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Original Article

Recognition of the Component Odors in Mixtures

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Abstract

Natural olfactory stimuli are volatile-chemical mixtures in which relative perceptual saliencies determine which odor-components are identified. Odor identification also depends on rapid selective adaptation, as shown for 4 odor stimuli in an earlier experimental simulation of natural conditions. Adapt-test pairs of mixtures of water-soluble, distinct odor stimuli with chemical features in common were studied. Identification decreased for adapted components but increased for unadapted mixture-suppressed components, showing compound identities were retained, not degraded to individual molecular features. Four additional odor stimuli, 1 with 2 perceptible odor notes, and an added "water-adapted" control tested whether this finding would generalize to other 4-compound sets. Selective adaptation of mixtures of the compounds (*odors*): 3 mM benzaldehyde (*cherry*), 5 mM maltol (*caramel*), 1 mM guaiacol (*smoke*), and 4 mM methyl anthranilate (*grape-smoke*) again reciprocally unmasked odors of mixture-suppressed components in 2-, 3-, and 4-component mixtures with 2 exceptions. The *cherry* note of "benzaldehyde" (itself) and the shared note of "methyl anthranilate and guaiacol" (together) were more readily identified. The pervasive mixture-component dominance and dynamic perceptual salience may be mediated through peripheral adaptation and central mutual inhibition of neural responses. Originating in individual olfactory receptor variants, it limits odor identification and provides analytic properties for momentary recognition of a few remaining mixture-components.

Key words: chemosensory coding, dynamic odor sensing, human olfaction, mixture suppression, odor intensity adjustment, selective adaptation

Introduction

The human olfactory system operates in environments containing stimulus mixtures from which, at most, 4 single stimulus component odors or complex odor-objects are reliably identified (Livermore and Laing 1996, 1998a, 1998b). Furthermore, odors enter and exit, providing the olfactory system with a forever dynamic stimulus array. Such an array was simulated in a "selective adaptation" model to document how the human olfactory system captures necessary olfactory information. Subjects identified odor-mixture components after 5 s of selective adaptation (Goyert et al. 2007; Frank et al. 2010). An adapting mixture was sniffed (once or twice) and then a second mixture was presented containing the same "ambient" components with an "extra" component added. Consistent with earlier anecdotal accounts of exhaustive selective adaptation (Moncrieff (1956, 1967), Goyert et al. (2007) found "ambient" odors faded over seconds of sniffing while "extra" odors emerged from mixture-suppression to perceptually dominate test stimuli. Selective adaptation affected perception of entire molecules within a set of molecules with distinct odors not their common chemical features. This result challenged coding theories proposing extraction of chemical structural-features to be

synthesized subsequently into odor perceptions by the olfactory system (Malnic et al. 1999; de March et al. 2015).

The current study tests the generality of "retention of odor identities" with a new set of 4 water-soluble, feature-sharing compounds (benzaldehyde, maltol, guaiacol, and methyl anthranilate with odors of *cherry*, *caramel*, *smoke*, and *grape*, respectively) and, unlike Goyert et al. (2007), includes a water control. If proven general, that is not "compound-specific," consequences include facilitation of future work on selective adaptation of mixtures of as many as 8 single compounds. Three of the new chemical stimuli elicited the percepts designated during label training. However, subjects used 2 of the designated labels (*grape* and *smoke*) for methyl anthranilate, suggesting it has 2 perceptible parts (odor notes).

Despite substantial species differences, human odor coding models benefit from considering olfactory genomics and neurophysiology of other species. Many other species have more functional molecular receptors (ORs) than humans. Most are known to have about 1000, likely needed to detect the diverse volatiles relevant to the species needs (Hughes et al. 2014). The number of distinct human OR is about 400 but ligand specificity is uncertain for most of them (Poivet et al. 2016). Single OR variants are expressed in each olfactory sensory neuron (OSN) and the many OSN expressing a single variant converge onto a few glomeruli (GL) in the olfactory bulb (OB). These 2 important features of the olfactory pathway define "OR-OSN" to "OB-GL" lines. Thus, the OR response is transmitted to the brain essentially unchanged.

It is hypothesized that recognition of component odors in mixtures under natural conditions is often regulated by perceptual saliency and quality overlap. Figure 1 diagrams the case for binary mixtures representing 2 odor sets (A, B), each activating independent OR. Component odors emerge from mixture suppression with selective component adaptation. Conversely, shared odors may add together to increase shared-note salience.

Given methyl anthranilate has a *grape* note and a note it shares with guaiacol, the "quality-overlap" hypothesis is testable with the present dataset. Importantly, if the 2 arms of the hypothesis are upheld, odor perceptions under natural conditions can be predicted by operationally measured, componental outcomes to rapid selective adaptation and mixture suppression. Dominant odor notes, either single or shared, will simply suppress less intense odors, including those weakened by rapid selective adaptation.

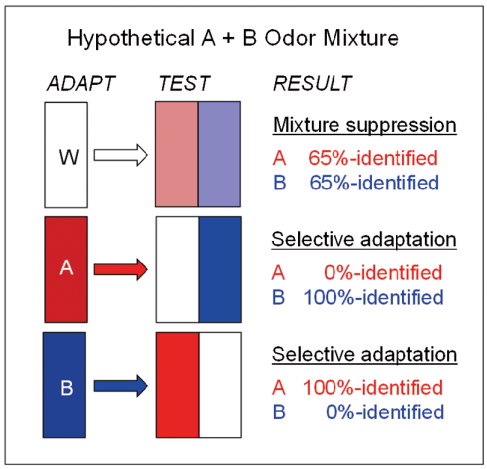

Figure 1. Rapid selective adaptation of odors suppressed in mixtures. When preceded ("adapted") by water (W), identification of individual mixture components is compromised due to mixture suppression (represented by less saturated colors). However, odor B (blue) dominates after a 5-s prior adaptation with odor A; and odor A (red) dominates after prior adaptation with odor B. This process is used by the olfactory system to dynamically adjust salience of mixture components by selective adaptation.

