DOES CHEMICAL SIMILARITY PREDICT ODOR SIMILARITY?

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An important computational problem in the study of olfaction is how much the chemotopic organization of olfactory bulb input participates in determining perceived odor quality or similarity. This organized input combines with contextually driven centrifugal input in behaving animals to produce the complex meaning-based signals we record in behaving animals [1, 2].

Odorants of similar molecular structure activate topographically adjacent regions of the olfactory bulb in mice [3] and rats [4, 5] with a fine-grained odor map. Chemicals with the same functional group activate the same broad area, but secondary characteristics (*e.g.* carbon chain length) activate overlapping, but gradually shifting clusters of glomeruli in the olfactory bulb [4, 5]. This suggests that perceived odor similarity may occur among chemicals that are structurally similar, but not among those of different classes or of very different carbon chain lengths. Previous studies on rats and primates [6, 7] suggest that chain length is relevant in predicting the kinds of mistakes that animals make in identifying odors of a chemical class. We set out to test this theory in mice, in order to be able to use genetically altered strains in later behavioral tests. We also tested a small group of rats, to replicate previous results [7].

Our behavioral paradigm was modified from those used previously [7, 8], to assess the identification abilities of 24 mice (C57BL6) and 6 rats (Sprague-Dawley) among series of structurally related odorants. We trained male animals to dig in a small dish of scented cage bedding (one drop of odorant - 5% dilution in mineral oil - placed near the surface of the bedding) and to avoid digging in a control dish (one drop of mineral oil) for a reward (piece of Froot Loop® cereal). Odorants for these experiments were series of 8 aliphatic alcohols (3-10 carbons) and 3 non-alcohol controls (isoamyl acetate, geraniol, eugenol) or 8 aliphatic aldehydes (3-10 carbons) and 3 non-aldehyde controls (diacetyl, cineole, ethyl 2-methylbutyrate). After training for each odor, animals were tested for recognition on all odors of a set in random order.

Odor test sessions began with 10 training trials, in which the conditioned odor was paired with the reward. After training, each animal was tested with no reward on all odors of a set (alcohols and non-alcohol controls or aldehydes and non-aldehyde controls) in random order. Between the 30-second test trials the animal was given 1-2 rewarded reinforcement trials. For behavioral extinction, following testing in one group of mice, a dish scented with the training odor for that day was presented repeatedly without reinforcement until digging ceased. Test sessions were given in random order or set order (depending on the group of animals) every 2-3 days or once per week.

Recognition was assessed by time spent digging in the odor dish during unrewarded test trials. Digging times were normalized to their Z-scores to appropriately use statistical measures that assume normality. Significant variation across an odor test set was evaluated with one-way ANOVA and pairwise comparisons with Newman-Keuls post hoc tests.

Neither mice nor rats significantly mistook chemically similar alcohols or aldehydes (chain lengths within 1 or 2 carbons of the trained odor) for each other, except in special circumstances (see below). In all experiments, rats and mice dug significantly in the trained odor and those most recently learned. In most experiments the animals trained to a member of the alcohol or aldehyde class dug in the one or two most recently learned alcohols or aldehydes, skipping over even more recently learned control odors, suggesting odor class generalization. As more alcohols or aldehydes were learned, identification became increasingly difficult, suggesting selective interference among odors of a class. This interference did not extend to non-alcohols and non-aldehydes. When trained on non-alcohol or non-aldehyde controls, animals spent more time digging in the trained odorant than when trained on an alcohol ($p<0.05$), suggesting that the animals noted a qualitative difference between alcohols or aldehydes and the control odors and a qualitative similarity among members of the same class, regardless of differences in chain length.

In special circumstances some effect of chain-length generalization was seen. Mice generalized to similar chain length odors when naïve to the task. After learning 2 alcohols, chain length generalization ceased and mistakes were made only to previously learned odors (those most recently learned and of the same odor class, as discussed above). Behavioral extinction produced some generalization to chain length for alcohols only (significant digging in alcohols one carbon different from the trained odor), as well as to previously learned odors. We therefore conclude that while prior learning has the largest effect on performance, functional group is very important and chain length less so.

Our results do not support the chemotopic hypothesis in most circumstances, that odors differing by only one or two carbons should smell more similar than those more widely separated, but they do support the notion that chemicals of the same functional group have a similar odor quality. Since naïve mice show some chain-length generalization, it is likely that as learning continues and more odorants are introduced and reinforced, the synaptic connections within the olfactory bulb are altered somehow. We found that behavioral extinction improves discrimination ability in mice, which suggests that increased processing of odors may to allow more lateral inhibition, and therefore less confusion, as has been suggested by other studies [5].

Our results are significantly different from those reported previously [6, 7]. These differences may be due to several factors, two of which are probably the most important. First, our method of testing involved training an animal only once on a particular odor and testing all the odors on the same day. In Linster's study, the rats were trained several times on the same odor on different days and tested on only 3 odors on each day. There may be a confound in those data between odor class confusion and chain length generalization. Second, their odors were delivered in a swab the bottom of the dish, while ours were in a drop near the top. Thus, the effective concentrations of our odors may be higher than theirs, and this may facilitate odor discrimination. Although our results are different from previous findings, the studies together may help resolve the interaction of prior experience and odor concentration in odor psychophysics.

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