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Receptor Contributions to Configural and Elemental Odor Mixture Perception

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Odor mixture perception can be configural (the mixture is qualitatively different from the components) or elemental (the components are recognizable). Some have argued that configural properties are dependent on chemical similarity and possible overlap at the receptor level. The authors show that a binary mixture in which both components activate the same receptor (I7) has a configural odor, whereas a mixture that suppresses overlap has elemental odor properties. Rats trained to recognize mixtures of citronellal and octanal (strong I7 agonists) in many ratios rarely recognize the components, supporting configural representation of the odor mixture. However, when trained to recognize mixtures of citral (partial I7 agonist, inhibitor) and octanal, rats recognize 1 or both components over a wide range of ratios.

Odor mixture perception is influenced by many factors, including relative intensities of odorants (Bell, Laing, & Panhuber, 1987; Livermore & Laing, 1998b), mixture complexity (Jinks & Laing, 2001; Livermore & Laing, 1998a), component salience (Bult, Schifferstein, Roozen, Voragen, & Kroeze, 2001; Livermore, Hutson, Ngo, Hadjisimos, & Derby, 1997), trigeminal interactions (Cometto-Muniz, Cain, Abraham, & Gola, 1999), chemical structure (Laing, Panhuber, & Slotnick, 1989; Wiltrout, Dogra, & Linster, 2003), and possible peripheral interactions (Bell et al., 1987). Over the last decade, progress in the understanding of olfactory receptor mapping to the mammalian olfactory bulb has contributed to the understanding of peripheral involvement in the perceived quality of monomolecular odorants (Johnson & Leon, 2000a, 2000b; Laska & Teubner, 1999; Laska, Trolp, & Teubner, 1999; Linster & Hasselmo, 1999; Linster et al., 2001; Mombaerts, 1999; Uchida, Takahashi, Tanifuji, & Mori, 2000; Wachowiak & Cohen, 2001). It is now known that receptor neurons that are distributed in the olfactory epithelium and express the same receptor type send their axons to a few identified glomeruli in the olfactory bulb (Mombaerts, 1999), that stable sets of glomeruli are activated when animals are exposed to monomolecular odors, and that new glomeruli may be recruited with increasing concentration (Fried, Fuss, & Korsching, 2002; Johnson & Leon, 2000a; Rubin & Katz, 1999; Stewart, Kauer, & Shepherd, 1979; Wachowiak & Cohen, 2001). It is also known that mitral cells that underlie identified areas of the olfactory bulb respond in a structured way to series of chemically similar odorants in anesthetized animals (Mori, 1995), and that this ordered mapping of chemical structure can predict rats' performance on discrimination of some chemically similar odors (Linster & Hasselmo, 1999; Linster et al., 2001). However, relatively little has emerged to explain the role that peripheral factors such as receptor binding may play in mixture perception.

Odor mixtures can exhibit configural or synthetic properties, whereby the mixture smells qualitatively different from a simple sum of the components. Suppression or synergism at the receptor level (Steullet & Derby, 1997) or central mechanisms may influence the suppression of component perception within mixtures. Some studies have suggested that mixtures of odors that are very similar in chemical structure and presumed glomerular representation smell different from their components, whereas those composed of structurally dissimilar chemicals have more elemental properties (Laing et al., 1989; Wiltrout et al., 2003). This suggests that mixtures of chemicals that activate overlapping receptor sets will have configural properties. However, examination of mixtures at the receptor level is difficult, unless the odors can be chosen with some knowledge of receptor ligand profiles and testing is done at many different concentration ratios (Price, 1987). Thus, recent identification of the ligand repertoires of some olfactory receptors (Araneda, Kini, & Firestein, 2000; Gaillard et al., 2002; Hatt, Gisselmann, & Wetzel, 1999; Krautwurst, Yau, & Reed, 1998) has now made possible the examination of single receptor contributions to odor mixture psychophysics.