Materials and methods

Simulation of natural human "odor-sensing" conditions was achieved with adapt-test stimulus pairs (Goyert et al. 2007). Each trial lasted a few seconds before ending with sniffing water vapor to clear the palate. Data interpretation is straightforward for independent odors that do not cross-adapt (Frank et al. 2010). Correct identification of designated labels objectively assesses component perceptual saliency, quantified as proportions, percentages, or frequencies. Neither odor intensity or quality (Keller and Vosshall 2016) nor typicality (Sinding et al. 2015) was rated. To complement a 2-component mixture model shown in the Introduction, selective-adaptation paradigms for the 4-component test mixture are presented in Supplementary Table 1. The subject's task is to name as many components detected in either session. The same component names: "ambient" and "extra," operationally defined for the experimental session, are applied to the control session.

Subjects

Fourteen nonsmokers without histories of taste or smell disorders participated with approval of the UConn Health Institutional Review Board (IE-01-262-1). The compensated 8 women and 6 men of average age (SD) 23 (1.4) years provided written informed consent. All work complied with the *Declaration of Helsinki* for Medical Research involving Human Subjects.

Component stimuli and component odors

Pure single stimulus compounds, dissolved in deionized water, were presented to subjects in squeeze bottles to be sniffed orthonasally from solution headspaces. The nontoxic compounds (FDA GRAS or synthetic food flavors; Furia 1972; Swaine 1972) had both distinct and overlapping chemical features (Figure 2) and reasonably pleasant distinct odors (Dravnieks 1985; Pittet et al. 1970; Keller et al. 2012). Odor-chemical vapor pressures, which are much lower than saturated vapor pressures because of water interactions, were not

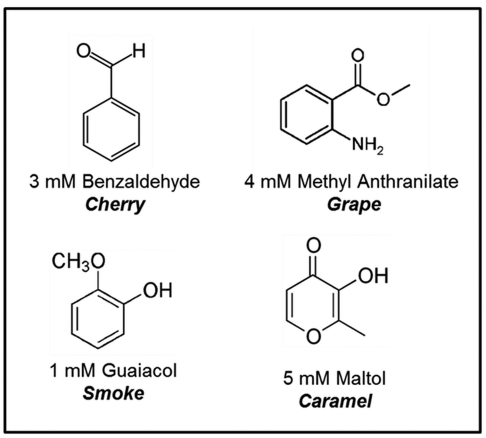

Figure 2. Chemical structures of mixture components with distinct odors. Structures of the aldehyde (benzaldehyde), methyl ester (methyl anthranilate), methyl ether (guaiacol), and ketone (maltol) are represented above veridical odor labels used in testing identification. Whole chemicals, in contrast to subsets of structural features of component compounds, appear to determine odor quality.

measured. No odor was noticeably pungent or "trigeminal," which would require 10 000 to 100 000 times higher concentrations to reach threshold (Cometto-Muñiz and Abraham 2016). The single concentrations used were tested in a pilot study (N = 4) to assure odors would be easily identifiable. Stimulus quality identifications and intensity ratings (0 [none] to 10 [very strong]) showed water was always rated 0. Designated odor stimuli were never rated 0 but had an average intensity of 4.5 (range: 3.5 for guaiacol to 6.0 for benzaldehyde). The stimuli/CAS numbers and designated odor labels are: 1 mM guaiacol/90-05-1 for *smoke*; 3 mM benzaldehyde/100-52-7 for *cherry*; 5 mM maltol/118-71-8 for *caramel* or *cotton candy*, and 4 mM methyl anthranilate/134-20-3 for *grape*. Three subjects preferred identifying the odor of maltol as *cotton candy* rather than *caramel*. Concentrations (mM) in mixture and single-component solutions were identical. Associated with veridical labels (Ferdenzi et al. 2017), the odors were expected to be readily identified; nonetheless, "control" presentations of component single stimuli were included in the experimental design to test this important assumption.

Stimulation procedures

All testing was performed in a room with nonrecirculating air maintained at a moderate temperature of 18–21 °C. Stock solutions were made fresh every 2 weeks and stored in tightly capped bottles (Goyert et al. 2007). Copies of a printed "odor list" of the 4 odor labels shown in Figure 2 and the label "odorless" for "water" were given to subjects during odor familiarization and placed before them for reference during testing. Fifty milliliters of solution in 250 mL polyethylene squeeze bottles (fitted with caps having flip-up spouts) was used for stimulus delivery. Subjects were trained to squeeze a solution bottle 1–2 times and sniff to capture the odor (Laing 1983). After completing odor-label familiarization with positive feedback, subjects were tested with the 4 component single compounds and water in random orders until they were able to correctly label them twice in a row. Experimental and control sessions began following successful training when subjects were verbally instructed to identify every odor recognized in each test solution as follows: "I will ask you to first sniff a bottle, then we will exchange bottles, and you will sniff the second bottle I give you. I will ask you to identify any odor you smell from the *second* bottle only." The experimenter recorded subjects' responses on a spreadsheet.

Experimental design

Each solution was presented 4 times per session on "adapt-test" trials that were spaced one minute apart to re-establish head-space vapor concentration (Rabin and Cain 1986). Figure 3 shows the 32 experimental "adapt-test" odor pairs and corresponding 32 control pairs. They each include the 4 single-components to assess identifiability of a component presented within a mixture series. Presentation of adapt-test pairs in the same random order occurred on separate days at least one day apart for experimental and control sessions. Orders of the 4 "extra sessions" and the 2 "experimental/control" sessions were randomized across subjects. Label choices after selective adaptation in experimental sessions were compared to choices made after water (the adapting stimulus) in control sessions.

Data analysis

1) ANOVA of "proportions correct" was used for mixtures; 2) *t*-tests of "proportions correct and incorrect" used for single compounds; and 3) χ^2 used for binary mixture frequencies.

