

Perceptual convergence of multi-component mixtures in olfaction implies an olfactory white

Tali Weiss^{a,1,2}, Kobi Snitz^{a,1}, Adi Yablonka^a, Rehan M. Khan^a, Danyel Gafso^b, Elad Schneidman^a, and Noam Sobel^{a,2}

^aDepartment of Neurobiology, Weizmann Institute of Science, Rehovot 76100, Israel; and ^bVia-Scent, Rishon Le Zion 75256, Israel

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In vision, two mixtures, each containing an independent set of many different wavelengths, may produce a common color percept termed “white.” In audition, two mixtures, each containing an independent set of many different frequencies, may produce a common perceptual hum termed “white noise.” Visual and auditory whites emerge upon two conditions: when the mixture components span stimulus space, and when they are of equal intensity. We hypothesized that if we apply these same conditions to odorant mixtures, “whiteness” may emerge in olfaction as well. We selected 86 molecules that span olfactory stimulus space and individually diluted them to a point of about equal intensity. We then prepared various odorant mixtures, each containing various numbers of molecular components, and asked human participants to rate the perceptual similarity of such mixture pairs. We found that as we increased the number of nonoverlapping, equal-intensity components in odorant mixtures, the mixtures became more similar to each other, despite not having a single component in common. With ~30 components, most mixtures smelled alike. After participants were acquainted with a novel, arbitrarily named mixture of ~30 equal-intensity components, they later applied this name more readily to other novel mixtures of ~30 equal-intensity components spanning stimulus space, but not to mixtures containing fewer components or to mixtures that did not span stimulus space. We conclude that a common olfactory percept, “olfactory white,” is associated with mixtures of ~30 or more equal-intensity components that span stimulus space, implying that olfactory representations are of features of molecules rather than of molecular identity.

odor | sensory perception | smell

Several studies have linked human perception of monomolecular odorants to their physical structure (1, 2) and specific receptors (3, 4). The real olfactory world, however, is made not of monomolecular stimuli but rather of complex olfactory mixtures, and the rules underlying the perception of such mixtures remain largely unknown. On one hand, humans are very poor at identifying the components of a mixture, even when they are able to identify the components alone (5–7). However, humans remain exquisitely capable of discriminating one mixture from another, and mixtures containing hundreds of different volatile molecules are associated with unique olfactory percepts such as wine (8), roasted coffee (9), or rose (10). At first, that such large odorant mixtures diverge in perception is apparently at odds with two standout phenomena of mixture perception in vision and audition. In color vision, if one combines more and more different wavelengths, one eventually obtains the convergent color percept of white. In tonal audition, if one combines more and more different frequencies, one eventually obtains the convergent perceptual hum termed “white noise.” Thus, whereas in color vision and tonal audition large mixtures converge perceptually, olfactory large mixtures remain perceptually diverged into objects as distinct as wine, coffee, and rose. This comparison, however, overlooks two key characteristics of the perceptual phenomena of the color white and the sound white noise. For these convergent percepts to materialize, two critical conditions must be met: Mixture components must span stimulus space and

be of equated intensity. These two conditions have yet to be applied in the study of large olfactory mixtures. With these two conditions in mind, we set out to test the hypothesis that if we select odorant mixture components to span olfactory space and equate component intensity, such mixtures may converge to a common olfactory percept.

Results

Mixtures with Many Equal-Intensity Spanned Components Begin to Smell the Same. We obtained 86 monomolecular odorants that were well distributed in both perceptual (Fig. 1A) (1, 11–13) and physicochemical (Fig. 1B) (1, 14, 15) stimulus space. We then diluted each of these odorants separately to a point of about equal perceived intensity as estimated by an independent group of 24 participants (SI Appendix, Table S1A) and prepared various odorant mixtures containing various numbers of such equal-intensity odorant components. Importantly, to prevent the formation of novel compounds, odorant mixtures were not mixed in the liquid phase; instead, each component was dripped onto a common absorbing pad in a sniff-jar, so that their vapors alone mixed in the jar headspace. To select the components of each mixture, we used an algorithm that automatically identified combinations of molecules spread out in olfactory stimulus space (SI Appendix). We prepared several different versions for each mixture size containing 1, 4, 10, 15, 20, 30, 40, or 43 components, so that half of the versions were spread optimally in perceptual space, and half of the versions were spread optimally in physicochemical space. Note that although Fig. 1 is limited to a 2D representation, our algorithm selected mixtures based on their multidimensional features (SI Appendix).