We examine here the perceptual consequences of known receptor-level interactions between odorants. Olfactory receptor neurons expressing the rat I7 receptor are maximally activated by octanal and a number of structurally related odorants, including citronellal (Araneda et al., 2000). They are very weakly activated by citral in high concentration, and citral in combination with octanal significantly reduces a receptor neuron's normal octanal response. If overlap at the receptor level affects mixture perception, then we expect that mixtures of citronellal and octanal should have configural properties over a range of concentration ratios, as

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both are strong activators of receptor neurons expressing the rat I7 receptor. Because citral inhibits the octanal response in these receptor neurons, we expect that this inhibition will cause the mixture to activate primarily receptor populations separate from the I7 receptor, producing elemental perceptual qualities.

Method

Subjects

Twelve adult male Sprague–Dawley rats were procured from Harlan Sprague–Dawley, housed singly, and maintained on a 12-hr light–dark schedule (lights on at 8 a.m.). They had unlimited access to food and water for 1 week after their arrival, at which time their ad-lib weight was recorded (~ 450 g). They were reduced to 85% of this weight by restricting food only. All experiments were performed with approval and oversight by the University of Chicago Institutional Animal Care and Use Committee.

Training and Test Procedures

Using a protocol modified from that previously used for rats and mice (Linster & Hasselmo, 1999; Nusser, Kay, Laurent, Homanics, & Mody, 2001), we trained the rats to dig for a food reward in a glass dish (70 x 50 mm) of bedding. Dishes were scented with one drop of odor solution near the top of the bedding. Unscented dishes contained one drop of mineral oil. Odor training and test sessions were conducted in a modified home cage fitted with a sliding divider. Rats were trained to wait in the rear of the chamber until the door was raised and then to enter the test chamber to search for the buried reward. Each test session began with 10–12 training trials, in which a training mixture (citral–octanal or citronellal–octanal at one of the ratios listed in Table 1) was paired with the reward. After training, each rat was tested with no reward on the four odors of a set (the trained mixture, each of the two components, and a control odor; see below) in random order. Between the 30-s unrewarded test trials, the rat was given 1–2 rewarded reinforcement trials with the trained mixture. Time spent digging in the scented dish during test trials was used to assess odor recognition. Test sessions were conducted every 2–4 days, and the mixture for each test and rat was assigned pseudorandomly, as was the order of test odors within a session. (Interspersed with these tests were 21 additional mixture tests with different odor sets, not reported here, so that the interval between tests on the odor sets reported here was approximately 1 week.) Each rat was trained and tested on all odor mixture ratios. The experimenter was unaware of the composition of the test odors.

Table 1
Ratios and Percentages of Odorants

Ratio	Mixture	Citral	Octanal	Cineole
		Citral-octanal		
50:1	25.0% : 0.5%	50%	1%	1.25%
29:1	14.5% : 0.5%	29%	1%	1.25%
20:1	10.0% : 0.5%	20%	1%	1.25%
10:1	5.0% : 0.5%	10%	1%	1.25%
5:1	2.5% : 0.5%	5%	1%	1.25%
1:1	0.5% : 0.5%	1%	1%	1.25%
1:10	0.5% : 5.0%	1%	10%	1.25%
		Citronellal-octanal		
		Citronellal	Octanal	Hexanol
50:1	25.0% : 0.5%	50.0%	1%	2%
20:1	10.0% : 0.5%	20.0%	1%	2%
9.6:1	4.8% : 0.5%	9.6%	1%	2%
5:1	2.5% : 0.5%	5.0%	1%	2%
1:1	0.5% : 0.5%	1.0%	1%	2%
1:10	0.5% : 5.0%	1.0%	10%	2%
1:20	0.5% : 10.0%	1.0%	20%	2%

Odors and Dilutions

Odors were procured from Sigma-Aldrich (St. Louis, MO) or Fisher Scientific (Atlanta, GA), and all were at ≥98% purity. Citral, octanal, and citronellal were chosen as known ligands of the rat I7 receptor. The control odors, cineole and hexanol, were chosen to be chemically dissimilar to the other three odors. All concentration ratios were in the liquid phase, diluted in mineral oil. Citral stock was a mixture of cis- and trans-isomers, and octanal was 1-octanal. Dilutions were made so that the concentration of a single odorant was not below 0.5% and not above 50%, except for extra concentration tests done at the end of the main body of the experiments. Individual component test odors were diluted to be at twice the concentration of the component within the odor mixture, with control odorants kept at a constant concentration for all tests in an odor group. For example, the 20:1 citronellal–octanal training mixture was diluted in mineral oil to contain 10% citronellal, 0.5% octanal and 89.5% mineral oil. The test odorants were the training mixture, 20% citronellal, 1% octanal, and 2% hexanol. A complete list of odorant dilutions is shown in Table 1.