Experimental Design: Adapt-Test Rapid Selective Adaptation

A. Experimental Extra Session				B. Control Extra Session			
1. Guaiacol (**G**)		2. Benzaldehyde (***B***)		*1. Guaiacol (**G**)*		*2. Benzaldehyde (**B**)*	
Adapt	*Test*	*Adapt*	*Test*	*Adapt*	*Test*	*Adapt*	*Test*
W	G	W	B	W	G	W	B
B	GB	G	GB	W	GB	W	GB
M	GM	M	BM	W	GM	W	BM
A	GA	A	BA	W	GA	W	BA
BM	GBM	GM	GBM	W	GBM	W	GBM
BA	GBA	GA	GBA	W	GBA	W	GBA
MA	GMA	MA	BMA	W	GMA	W	BMA
BMA	GBMA	GMA	GBMA	W	GBMA	W	GBMA
3. Maltol (***M***)		4. Me-Anthranilate (***A***)		*3. Maltol (**M**)*		*4. Me-Anthranilate (**A**)*	
Adapt	*Test*	*Adapt*	*Test*	*Adapt*	*Test*	*Adapt*	*Test*
W	M	W	A	W	M	W	A
G	GM	G	GA	W	GM	W	GA
B	BM	B	BA	W	BM	W	BA
A	MA	M	MA	W	MA	W	MA
GB	GBM	BM	BMA	W	GBM	W	BMA
BA	BMA	GB	GBA	W	BMA	W	GBA
GA	GMA	GM	GMA	W	GMA	W	GMA
GBA	GBMA	GBM	GBMA	W	GBMA	W	GBMA

Figure 3. Adapt-test stimulus presentations. (A) Experimental session adapt-test pairs are shown. Each stimulus is presented as an "extra" mixture component seven times, an "ambient" mixture component 12 times and a single component after water once, shaded blue. For example, Guaiacol is "extra" in the 7 mixtures shaded yellow and "ambient" in 12 mixtures shaded green. Binary-mixture rows are tagged on the left side by black rectangles. (B) Control session adapt-test pairs mirror experimental pairs except water (W) vapor was always the adapting stimulus. Subjects were tested once on each single compound, twice on each binary mixture, 3 times on each ternary mixture, and 4 times on the quaternary mixture. Binary-mixture rows are tagged on the right side by black rectangles.

Mixtures

Successful component-odor identification was quantified as proportion of component correctly identified in test-stimulus mixtures by each subject. For example, benzaldehyde was presented in 3 binary mixtures; the proportions-correct for any subject could be 0.0 for 0 correct identifications in 3 mixtures (0/3), 0.33 for 1/3, 0.67 for 2/3 or 1.0 for 3/3. A 4-way repeated measures analysis of variance of the mixture data examined effects of 1—session (experimental or control), 2—test-stimulus condition (extra or ambient), 3—mixture size (2, 3, or 4 components), and 4—compound (guaiacol, benzaldehyde, maltol, or methyl anthranilate), with $\alpha = 0.05$ and Student Neuman–Keuls tests used for post hoc comparisons.

Single compounds

Distributions of replicate identifications ($N = 28$) of the 4 labels (*cherry*, *smoke*, *caramel, grape*) quantified as percentages for "designated" (predicted to approach 100%) and "un-designated" (defining secondary odors when >0); and labels used for dominant *cherry* and grape/guaiacol secondary-odor response proportions were evaluated with Student's *t*-tests, $\alpha = 0.05$. With regard to the secondary odor, Dravnieks' (1985) descriptors identified by 120–140 panelists included *woody* 80% as frequently as our label *smoke* for guaiacol and 30% as frequently as our label *grape* for methyl anthranilate.

Binary mixtures

χ^2-analysis of subjects' identification frequencies under control ($N = 28$) or selectively adapted ($N = 14$) conditions ($\alpha = 0.05$) determined significance of atypical binary-mixtures, with a dominant "single-quality" or "shared-quality." (Experimental ambient-extra binary mixtures correspond to replicate control water-adapted mixtures (B→GB and G→GB become W→GB and W→GB). See Figure 3 and Supplementary Tables 2–6.) "Maltol standards," binary mixtures of atypical components mixed with maltol *caramel* (*cotton candy*), neither unusually salient nor sharing an odor quality, were crucial. Identification advantage/disadvantage and benefit were calculated for shared/unshared odors.

Results

Results of experimental and control sessions are reported for: (A) percentage of identified single-compound-odors; (B) proportions of identified "extra" and "ambient" or (C) identified benzaldehyde, guaiacol, maltol, and methyl anthranilate in binary, ternary, and quaternary mixtures in designated-odor components; and (D) frequency of identifications of shared-odors in binary mixtures.

Compounds with single and dual odors

Odor identification profiles for single compounds presented alone (after water in experimental and control sessions combined) are illustrated in Figure 4. Average percent correct (e.g., detecting the designated *cherry* for benzaldehyde) and incorrect (e.g., detecting undesignated *smoke*, *caramel*, or *grape* for benzaldehyde) identifications are shown. (The 28 single "odor-compound" label identifications were quite limited, ranging from 28 to 31 of a possible 56 if 2 labels had been used for each compound. Benzaldehyde elicited 28 *cherry* plus 1 *grape*. Guaiacol elicited 27 *smoke* plus 2 *caramel*, 1 *cherry*, and 1 *grape*. Maltol elicited 22 *caramel* + 4 *cotton candy* plus 2 *grape*. Methyl anthranilate elicited 17 *grape* plus 8 *smoke*, 3 *caramel*, and 2 *cherry*.) Subjects consistently used designated labels for benzaldehyde (*cherry*, 100%), guaiacol (*smoke*, 96%) and maltol (*caramel*, 93%). However, 2 labels were chosen consistently (90%) for methyl anthranilate (*grape*, 61%, *smoke*, 29%). The cluster of methyl anthranilate *smoke* identifications represents a significant secondary odor ($t = 2.83$, $P = 0.007$). It was the only undesignated label that subjects so used, suggesting odor commonality in methyl anthranilate and guaiacol, a stimulus known for OR genetic diversity (Mainland et al. 2014). Guaiacol was not significantly identified as *grape*. Subjects, not trained to detect *woody*, may have missed it in methyl anthranilate compared to the guaiacol, easily detected, primary *smoke* odor. The average designated correct single-compound identification of 89 ± 7.1% compares to the 50 ± 4.5% for binary, ternary, and quaternary mixtures reported below.