We conducted pairwise similarity tests (using a nine-point visual analog scale, VAS) of 191 mixture pairs, in 56 participants (average of 14 participants per comparison). Each target mixture (1, 4, 10, 15, 20, 30, 40, or 43 components) was compared with all other mixtures (1, 4, 10, 15, 20, 30, 40, or 43 components) and, as a control, with itself. Other than comparisons of a mixture with itself, all comparisons were nonoverlapping; in other words, each pair of mixtures being compared had no components in common.

Consistent with our hypothesis, there was a significant relationship between the number of components in each of two mixtures and their perceived similarity, in both perceptual [$F(1,17) = 124.8$, $P < 0.0001$] and physicochemical [$F(1,28) = 34.1$, $P < 0.0001$] space, reflecting increased similarity with an increased

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¹T.W. and K.S. contributed equally to this work.

²To whom correspondence may be addressed. E-mail: tali.weiss@weizmann.ac.il or noam.sobel@weizmann.ac.il.

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a gestalt identity, we conducted an odor-identification experiment. Selecting from physicochemical space, we generated four versions of 40-component mixtures. To prevent any cognitive influences of the label “white,” we labeled these mixtures with the meaningless name “Laurax.” Each of the four versions of Laurax was assigned to three different participants from a group of 12. To acquaint themselves with the odor, each participant came to laboratory on three consecutive days, and every day repeatedly smelled and rated the applicability of 146 verbal descriptors (16) to only their version of Laurax. On the fourth day, test day, participants performed a four-alternative forced-choice identification task for 23 different, novel, but partially overlapping target odorant mixtures of 1, 4, 10, 20, 30, or 40 components, all selected to span physicochemical space. Each target mixture was provided with four alternative labels: Three labels were assigned by an expert perfumer (coauthor D.G., who was blinded to experimental aims and conditions) as optimal identifiers for each mixture (*SI Appendix, Table S2*), and the fourth label was “Laurax.” Consistent with our prediction, the probability of assigning the name “Laurax” to a novel mixture increased as the number of components increased (KC, $\tau = 0.73$, $P < 0.05$) (Fig. 3A). Moreover, novel target mixtures with fewer than 20 components were significantly less likely to be identified as Laurax than novel targets with 20 or more components