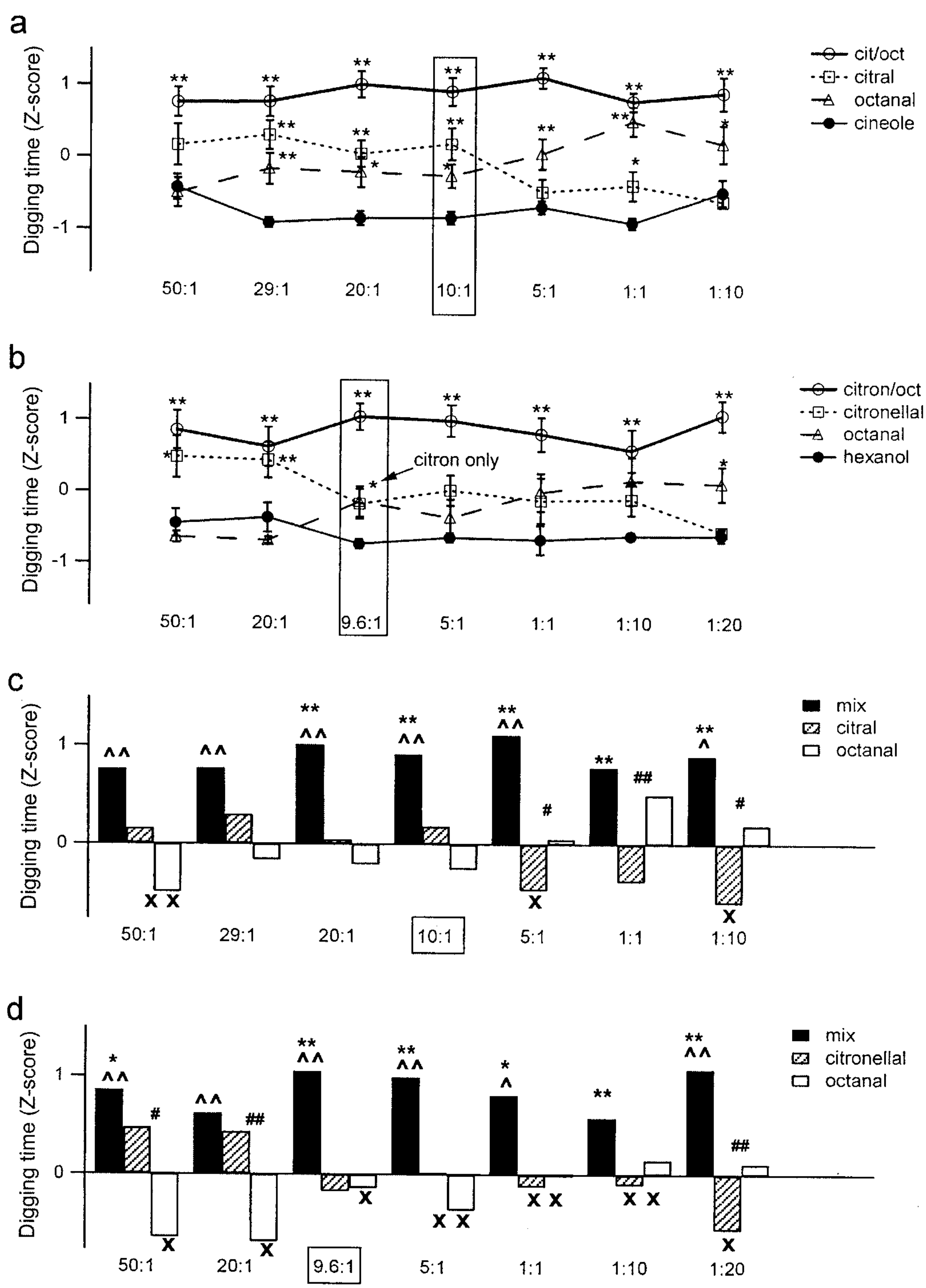
Ratios of odors within blends were chosen with respect to the chemicals' physical properties so that the range of mixture concentration ratios crossed the point at which the ratios were in inverse proportion to the theoretical vapor pressures (approximately 10:1 for citral–octanal mixtures and 9.6:1 for citronellal–octanal mixtures). Theoretical vapor pressures were estimated by using the ACD/I-Lab Web service, ACD/Vapor Pressure 5.0 (Advanced Chemistry Development, 2003).