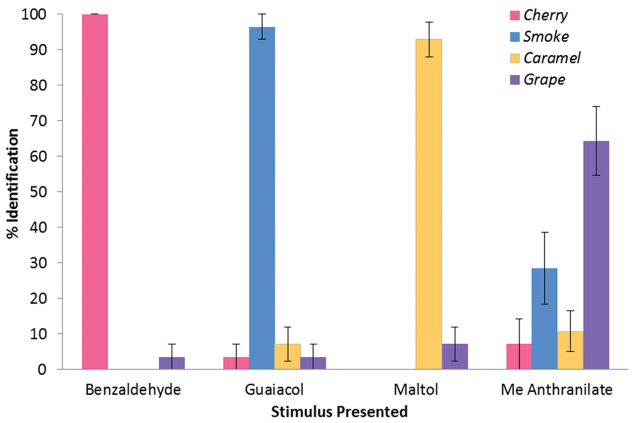

Figure 4. Four-quality identification profiles for single compounds after water. Benzaldehyde (*cherry*), guaiacol (*smoke*), and maltol (*caramel*) were each uniquely identified; methyl anthranilate was identified as either the designated *grape* (61%) or undesignated *smoke* (29%). All designated identifications and the secondary *smoke* identification of methyl anthranilate are significant ($P < 0.01$). A subject's % identification could be 0%, neither of the 2 identified (0/2), 50% for 1/2, or 100% for 2/2 identified. Designated labels are color coded: *cherry* is pink, *smoke* is blue, *caramel* is gold, and *grape* is purple. Mean % identifications ± standard errors are presented for 14 subjects.

Identification of "extra" odors after selective adaptation

The 4-way ANOVA (Table 1) of component designated-odor identification data reveals an important "session by condition" interaction. This "selective adaptation" interaction [$F = 10.21$, df (1, 13), $P = 0.007$] illustrated in Figure 5 shows water-adapted "extra" and "ambient" components were each 50% correctly identified (white bars); whereas selectively adapted components (pink bars) were identified with greater accuracy when "extra" than when "ambient" [$t = 3.54$, df (13), $P = 0.002$]. "Ambient" identification declined compared to water controls [$t = 3.17$, df (13), $P = 0.004$], while the "extra" identification increase was not itself significant [$t = 1.61$, df (13), $P = 0.07$]. Designated-component-odor identification also depended on 3 of the main effects: "condition," "mixture size," and "odor compound"; with an extra over ambient condition identification advantage [$F = 9.93$, df (1, 13), $P = 0.008$] and mixture-size identification disadvantage [$F = 5.84$, df (2, 26), $P = 0.008$]. Results are consistent with "extra/ambient" identification advantages at each mixture size: binary [$t = 3.65$, df (13), $P = 0.001$], ternary [$t = 3.15$, df (13), $P = 0.004$] and quaternary [$t = 2.6$, df (13), $P = 0.01$)]. Selective-adaptation advantage was ubiquitous in designated correct identification data. The "odor compound" effect [$F = 7.12$, df (3, 39), $P = 0.001$] is considered in *Identification of dominant stimulus and after selective adaptation* section.

Table 1. Mixture component odor identification proportions 4-factor analysis of variance

Source[a]	df (factor, error)	*F*	*P*-value
[1] Experimental/control session	(1, 13)	1.83	0.199
[2] Extra/ambient condition	**(1, 13)**	**9.93**	**0.008**
[3] Mixture size (2/3/4)	**(2, 26)**	**5.84**	**0.008**
[4] Compound (B,G,M,A)	**(3, 39)**	**7.12**	**0.001**
[1 × 2] Selective adaptation	**(1, 13)**	**10.21**	**0.007**
[1 × 3] Session × size	(2, 26)	1.97	0.159
[1 × 4] Session × compound	(3, 39)	0.73	0.538
[2 × 3] Condition × size	(2, 26)	0.24	0.786
[2 × 4] Condition × compound	(3, 39)	0.01	0.999
[3 × 4] Compound × size	(6, 78)	1.97	0.080
All other interactions			ns

N = 14 subjects; (X × Y) = 2-way interaction; bold type = statistically significant. ns, not significant; B, benzaldehyde; G, guaiacol; M, maltol; A, Me-Anthranilate.

[a]Source numbers in brackets, are cited in text.

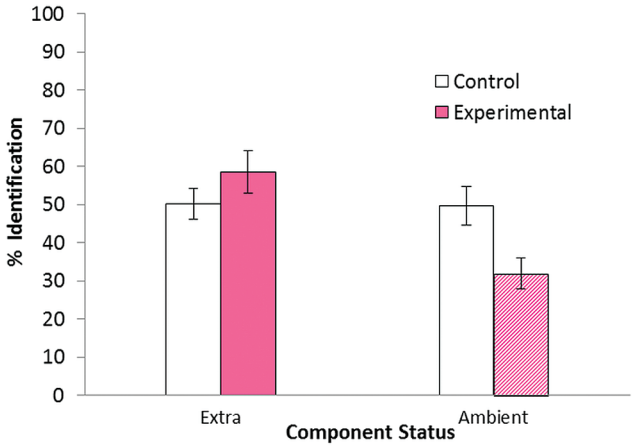

Figure 5. Extra test-stimulus-components retain individual odor identities in selectively adapted mixtures. Experimental = selectively adapted (rose-colored bars). Control = water-adapted (white bars). [Selective adaptation, $F = 10.21$, df (1, 13), $P = 0.007$]. Mean % correct identification ± standard errors of means for 14 subjects are presented. (Based on 4-factor ANOVA, Table 1.)