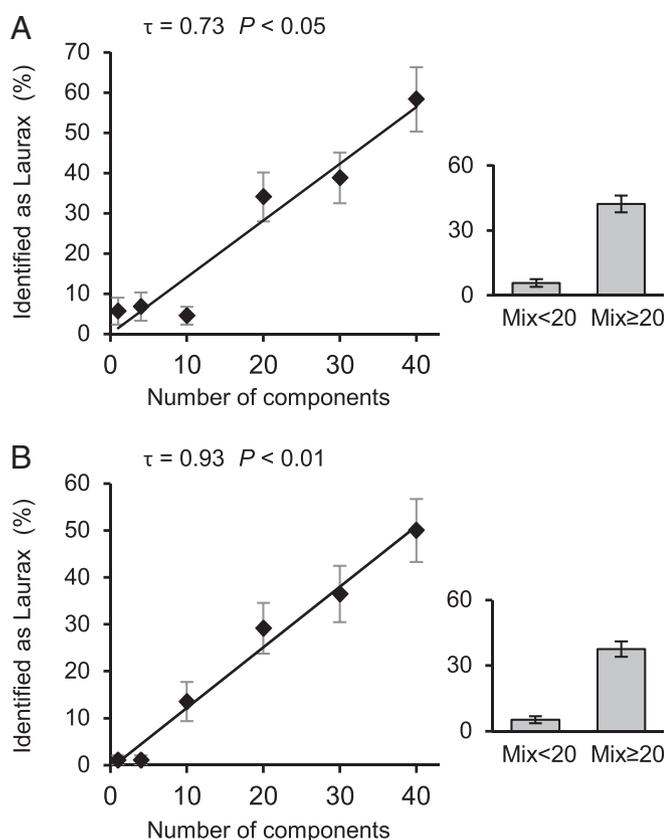


Fig. 3. Mixtures made of many equal-intensity spanned components are identified as olfactory white. *A* and *B* show the average probability of identifying a novel odorant mixture as white (Laurax) as a function of the number of components in the mixture in a four-alternative (*A*) or five-alternative (*B*) forced-choice identification test. Each dot represents the average rating for four versions of a given number of components. Error bars indicate SE. (*Insets*) The average probability of identifying a novel odorant mixture as white (Laurax) for mixtures of fewer than 20 components, compared with mixtures of 20 or more components in four-alternative (*A*) or five-alternative (*B*) forced-choice identification tests.

[$t(10) = 5.54$, $P < 0.001$; Fig. 3A, *Inset*]. Finally, although chance application of a label in the four-alternative task is 25%, the label “Laurax” was applied to novel 40-component mixtures 57.6% of the time [$t(10) = 3$, $P < 0.02$].

The descriptors we used for Laurax, although provided by a professional perfumer, nevertheless may lack universal applicability. To address the possibility of “dumping” (17), namely the assignment of inappropriate labels in the face of limited alternatives, we repeated the experiment with a different group of 13 participants and with the additional response option of “other.” Again, the probability of assigning the name “Laurax” increased as the number of components increased (KC, $\tau = 0.93$, $P < 0.01$) (Fig. 3B), and novel target mixtures with fewer than 20 components were significantly less likely to be identified as Laurax than novel targets with 20 or more components ($t(11) = 5.68$, $P < 0.001$; Fig. 3B, *Inset*). Finally, although the chance application of a label in the five-alternative task is 20%, the label “Laurax” was applied to novel 40-component mixtures 50% of the time ($t(11) = 3.35$, $P < 0.007$).

Because we were limited by the available components for which we had equated intensity, but we wanted to have meaningful differences across the various target mixtures, in the two above experiments there was inevitable, minimal overlap of the components in the learned Laurax mixture and in target mixtures. Moreover, despite the addition of “other” as a viable response, dumping remained possible. With these considerations in mind, we applied even stricter conditions in the following experiments: After 2-d acquaintance with 30-component Laurax, 12 participants smelled 21 target mixtures of various numbers of components but with no component overlap with the mixture they had learned to identify as Laurax, and judged whether these mixtures were or were not Laurax; i.e., no alternative labels were provided in this delayed match-to-sample task.

Consistent with the previous experiments, the probability of discriminating a mixture from the Laurax participants had learned decreased as the number of components increased (KC, $\tau = -0.68$, $P < 0.05$; Fig. 4A), and novel target mixtures with fewer than 20 components were significantly more likely to be discriminated from Laurax than novel targets of 20 or more components [$t(11) = 3.52$, $P < 0.005$; Fig. 4A, *Inset*]. Moreover, chance at this task is 50%. Although participants were significantly above chance (all $P < 0.05$) in discriminating smaller novel mixtures (with 1, 5, 10, or 15 components) from the percept of Laurax, they did not differ from chance in discriminating novel 20-, 25-, and 30-component mixtures from the percept of Laurax (all $P > 0.05$). It is important to acknowledge the perceptual memory component in the delayed match-to-sample task. Had participants been provided simultaneously with the Laurax they had learned previously and the novel 30-component mixtures, they likely would have discriminated them (as in Fig. 2B). However, when participants were given only the gestalt percept of the Laurax they had learned (which indeed was sufficient for 97% accuracy in identifying the learned Laurax), novel mixtures with ~30 components were deemed not significantly different from Laurax.