Analysis

Data are digging times, in seconds, normalized to Z-scores (zero mean and unit standard deviation) for each rat for each experiment, as reported earlier (Nusser et al., 2001). The normalization was chosen because digging times vary considerably across rats and sessions, and the time measurements do not conform to a normal distribution for standard statistical tests. Results were analyzed with a one-way analysis of variance across normalized digging times for each set of test odors and the Newman–Keuls post hoc test to assess all pairwise differences in these values among odors of a test set. Rats that did not dig in any of the four test odors for a given set were excluded from the analysis for that test.

Results

As concentration ratios of the trained mixtures varied, rats' ability to recognize the components also varied in a pattern dependent on the specific odors. We report these results in two sets of figures (Figures 1a and 1b, 1c and 1d) for ease of displaying significant comparisons. Figures 1a and 1b show significance comparisons between each of the test odors (trained mixture and the two component odors) and the control odors (cineole and hexanol). Figures 1c and 1d show the results from pairwise post hoc comparisons among the three test odors. Figures 1a and 1b compare the normalized digging times for all concentration ratios for both sets of odors. The response profiles for the two odor sets have some similarities and large differences. Digging times varied significantly within each test set (individual analyses of variance for each mixture ratio set gave $p < .01$). For each of these mixture tests, the rats dug significantly in the trained mixture as compared with the control odor ($p < .01$ for each trained mixture). We refer


a
Digging time (Z-score)
1
0
-1
50:1
29:1
20:1
10:1
5:1
1:1
1:10
cit/oct
citral
octanal
cineole
b
Digging time (Z-score)
50:1
20:1
9.6:1
5:1
1:1
1:10
1:20
citron only
citron/oct
citronellal
octanal
hexanol
c
Digging time (Z-score)
50:1
29:1
20:1
10:1
5:1
1:1
1:10
mix
citral
octanal
d
Digging time (Z-score)
50:1
20:1
9.6:1
5:1
1:1
1:10
1:20
mix
citronellal
octanal

to this type of comparison—significant digging in a test odor (mixture or one of the components) compared with the control odor—as *recognition* in the following. In the citral–octanal tests, the rats recognized one or both components for all ratio tests but one (Figure 1a). For many of the tests in this odor set, the responses were elemental in that both of the components were recognized (29:1, 20:1, 10:1, 1:1 citral–octanal). These responses to the mixture elements, although significant for both odors relative to the control odor, were often not significantly different from each other (29:1, 20:1, 10:1; Figure 1c). However, a trend is shown, such that responses to elements of trained mixture ratios above the inverse ratio of the theoretical vapor pressures (10:1 citral–octanal) show citral as the primary component (closer to the mixture response), and responses to elements when the trained mixture is below the 10:1 ratio are stronger to octanal. For the 50:1 test, neither component was recognized, and for the 5:1 and 1:10 tests, citral was not recognized as similar to the trained mixture.

In contrast to the citral–octanal tests, recognition of even a single component in the citronellal–octanal mixtures was limited to a small subset of tests. For several concentration ratios, mixture perception was configural in that neither citronellal nor octanal was recognized (5:1, 1:1, 1:10 citronellal–octanal; Figures 1b and 1d). Recognition of octanal occurred only at the most extreme ratio of 1:20 and of citronellal at ratios of 50:1, 20:1, and 9.6:1. Within these four tests, in all but the 9.6:1 mixture test, recognition of the single component was also significantly above any response to the other component (Figure 1d). In none of these tests were both components recognized.