Identification of dominant stimulus and after selective adaptation

Benzaldehyde *cherry* odor dominated the other odors although each odor stimulus had been rated of "moderate" intensity in the pilot study described in Methods, *B. 'Component Stimuli and Component Odors*. *Cherry* dominance is evident in Figure 6a, the average of duplicate water-adapted, extra-ambient controls [$F = 6.46$, df (3, 39), $P = 0.001$]. Average control 71%-identified *cherry* compares to average 43%-identified for the other 3 odors. Critically, selectively adapted "extra" components (Figure 6b) were identified more than twice (2.6 ± 0.6 times) as frequently as "ambient" components [$F = 12.53$, df (1, 13), $P = 0.004$]. Control mixture-suppressed odor salience was redistributed to the single extra component from selectively adapted ambient components (Figure 6b) regardless of component-odor salience (Figure 6a).

Extricating "shared-odor" identification within binary mixtures

Benzaldehyde had a dominant odor (Figure 6) already analyzed with ANOVA of identification proportions while methyl anthranilate, with a primary odor recognized as *grape* and secondary odor shared with guaiacol (Figure 4) requires analysis. Here, binary mixtures containing dominant or shared odor-notes and "maltol-standards" are compared by χ^2 analysis of identification frequencies. See Data analysis in Methods section.

Control binary-mixture identification frequencies

Benzaldehyde *cherry*-odor "dominance" over other primary odors and the methyl-anthranilate "secondary odor" were clear. Percentages of *cherry*-only detection mixed with *grape* (methyl anthranilate) or *caramel* (maltol) were 39%/11% for *cherry/grape* ($\chi^2 = 6.1$, $P = 0.01$) and 54%/3.6% for *cherry/caramel* ($\chi^2 = 17$, $P = 0.00003$). The methyl-anthranilate secondary odor, undetected mixed with benzaldehyde, was 29% detected mixed with maltol ($\chi^2 = 4.4$, $P = 0.04$). Notably, "shared-odor prominence," discovered for "guaiacol + methyl anthranilate," was evident in 64%/36% "*smoke/grape* detection ($\chi^2 = 4.57$, $P = 0.03$), giving an advantage of 1.78 (64/36%) to *smoke* but 0.56 (36/64%) disadvantage to grape detection. "Maltol standards," which in this case are guaiacol or methyl-anthranilate separately mixed with maltol, were 64%/57%: a nonsignificant, 1.12/0.89 *smoke/grape*, advantage/disadvantage. Normalized to controls, the *smoke* dominated with a 1.6 (1.8/1.1) times advantage compared to *grape's* 0.63 (0.56/0.89) times disadvantage: a 2.5 (1.6/0.63) *smoke/grape* benefit in water-adapted controls. The combined *smoke* odor may have dominated *grape* as *cherry* dominates *caramel* odor in mixtures.

Selectively adapted binary-mixture identification frequencies

"Ambient" ocomponents are usually detected less frequently than "extra" components (Figure 6b). Exceptions illustrate benzaldehyde *cherry*-odor dominance and "guaiacol + methyl anthranilate" *smoke*-odor predominance over the unshared *grape*-odor. Similar "ambient"/"extra" percent detections (57%/71%) of "ambient" benzaldehyde *cherry* and "extra" maltol *caramel* illustrate *cherry* odor dominance. Moreover, selectively adapting "guaiacol + methyl-anthranilate" revealed intensified *smoke/grape*, 71%/25%, component "odor predominance" [$\chi^2 = 12.1$, $P = 0.0005$]. Table 2-(1) shows *smoke* was more frequently identified than *grape* whichever component had been adapted. Table 2-(2–3) shows that components separately mixed with the "maltol standard" developed the usual selectively adapted "extra better than ambient" outcome. Selective adaptation of either guaiacol or methyl-anthranilate mixed with maltol yielded low 32% "ambient" and high 71% extra' identifications ($\chi^2 = 8.7$, $P = 0.003$).

Shared component-identification advantages and benefits

Average selectively adapted "guaiacol + methyl-anthranilate" *smoke/grape* odor identification advantage is 2.9 [0.5 × (11/3 + 9/4)] and complementary *grape/smoke* disadvantage is 0.35 [0.5 × (3/11 + 4/9)] (Table 2 (1)). Average "maltol standards" are 1.2 [0.5 × (5/4 + 11/9)] for *smoke/grape* (Table 2 (2)) and 0.81 [0.5 × (4/5 + 9/11)] for *grape/smoke* (Table 2 (3). Normalized to controls yields a 2.4 times (more than twice) mixture advantage for *smoke* compared to a 0.43 times (below one half) disadvantage for *grape*. The calculated 5.6 [2.4/0.43] *smoke/grape* selective-adapted benefit is more than twice the 2.5 water-adapted benefit calculated previously. Already disadvantaged when water-adapted, selective adaptation will quickly prune unshared odors in natural situations.