One may raise the possibility that Laurax became a percept associated with “large mixtures,” despite the mixtures’ olfactory identity. Ideally, to test this possibility, one would compare large mixtures that are spanned in olfactory space (Laurax) with equally large mixtures clustered in olfactory space. However, because we initially selected 86 molecules that span space, one could not extract from them a cluster of ~30 components. Any cluster of ~30 of these 86 components would, by definition, be relatively well spanned. To mitigate this limitation partially, we equated the perceived intensity of an additional 58 molecules, so that we had a pool of 144 molecules to choose from (*SI Appendix, Table S1B*). We then repeated the above strict delayed match-to-sample task with an additional 16 participants, and used test-target mixtures

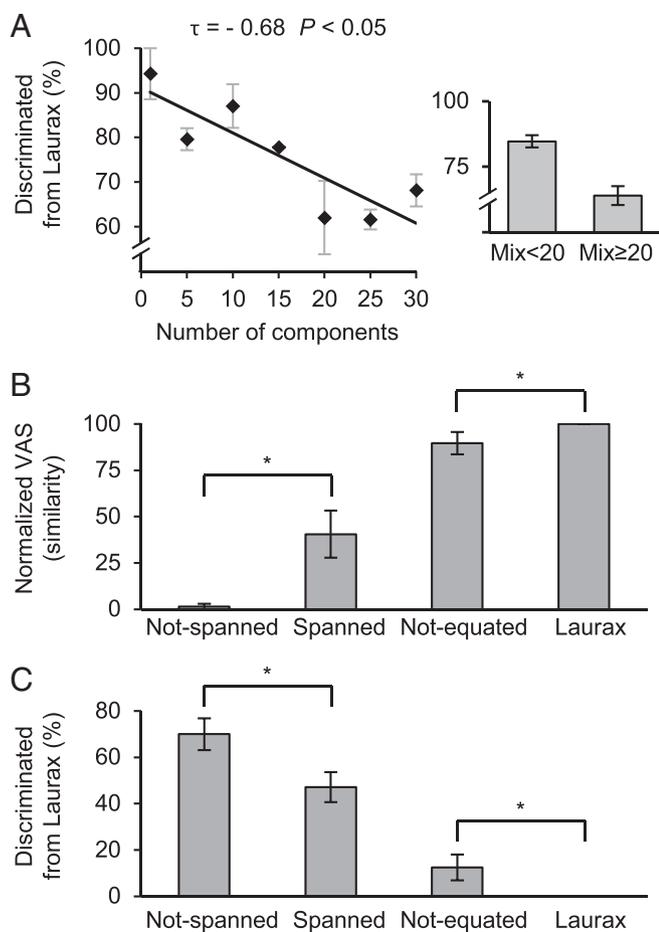


Fig. 4. Mixtures made of many equal-intensity spanned components match the perceptual memory of olfactory white. (A) Delayed match-to-sample between a learned Laurax and novel nonoverlapping mixtures of various sizes. Each dot represents the average rating for three versions of a given number of components. Error bars indicate SE. (Inset) The average probability of discrimination for mixtures of less than 20 components or mixtures of 20 or more components. (B and C). Delayed match-to-sample between a learned Laurax and a novel nonoverlapping 25-component mixture that was or was not spanned in space, was not equated for intensity, or was the very same mixture learned as Laurax (100% accuracy). (B) Continuous similarity score as reflected by location on the VAS (median \pm median absolute deviations across participants). (C) Probability of discriminating a mixture from Laurax (scores below 25%). * $P < 0.05$. Error bars indicate SE among participants.

with only 25 components. Thus we had nine versions that spanned physicochemical space, five versions that, although not perfectly clustered, were not spanned in physicochemical space, and two versions with components identical to the Laurax the participants had learned but that were not equated for perceived intensity (*SI Appendix*). Moreover, rather than a strict yes/no selection, we asked participants whether the odor was Laurax and provided participants with a VAS ranging between “yes” and “no.” This approach allowed us to conduct two complementary analyses: In the first we simply extracted the median VAS scores as a continuous measure of similarity (Fig. 4B), and in the second we arbitrarily parsed the VAS scale into dichotomous “yes” (above 75%) or “no” (under 25%) answers (Fig. 4C).