The concentration ratio series were chosen to span the point at which the relative concentrations of the odorants in the binary mixture were inversely proportional to the chemicals' theoretical vapor pressures (10:1 in Figure 1a and 9.6:1 in Figure 1b). In ideal circumstances, the amount of each component's vapor above the odor solution would then be nearly equal at these ratios. Although this odor delivery method is far from ideal, in both datasets, this point is associated with a change in component recognition. In the citral–octanal tests, this is the lowest ratio at which the response to the lower vapor pressure odorant (citral) is larger than that to octanal (boxed data set: Figures 1a and 1c). For the citronellal–octanal tests, this is the lowest mixture ratio in which the lower vapor pressure citronellal is recognized (Figure 1b).

To test the effect of intensity on the results, two concentration ratios were tested at different absolute concentrations than those displayed in Figure 1. One set of tests (1:1 citral–octanal and citronellal–octanal at 2.5:2.5%) was included within the original set of randomized tests. The second set (1:10 at 0.05:0.5% for both odor sets) was performed after all other tests had been completed. The comparisons are shown in Figure 2. The 1:1 citral–octanal tests (Figure 2a) show that the responses to 0.5:0.5% and 2.5:2.5% were nearly identical, with a decrease in the *p* value for the octanal response in the higher concentration set. The 2.5:2.5% citronellal–octanal 1:1 test (Figure 2c) showed the same trend as the 0.5:0.5% test reported in the main set of results, but the response to the trained mixture was not significant, primarily as a result of a relatively high response to the control odor.

The 1:10 low concentration tests (0.05:0.5%) were performed after completion of the other tests, and they show some marked differences compared with those performed at higher concentration (0.5:5%). Figure 2b shows the citral–octanal test comparison. For the lower concentration test, the identification of (amount of digging in) citral is greatly increased, and the mixture response decreased, over the original higher concentration test. The citronellal–octanal tests maintain the same trend as the higher concentration tests, but the citronellal and octanal are both recognized at the lower concentration.

Discussion

Recent studies in rats have shown configural effects for binary mixtures when the components are very similar in chemical structure (Linster & Smith, 1999; Wiltrout et al., 2003). These same odorants likely overlap in their glomerular activation (Belluscio &

Figure 1 (opposite). Digging times for all concentration ratio sets. Normalized digging times (± *SE*) for the four odors in each odor test set (indicated by the ratio below the data markers) are indicated for each concentration ratio test. Asterisks indicate a significant increase over the response to the control odor (* $p < .05$, ** $p < .01$; post hoc Newman–Keuls test). The boxed data sets are those closest to the inverse ratio of the theoretical vapor pressures for the two chemicals. a: Citral–octanal (cit/oct) tests. Rats were trained to recognize the mixture in the ratio of citral to octanal indicated below each set of four data points. They were tested on the noted mixture, each of the components, and an unrelated control odor (cineole). b: Citronellal–octanal (citron/oct) tests arrayed as in Figure 1a. The control odor was hexanol. Note the large range over which neither component was recognized. The arrow ("citron only") signifies that the post hoc comparisons were significant for citronellal versus hexanol but not for octanal versus hexanol. c: Citral–octanal pairwise comparisons among the set of noncontrol odors (mixture, citral, and octanal). There is no significant difference between citral and octanal responses over the training ratios of 29:1, 20:1, and 10:1. At smaller ratios of citral to octanal, the response to octanal is significantly greater than to citral, and in two of these tests, the response to citral is not significant. d: Citronellal–octanal pairwise comparisons: At higher ratios of citronellal to octanal, the response to citronellal is significantly higher than that to octanal, and at the very lowest ratio, the octanal response is significantly higher than the citronellal response. In none of the tests are both components recognized. Over the range of 5:1 to 1:10, only the mixture is recognized. Asterisks indicate that response to mixture was greater than response to citral or citronellal (* $p < .05$, ** $p < .01$); caret symbols indicate that response to mixture was greater than response to octanal (^ $p < .05$, ^^ $p < .01$); pound signs indicate a significant difference between citral or citronellal and octanal responses (# $p < .05$, ## $p < .01$); an X below the graph indicates that digging was not significantly greater than to the control odor (from Panels a and b).