Synopsis of results

(1) The new set of 4 stimuli each has a distinct, readily identified odor; but 2 share an odor. (2) In 2, 3, and 4 component mixtures,

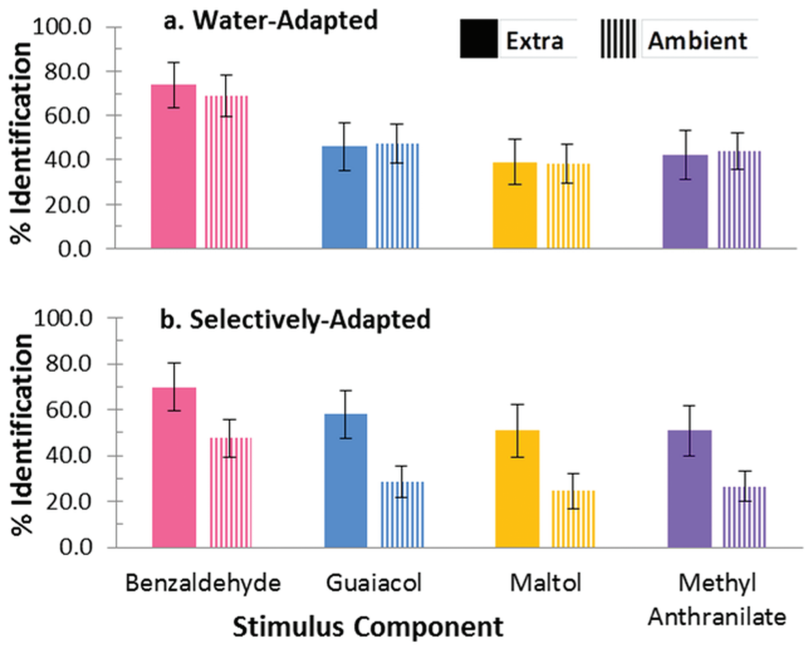

Figure 6. Benzaldehyde dominates water-adapted mixtures; extra components dominate selectively-adapted mixtures. (**a**) *Cherry* odor more readily identified than other water-adapted cases. Benzaldehyde odor identification exceeds the other 3 odor identifications [$F = 6.46$, df (3, 39), $P = 0.001$]. (**b**) Four extra components identified more readily than their ambient counterparts in selectively adapted cases. "Extra" %-odor identifications exceed 'ambient identifications [$F = 12.53$, (df 1, 13), $P = 0.004$]. Mean % identification ± standard errors are shown ($N = 14$). (Based on 3-factor ANOVA for water adapted control or selectively adapted experimental conditions.)

Table 2. Binary odor identification frequencies

Tested stimulus mixture	Stimulus selectively adapted			Stimulus selectively adapted		
	A	G	M	A	G	M
	Identify smoke odor			Identify grape odor		
1 Guaiacol + Me-Anthranilate	[11	9]	—	[3	4]	—
2 Guaiacol + Maltol	—	[5	11]	—	1	3
3 Me-Anthranilate + Maltol	3	—	4	[4	—	9]

1. Adapted by either methyl anthranilate (A) or guaiacol (G), 11 + 9 subjects identified *smoke*, 3 + 4 subjects identified *grape*, $P < 0.01$. *Smoke* (left) and *grape* (right) frequencies are bracketed.

2–3. Adapted by maltol (M), tested with either G or A: 11 + 9 subjects identified the extra component; adapted/tested by G or A: 5 + 4 subjects identified the ambient component $P < 0.01$. Ambient and extra frequencies are bracketed for each mixture.

Values are numbers of the 14 subjects identifying component odors.

identifications of "ambient" odors typically decrease with selective adaptation while "extra" odors increase. (3) Identification of water-adapted benzaldehyde *cherry* odor far exceeds identifications of other odors. (4) With selective-adaptation, "extra" odors grow quickly to 2.6 times "ambient" odors. (5) Stronger single odors and shared odors dominate weakened odors in water-adapted (2.5 times benefit) and more so in selectively adapted (5.6 times benefit) binary mixtures.

Discussion

In the current study, it was possible to show (with approximate matching of component salience of 4 water-soluble odor stimuli) characteristic component odors emerge from mixture suppression following rapid selective adaptation (Goyert et al. 2007) and increased 2-fold the odor stimuli that have been studied. The data also support a new "shared odor-note predominance" concept and the previously reported mixture-size limitation. Equally salient binary-mixture components are often identified, ternary mixtures are more difficult but quaternary mixture components are hardly recognized above chance levels (Laing 1983; Laing and Glemarec 1992; Livermore and Laing 1996, 1998a). Furthermore, effective selective adaptation is quite rapid, inducing odor-coding changes much faster than had been appreciated in humans. Five seconds is sufficient to reduce efficacy and complementally improve "other odor" recognition. In that short time, "ambient" components are identified about half as often as "extra" components suggesting an adaptation half-life (time required to reduce identification to half its original level) of 5 s. This is consistent with mixture components being identified half as frequently when half as intense (Ferreira 2012) and practically complete adaptation [$(1/2)^{12}$, (~0.02%)] in 1 min. Rapid adaptation is also seen for salamander and mouse OSNs (Zufall and Leinders-Zufall 2000). The limits of mixture-component identification in dynamic natural situations still need addressing. At this juncture, it is worthwhile to assess how well odor-potency and quality-overlap can

explain component odor identification with regard to (A) outcome consistency, (B) simulated natural conditions, and (C) distinguishable odors and odor objects.

Outcome consistency for 2 sets of 4 compounds with distinct odors

The current study is critical for determining whether the Goyert et al. (2007) findings are generalizable to another set of compounds. Quantitative results show the 2 studies to be consistent; even though earlier controls were reversed "test-adapt" stimulus pairs (Goyert et al. 2007) not the "water-test" stimulus pairs used in the current study. First, "extra" stimuli were identified about twice as often as "ambient" stimuli in both studies. Second, "extra minus ambient," "percent-identification differentials" for the average (binary, ternary, and quaternary) selectively adapted mixture was 26% (Figure 5 above) and 37% (Figure 2, Goyert et al. 2007); yielding "extra/ambient" identification ratios of 1.8 (58%/32%) and 2.0 (75%/38%), respectively. Third, mixture components were correctly identified less frequently than single compounds: binary 36%-less and "ternary and quaternary" 44%-less in each study. However, in the current study, benzaldehyde *cherry* was identified more frequently than other odors. Average identification of the "dominant" *cherry* odor in 2-, 3-, and 4-component mixtures ranged from 70% to 74%, far above the average 43% for the other stimuli, but still far below the 100% identification of benzaldehyde alone ($P < 0.01$). The *cherry* may not have been powerful enough to override interactions originating from the other odors (Livermore and Laing 1996). A stronger benzaldehyde test concentration may.