The similarity analysis revealed that tested Laurax was rated as identical to the remembered percept of Laurax (median VAS = 100% \pm 0); nonequated Laurax was less similar (when comparing Laurax with itself we used a one-tailed test because similarity cannot exceed 100%; Wilcoxon one-tailed test, median VAS Laurax =

100% \pm 0, median VAS nonequated = 89.64% \pm 6, $P < 0.03$); spanned mixtures were even less similar (median VAS spanned = 40.54% \pm 12.75, median VAS nonequated = 89.64% \pm 6, $t(15) = 7.56$, $P < 0.001$); and nonspanned mixtures were even further less similar (Wilcoxon test, median VAS spanned = 40.54% \pm 12.75; median VAS nonspanned = 1.5% \pm 1.5, $P < 0.03$) (Fig. 4B).

In the alternative analysis of the same experiment, nonspanned mixtures were more discernible from the remembered percept of Laurax than were novel spanned mixtures (Wilcoxon test, nonspanned = 70% \pm 27.3, spanned = 47.2% \pm 25.9, $P < 0.01$) (Fig. 4C), and the Laurax not equated for intensity was more discernible from the remembered percept of Laurax than was Laurax itself (Wilcoxon one-tailed test, not equated = 12.5% \pm 22.36, Laurax = 0% \pm 0, $P < 0.04$) (Fig. 4C). Repeating this analysis but parsing at the 50% mark (rating above 50% as “yes” and below 50% as “no”) revealed similar results.

Taken together, these analyses imply that the percept of Laurax was dependent more on spanning olfactory space than on equating intensity (Fig. 4B) and that only nonspanned mixtures were decidedly “not Laurax” (Fig. 4C). The full influence of spanning olfactory space is likely much greater than revealed here, because the possibility of selecting independent clusters comprising 25 out of the 144 molecules for which we have equated intensity remains limited. In other words, our “clusters” still were quite spanned. Thus, this result, although significant in itself ($P < 0.03$ in similarity or $P < 0.01$ in yes/no selection), likely underestimated the differences between spans and clusters.

Finally, to verify again the limits of this phenomenon, we repeated the delayed match-to-sample task in 18 participants testing only mixtures of up to 15 components (i.e., mixtures that on average should not converge) and in 14 participants testing mixtures of up to 60 components (i.e., mixtures well beyond our estimated point of convergence). Although participants were significantly better than chance in discriminating the novel 15-component mixtures from the percept of Laurax (Wilcoxon test, 10.1% \pm 22.33, $P < 0.002$), they were not different from chance in discriminating novel 60-component mixtures from the percept of Laurax (median VAS = 52.8% \pm 16.3, $t(11) = 0.012$, $P > 0.99$). Taken together, these experiments are consistent with the notion of a gestalt percept following combinations of ~ 30 equal-intensity components or more that are well distributed in physicochemical space. We call this percept “olfactory white.”

Olfactory White Smells Intermediately Pleasant and Edible. Our dilution procedure, in which all components were equated in magnitude with the least-intense component, rendered mixtures of overall low intensity. In other words, olfactory white was in no way overwhelming. What was its smell? Perhaps tellingly, the descriptors of white provided by the professional perfumer were quite variable. This variability can be taken to imply that white does not smell like any particular common object. To provide a better notion of what olfactory white does smell like, we summarized the applicability of 146 verbal descriptors provided by the 85 participants who smelled white repeatedly (*SI Appendix*, Table S3). Moreover, we asked 20 participants to rate 20 different odorants along VAS scales representing two principal axes of human olfactory perception, one axis ranging from very pleasant to very unpleasant and the other ranging from highly edible to highly poisonous (1, 13, 18). Of the 20 odorants participants rated, 12 were previously well-characterized monomolecular odorants that span the first principal component of perception, four were previously used versions of 40-component olfactory white, and four were 10-component mixtures which provided a maximal span of olfactory space. The pleasantness and edibility/poisonousness of the 20 odorants ranged from 0.10–0.86 and 0.11–0.70, respectively (after parsing the VAS to the range 0–1), whereas the average pleasantness and edibility/poisonousness of olfactory white were 0.46 \pm 0.08 and 0.37 \pm 0.05, respectively (Fig.

