidently provide quite a detailed odor representation, rats might be able to use multiple sniffs to perform more complex computations. For example, by tagging relatively non-volatile odors to spatial locations they could assemble an olfactory scene, much as a visual scene is composed by a series of brief fixations [52]. A further computation that could be facilitated by short discrete odor snapshots is odor tracking or source localization. Rajan *et al.* [53**] showed, using psychophysical methods, that rats can sense the disparity in timing in receiving information of odor onset between left and right nostrils (within one or two sniffs), information that they could use to help localize the source of an odor.

Single unit recording in behaving animals

Beyond the insights behavioral studies can provide, they can be even more penetrating when coupled with simultaneous neural recordings and more advanced techniques for monitoring and perturbing neural activity [54].

Although recording in the sensory system of behaving animals presents a variety of challenges not present in anesthetized animals, the payoff is likely to be worth the effort.

The physiology of the olfactory system has long been known to be sensitive to arousal state [5], and recent studies reinforce the idea that odor coding might look quite different in anesthetized and awake animals. Odor-selective responses are not difficult to elicit in the olfactory bulb under anesthesia, but appear much sparser in behaving animals [55,56]. The olfactory cortex, which provides a major centrifugal pathway to the olfactory bulb, exhibits state-dependent gating [57] and could help explain anesthesia-dependence of odor responses. In addition, the activity of central neuromodulatory systems, including those of norepinephrine, acetylcholine, and serotonin, are phasically and tonically activated by salient events [58] and affect processing in the bulb. Reward-selective responses reported in the bulb [55] might reflect these influences. Finally, respiration produces yet another essential top-down influence. Sniffing rates in anesthetized animals rarely exceed 1–2 Hz, yet behaving animals sniff at around 7–9 Hz while performing discriminations [20,53**]. The impact of sniffing (versus slow respiration) on bulbar coding and processing is largely unknown.

Beyond the potential differences between the awake and the anesthetized states, another important reason for extending anesthetized recordings to behaving animals is related to the ability to constrain possible codes and computations. With simultaneous recording and psychophysics it is possible to compare directly the performance of the animal with the performance of the neurons that are thought to underlie the task. This method of evaluating putative neural codes is particularly powerful when the animal is performing at sensory limits [12], and calls for the use of psychophysical paradigms in which olfactory stimuli and responses are tightly controlled and monitored over many trials. Psychophysical methods are also well suited to studying the decision process that links sensory representations to motor representations [59]. For different reasons, studying the neural basis of more complex ecologically relevant computations performed with the olfactory system (e.g. odor tracking) will obviously require behaving animals.

Conclusions

Behavioral studies indicate that odor discrimination behavior is remarkably robust and surprisingly rapid. Crucial roles for spatial maps, oscillatory synchrony and slow temporal decorrelation have not been easy to establish using behavioral discrimination assays. Although it is premature to rule out any of these coding mechanisms, it is becoming clear that precise psychophysical assays capable of measuring near-threshold performance will be

important to push these lines of analysis further. It is also important to consider the possibility that the olfactory capabilities of rodents are not being adequately probed by the task of odor discrimination, even when it is made exquisitely difficult by increasing the similarity of stimuli. It is not difficult to imagine that there are more complex computational problems for the olfactory system to solve, even if it is not easy to intuit exactly what they are. Imagine if the problem of vision were reduced to discrimination of pairs of images while neglecting object recognition, smooth pursuit, color constancy, and so on. Concentration-invariant recognition, mixture segmentation, and source localization are examples of computations that have been proposed but remain poorly characterized at the behavioral level, and largely unexamined at the neural level. Challenges for future work will include not only merging well-controlled psychophysical tasks with neural recording and intervention but also exploring and seeking to better define the more sophisticated capabilities of olfactory-guided behavior through ethologically minded studies.

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