Thus, 8 distinct, water-soluble compounds, in aggregate, were characterized in experimental, controlled, dynamic odor environments, within which mixture-components are rapidly modified (Frank et al. 2010). These odor stimuli can be used to address additional questions such as whether odors of single "extra" components can be identified in mixtures after adapting to more than 3 other components. Theoretically, single "extra" odors are identified more readily than "ambient" odors; but measurable outcomes may be limited by the accumulating mixture suppression in quintuple mixtures.

Odor notes and coding under simulated natural conditions

Hundreds of detectable odors neither exist simultaneously in natural environments nor are they equally salient independent odors. Below, (a) saliency is suggested to limit identification of "odor notes" and (b) a "perceptual-limit" theory is compared to other "odor coding" theories.

Odor notes

Identification relies on (1) individual component salience and (2) summed salience of components with mutual odor-notes. Accordingly, (1) most-salient benzaldehyde *cherry* is recognized at the highest levels in control quaternary mixtures in which less-salient, maltol *caramel* is recognized at chance levels (with half the subjects failing to identify it); and (2) water-adapted *grape* odor of "guaiacol + methyl-anthranilate" (already identified 28% less frequently than the 64%-identified smoke) is identified 46% less frequently than 71%-identified smoke when selectively adapted. As shown in Supplementary Figure 1, single un-shared odors may be dominated by shared odors in which the dual sources add together to produce "stronger" odors. In the figure, shared dominance, shown to the left of the vertical dashed line, shows *smoke* odor identified more often than *grape* odor (71% > 25% averages) regardless of which component was adapted. But, *grape* identification approximates *smoke* identification when no odor is shared, as seen in "*maltol standard*" "extra"-component data on the right. *Smoke* and *grape* "extra" odors are an average 71%-identified when separately mixed with maltol.

Odor notes of methyl anthranilate: *grape* and perhaps *woody*, the "something like guaiacol" suggested by Dravnieks (1985), may be derived from distinct receptors. Separately adapted-out, chemical features of compounds specific to a shared odor-note could help define odor qualities and, possibly, even OR chemistry. Methyl anthranilate and guaiacol are ortho-di-substituted benzenes of comparable size with related functional groups of "methyl ester versus methyl ether" and "amino versus hydroxyl" (Figure 2). Distinctive methyl anthranilate chemical features could help define *grape* quality. Butyl anthranilate has a *grape* but no guaiacol-like note, pointing to ortho-amino ester functional groups as key *grape* contributors. The longer chain length may conceal necessary features for a guaiacol-like note present in the butyl compound. Another way to approach the *grape* odor-note is to adapt-out the guaiacol-like note of methyl-anthranilate with guaiacol. The remaining quality should be uncontaminated *grape*. This is, in essence, the same procedure used for selective mixture adaptation except both adapting and test stimuli are single compounds with dual odor-notes. With notes isolated in this way, odor stimuli with multiple notes associated with genes (Brenna et al. 2002; McRae et al. 2013) may inform OR structure-function analysis as phenylthiocarbamide tasters and nontasters has bitter taste (Kim and Drayna 2005).

Coding odors

OR signals are carried unchanged centrally by OSNs to a few devoted OB-GL in rodents (Buck and Axel 1991; Ressler et al. 1994; Mombaerts et al. 1996; Axel 2005; Buck 2005) to form rodent "OR-OSN" to "OB-GL" labeled lines. The 400 human OR may be needed to represent the totality of our distinct odors, which may combine several chemicals (Sell 2006) or even represent familiar "odor objects" (Livermore and Lang 1998b; Thomas-Danguin et al. 2014). If each human OR variant were associated with 1 "odor note," this arrangement itself could handle about 80 000 (400 × 399)/2) different cognate odors each with an average 2 notes (Goyert et al. 2007). But studies show rodent OR lack specificity. Many of the OR respond to the same ligand, multiple ligands with common functional groups or simply respond very broadly (Malnic et al. 1999; Araneda et al. 2000; Nara et al. 2011; Poivet et al. 2016; Tazir et al. 2016). Clearly, peripheral adaptation and central bulbar or cortical inhibition (Shepherd 1977; Yokoi et al. 1995; Lecoq et al. 2009; Isaacson 2010; Boyd et al. 2012; Yu et al. 2013) is needed to refine OR signals before perception.

Approaches to the quandary regarding recognition of thousands of vaporous odor stimulus molecules have been (1) theoretical: "*deconstruction*" into fewer numbers of chemical features to manage thousands of rodent OR (Malnic et al. 1999), (2) psychophysical: formation of momentary "*perceptual limits*" in natural situations to accommodate 400 human OR a few at a time (Goyert et al. 2007); and (3) pragmatic: limitation of molecular-feature study to those "*most-relevant*" to perception (Poivet et al. 2016). The first, *combinatorial*, requires re-combining molecular features to generate a perception. It is disadvantaged by chemical-structure ambiguity and loss of distinctions among isomers (optical, geometrical, and positional). Many enantiomeric pairs are distinguished by odor quality and threshold, notably the numerous wine-lactone enantiomers (Guth 1996). The second, *rapid selective mixture adaptation*,

involves modification of odor saliency to specify a few simultaneously identifiable independent odor-notes (Goyert et al. 2007). It can accommodate 400 OR; however, how unitary recognition of familiar multi-odor objects is achieved remains unresolved (Livermore and Laing 1998b; Sinding et al. 2015; Zhaoping 2016). The third, *relevant receptive mechanisms*, is a new approach. So far, *molecule-panels* show stimulus "topological polar surface area" is more important for acetophenone odor detection than benzene ring-size (Poivet et al. 2016). Pursuing a variety of approaches linking chemistry to sensation in chemical senses will be advantageous to discovery.