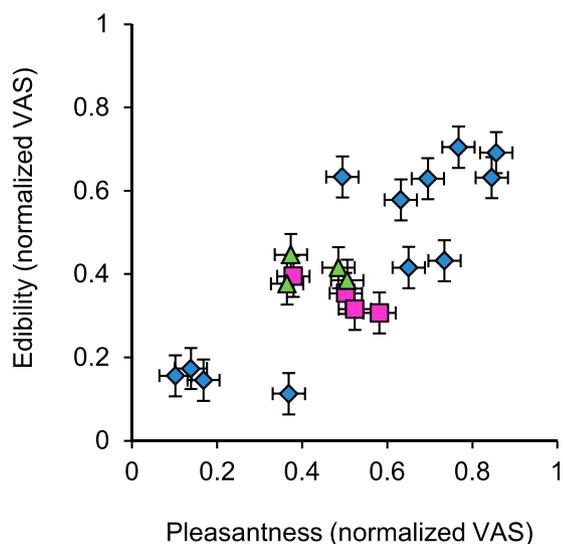


Fig. 5. The smell of olfactory white. Ratings given to 12 monomolecular odorants (blue diamond), four 10-component mixtures that optimally spanned space (magenta square), and four 40-component mixtures that optimally spanned space (green triangle), along the two key axes of human olfactory perception, one ranging from very unpleasant to very pleasant (horizontal axis), and one ranging from highly poisonous to highly edible (vertical axis). Error bars indicate SE among participants.

5). In other words, olfactory white was largely intermediate along the key axes of human olfactory perception. Finally, the best way to appreciate the qualities of olfactory white is to smell it. *SI Appendix, Table S4* contains recipes for olfactory whites of 60 and 30 components, so that two mixtures can be prepared that share no components in common but smell alike and “white.”

Olfactory White Is a Gestalt That Persists over Time. Finally, to determine whether the percept of white is maintained over time, we invited 20 participants from the previous studies to participate in an additional study conducted about 6 mo after their initial and only acquaintance with Laurax. Moreover, in this experiment we also asked whether Laurax can mask other odors. We presented participants with 12 odorants, each delivered twice. Four of the odorants were the monomolecules most prominent in rose (19), a fifth odorant was a rose mixture made of these four monomolecules combined (*SI Appendix, Table S5*), five odorants were 30-component mixtures (white) which each contained the four rose monomolecules mixed with 26 additional molecules selected to span physicochemical space (*SI Appendix, Table S6*), and the remaining two control odorants were the monomolecules isoamyl acetate and S-(methylthio)butyrate. We asked participants to identify the odorants in a seven-alternative (10 participants) or four-alternative (10 participants) forced-choice identification task that always included the alternatives rose, Laurax, “other,” and either one (4AFC) or four (7AFC) additional odor names, selected to fit best the monomolecules used (*SI Appendix, Table S5, legend*).

Despite their brief and limited past exposure to Laurax, participants largely maintained the percept in mind. Although the chance of selecting Laurax was 14.3% in the first experiment and 25% in the second, Laurax was selected correctly 54% of the time in the first experiment [$t(9) = 7.96, P < 0.001$] and 65% of the time in the second experiment [$t(9) = 5.05, P < 0.001$]. Moreover, the percept of Laurax largely obscured the percept of rose. Specifically, across both experiments the mixture of rose was identified correctly 70% of the time, but it was labeled “Laurax” only twice in 40 trials (5%) [$t(19) = 7.25, P < 0.001$]. In contrast, Laurax (which contained the four molecules of rose) was correctly identified 59.5% of the time but was labeled “rose”

14 times in 200 trials (7%) [$t(19) = 9.52, P < 0.001$] (full results of this experiment are in *SI Appendix, Fig. S3*). In other words, participants remembered the percept of olfactory white, and it served to obscure the percept of rose effectively.