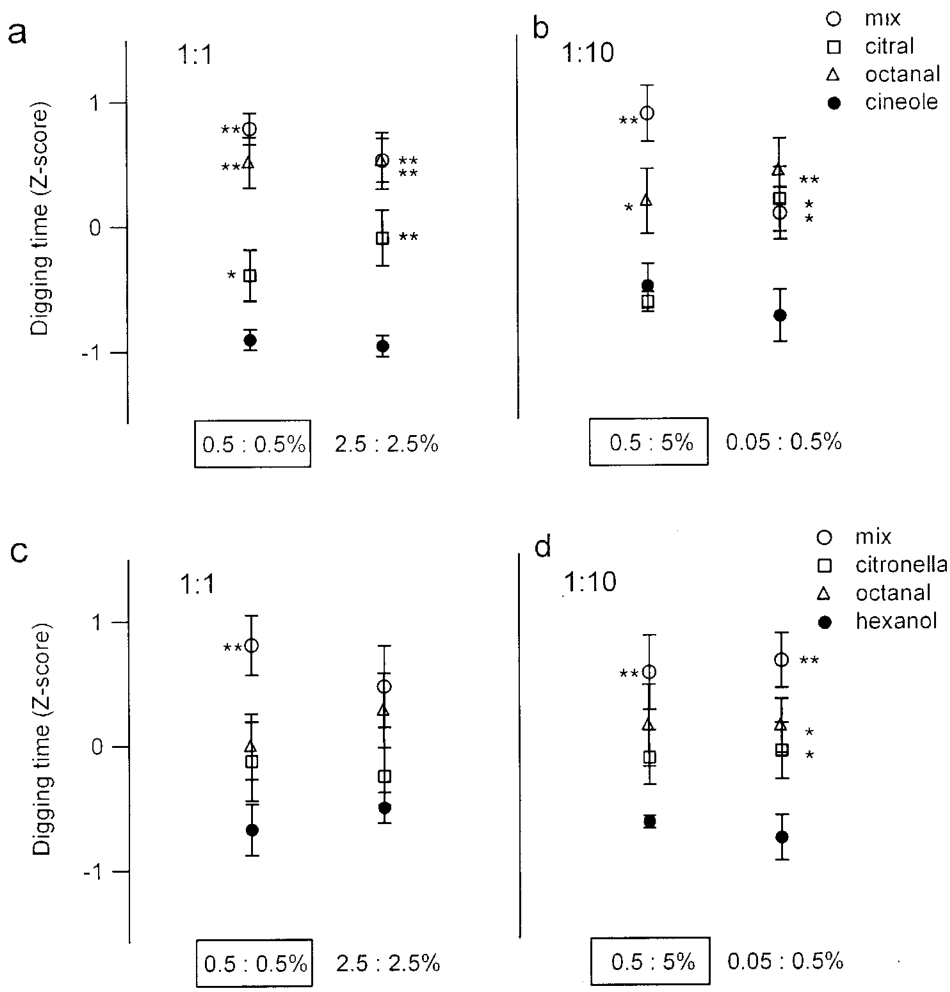


Figure 2. Comparison at two different absolute concentration sets. Normalized digging times for 1:1 and 1:10 concentration ratios for the two odor sets (citral–octanal and citronellal–octanal). Asterisks indicate that response to mixture was significantly different than response to individual odorants (* $p < .05$, ** $p < .01$). The boxed values are those presented in Figure 1. a: Citral–octanal tests with 1:1 training mixture at 0.5:0.5% and 2.5:2.5%. The results are comparable for the two tests. b: Citral–octanal tests with 1:10 training mixtures at 0.5:5% and 0.05:0.5%. In the second set, citral is recognized, whereas it was not in the original test. c: Citronellal–octanal tests with 1:1 training mixtures. The results for the two tests are comparable, although mixture digging is not significant for the higher concentration test. d: Citronellal–octanal tests with 1:10 training mixtures. Both components are recognized in the second test, whereas they were not recognized in the first test.