Separable odors and odor objects in mixtures

The componental mixtures concept is based on the understanding that chemical senses are fundamentally different from vision or hearing. Odor and taste perception do not have characteristics well-suited to models of synthesized color mixtures or synthesized 3-dimensional spaces. Chemicals themselves are discontinuous and chemosensory perceptions have practically no spatial component. Anatomical, neurological, and psychophysical distinctions between vision and olfaction may reflect a tradeoff between spatial needs for vision and the absolute need for olfaction to detect and recognize odor quality/preference of many unrelated chemicals (Lapid et al. 2011; Cameron et al. 2014). While 3 cones with distinct opsin receptors, most sensitive to overlapping segments of the visible spectrum, synthesize a rainbow of colors through red-green and yellow-blue retinal "opponencies" (Shapley and Hawken, 2002; Dacey and Packer, 2003) and juxtaposition of slightly different binocular/binaural, visual/auditory fields synthesize 3-dimensional space, olfaction has only 2 critical spatial locations derived from ortho-nasal sniffing of the external world and retro-nasal sensing of food in the mouth (Small 2012). With odors rapidly adapting on the same few-second time scale as sniffing (Laing 1983), odor sampling quickly shifts from the outdoors to inside the mouth. By comparison, sights last more or less continuously, with adaptation of receptors requiring minutes to reach maximum sensitivity in the dark or reappearance of function with lights-on (Goldstein 1999). In the following sections what *can be* (a) and *cannot be* (b) identified in odor mixtures is discussed.

Identified components in odor mixtures

An OR-based, "subtle combinatorial code" is appealing for its potential "extraordinary discriminating power" (de March et al. 2015). However, a synthetic processing of odor, especially of all possible odor mixtures, is daunting. Even fashioning an "olfactory nervous system" dealing with 400 separate labeled "OR-OSN to OB-GL" lines is a challenge. But, in either case, rapid selective adaptation in natural situations dynamically and momentarily reduces identifiable mixture components to a few. When 2 odor mixtures are quickly sampled sequentially, odors common to both mixtures are diminished by adaptation; at the same time, odors distinct to the second mixture gain strength and become easier to recognize than earlier, when they were mixture-suppressed. This rapid process is a major factor in deciding odor or taste quality of pairs of mixtures presented successively for identification or discrimination (Frank et al. 2012; Bushdid et al. 2014). Rodent taste receptors (TR) (Yarmolinsky et al. 2009) are coupled with gustatory sensory neurons (GSN) to form "TR to GSN" dedicated labelled lines (Nowlis et al. 1980; Hettinger and Frank 1990, Frank et al. 2008; Barretto et al. 2015) for single-taste qualities (Formaker and Frank 1996; Frank et al. 2003). Thus, the practical endpoint of chemosensory processing is likely a few perceived odor or taste mixture-components.

Unnoticed odor components in mixtures

Interpretations of psychophysical studies of higher-order odor mixtures invoke visual-like mixture synthesis of new odors (Bushdid et al. 2014), including an "olfactory white" (Weiss et al. 2012). While the current 4-component rapid selective-adaptation study did not directly test for synthesis, component odors mixed with other component odors maintained their own identities. Also, the few attempts at synthesizing odors of pure chemicals by mixing 2 other chemicals having distinct odors (analogous to creating metameric colors) were unsuccessful. Vanillin's *vanilla* odor was not produced by a mixture of guaiacol *smoke* + benzaldehyde *cherry* odors as predicted (Keller and Vosshall 2004). And, although the eugenol *clove* + phenethyl-alcohol *rose* mixture may be *carnation*-like, a single chemical with that specific floral odor is unidentified (Zou and Buck 2006). Instead, *carnation* may be a "2-note" floral odor.

Ferreira's (2012) thorough review of psychophysical odor-mixture studies concludes that most often, but not necessarily, binary-mixtures have the same odor as one or both mixture components. Successful identification is biased towards more-intense components. Identification of higher-order mixture components rarely include descriptors not belonging to individual components in the mixture (Kurtz et al. 2009, 2010, 2011). Rather, they fell among the entire set of descriptors (Dravnieks 1985) used for all of that mixture's components. Nonetheless, like visual objects, familiar complex "odor objects" with multiple odor-notes can be wholly identified by trained subjects. At most a few mixed complex "odor-objects" (such as *kerosene* or *chocolate*) were identified (Livermore and Laing 1998b), as are a few mixtures of single odor-chemicals. It seems possible that those identified were keyed by a few distinct, single odors, each associated with one of the "objects".

Large olfactory databases of odor-quality labels had sparsely approached odor-quality coding until recently (Keller et al. 2012; Keller and Vosshall 2016). Yet odor quality has been studied steadfastly without "subjective" quality labels but *odor typicality* ratings (0—not at all, to 10—perfectly) for a practical limited number of odor-stimuli. Subjects rate how closely an odor stimulus ("component" or "complex odor-object") matches example odor stimuli (Thomas-Danguin et al. 2014). Experience (Le Berre et al. 2008a), general-odors training (Barkat et al. 2012) and component "just noticeable differences" (Le Berre et al. 2008b) affect the *typicality* of detecting complex odor-objects. This choice of "odor" or "odor-object" mixture-processing strategy warrants further study (Sinding et al. 2015). Importantly, uncertainty remains over the precise function of the olfactory system in modifiable odor-mixture perceptions; that is, the flexible decisions to use elemental (component) or configural (whole) odor-mixture coding (Sinding et al. 2015).

Précis

The relationship between "odor-mixture suppression and rapid selective adaptation" and "odor recognition and discrimination" prompts consideration of specific ligand-receptor interactions. Human quality-identity of detectable odor-notes could rely on cognate pairing of distinct odor chemicals with each of the 400 human OR variants. Recognition of chemical classes of characteristic tastes depends on the 40 TR without combinatorial complications. It is possible receptor domains of the chemosensory systems differ in size (Dunkel et al. 2014) because of the practical need to identify a few tastes within a limited universe of tastes but identify a few odors at a time from a virtual infinity of smells.

Supplementary Material

Supplementary data are available at *Chemical Senses* online.

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