Katz, 2001; Fried et al., 2002; Johnson, Woo, Hingco, Pham, & Leon, 1999; Rubin & Katz, 1999). In this study, we show that perception of components within an odor mixture can be correlated with the mode of interaction at the receptor level. This interaction can determine whether or not a particular mixture exhibits elemental or configural properties. We also show that mixture psychophysics are enhanced by using a wide range of concentration ratios, as recognition of components can vary significantly, depending on relative concentrations.

The two sets of chemicals were chosen because they are known to interact with the rat I7 olfactory receptor (Araneda et al., 2000). In Araneda et al., octanal and citronellal were seen to be strong activators of receptor neurons expressing the I7 receptor, whereas citral was seen to be a weak activator and possible antagonist. When a 10:1 mixture of citral and octanal was applied in liquid phase to the receptor neurons, the octanal response was decreased by 40%. Our experiments show that citral and octanal act as if they compete for perceptual recognition within a binary mixture in a manner consistent with chemicals that are structurally unrelated (Linster & Smith, 1999; Wiltrout et al., 2003; Figures 1a and 1c).

Citral–octanal mixture perception is primarily elemental except at the most extreme ratio (50:1). This profile can be explained if both citral and octanal activate other, nonoverlapping populations of receptor neurons. It is known that even monomolecular odorants likely activate at least a small number of different receptor populations, depending on concentration (Malnic, Hirono, Sato, & Buck, 1999; Rubin & Katz, 1999; Wachowiak & Cohen, 2001), and that individual receptor neurons can be responsive to several odorants (Duchamp-Viret, Chaput, & Duchamp, 1999). Thus, reduction of the I7 response by the presence of citral could cause the system to rely on other receptors not responsive to both citral and octanal to represent the mixture during training. This provides an explanation for enhanced elemental representation of binary mixtures of chemically dissimilar odors.

Perceptual competition is also suggested by the citronellal–octanal tests, but recognition of the components is markedly decreased (Figures 1b and 1d), producing a primarily configural representation of the mixture. As identification of citronellal occurs over a much wider range than identification of octanal, the profile suggests that citronellal may be a more potent activator of the I7 receptor or that it activates a larger number of receptor types than octanal. These two odors maximally activate at least some of the same receptor neurons (Araneda et al., 2000), and in combination, prevent recognition of individual components over a large range of concentration ratios. This supports the receptor-based model for configural representation of an odor mixture, in which individual components are suppressed in a binary mixture of chemically similar odors. A recent study in humans found configural effects for mixtures of four different odorants, judged so by differential qualitative descriptors (Jinks & Laing, 2001). However, the odorants used were somewhat similar in chemical structure, and it is likely that in a quaternary mixture there was significant receptor overlap. In addition, the tests were conducted at only one set of concentration ratios, and the results reported here show that there can be variation in configural properties, depending on the relative concentrations of even two odorants.

Qualitative differences due to absolute concentrations may occur, particularly in light of the fact that some odorants are known to change quality at high concentrations. Our limited tests of higher absolute concentrations within the main body of experiments were not appreciably different from the lower concentration tests (Figures 2a and 2c). However, the 1:10 low concentration tests (Figures 2b and 2d) done at the end of the experiment did show some significant changes. Whether these differences are due to absolute concentration or to the nonrandom test order cannot be answered with these data. It is likely that absolute concentration does affect these results, especially at the extremes, as odor concentrations near thresholds for receptor activation and identification on one end or recruitment of additional receptor types (Rubin & Katz, 1999; Stewart et al., 1979) and possible trigeminal effects (Cometto-Muniz et al., 1999) on the other. These results show that within a limited range the ratio of concentrations may be more salient than absolute concentrations in mixture perception.

In summary, we show that the configural and elemental properties of some binary odor mixtures can be accounted for by olfactory receptor biophysics. We also show that studies using a wide range of concentration ratios and known receptor ligands may be guided by, as well as aid, psychophysical analysis of odor mixtures.

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