Discussion

The chief finding of this study is illustrated in Fig. 24: The more components two mixtures have, the more similar they smell, even though they have no individual components in common. Moreover, odorant mixtures with ~30 components or more begin to smell alike, having a quality we call “olfactory white.” So why, in the real world, do not large mixtures of many components, such as wine, coffee, and rose, all smell similar and white? The answer to this question reflects two conceptual considerations regarding the perception of complex olfactory objects. The first is that, unlike the olfactory whites we generated, the components of wine, coffee, and rose were not designed to span stimulus space. As seen in Fig. 4 *B* and *C*, if mixture components are less spanned, the ensuing odorant is different from white. The second consideration is that, unlike the olfactory whites we generated, wine, coffee, and rose do not contain components of equal intensity. As seen in Fig. 4 *B* and *C*, if components of a mixture are not equated for intensity, the ensuing odorant smells less white. Such imbalance is typical in natural mixtures. For example, computing the spread of the key components of rose (19) in physicochemical space reveals that they reflect an extreme cluster, whereas the mixtures of whites we generated (Laurax) reflected an average span (see *SI Appendix, Fig. S4* for this and additional examples). Moreover, one of the components of rose alone, phenylethyl alcohol, contributes ~70% of rose headspace (10), and indeed this component alone generates a poor-quality but unmistakable smell of rose. In other words, a natural olfactory object such as rose contains components that are clustered in olfactory space and are of unequal intensity and therefore does not smell white.

Olfaction is considered a synthetic rather than analytical sensory system (20–24). For example, humans are very poor at identifying components in a mixture, even when they are familiar with the components alone (5–7). Similarly, cortical patterns of neural activity induced by a mixture are unique, not a combination of neural activities induced by the mixtures’ components (25–29). Moreover, the pattern of neural activity in the olfactory bulb induced by the smell of a natural object typically reflects the pattern associated with the dominant monomolecular odorant (alone) associated with that object (30). In other words, the olfactory system treats odorant mixtures as unitary synthetic objects and not as an analytical combination of components (20–24, 28, 29, 31), and the current results are consistent with this notion. Indeed, a main implication of this study is that olfactory representations are of features of molecules rather than of molecular identity per se. Beyond this general implication, it indeed is tempting to speculate about the neurobiological implications of olfactory white. However, because we did not simultaneously record neural activity in this study, we limit ourselves here to describing the psychophysical phenomenon alone rather than speculating on neural substrates.

The main limitation of this study is that, unlike a pair of visual or auditory whites that can (although do not necessarily) obtain a level of similarity that renders them perceptually identical, our olfactory whites remained discernible from one another. We think that this result reflects inherent limitations related to this study’s two defining features described above. The first is spanning olfactory space. In vision and audition, the clear mapping between physical and perceptual dimensions allowed identification of the physical limits of perception (~390 to ~750 nm in color vision and ~20 Hz to ~20 kHz in auditory pitch). Therefore, spanning physical space in these domains is relatively straightforward. In contrast, the full extent of olfactory physicochemical space remains unknown, and its key axes remain poorly defined. Therefore, the odorants we selected span a physicochemical space

(Fig. 1B) but not necessarily the physicochemical space that bounds human olfactory perception. To account for this potential limitation, we used a large number (1,492) of molecules, thereby reducing the likelihood of a biased representation but not eliminating the possibility altogether. Notably, as indicated by the initial similarity experiment (Fig. 2A), had we selected components from perceptual rather than physicochemical space, the different whites likely would have been more similar (based on the $r = 0.94$ in perceptual space versus the $r = 0.75$ in physicochemical space). Nevertheless, we chose to avoid such a path so to prevent concerns about a circular design.

The second feature that may have prevented olfactory whites from being identical is equating perceived component intensity. Whereas equating physical intensity in vision and audition implies equated magnitude of perception, this is not the case in olfaction. Equating chemical concentration, even after factoring of vapor pressure, does not assure equated perceived suprathreshold intensity. Thus we are left with a method for equating intensity that is extremely labor intensive but yields suboptimal results (*SI Appendix*).

With these considerations in mind, we speculate that, had we been able to define and span physicochemical space optimally and achieve better intensity-equation of components, the number of components that generate white might have been lower and more stable, and the resultant white might have been more constant and similar. Indeed, there probably are several paths to olfactory white, and ours (30 ± 10) is likely not the shortest (we indeed encountered occasional whites with far fewer components) or the whitest but rather reflects the inherent limitations in our study.

Finally, naming a percept “white” may be taken as having various implications. Indeed, there are profound differences between white light and white noise, and olfactory white differs in some profound aspects from both. From the visual and auditory neural perspective, “white” typically implies wide activation. Paradoxically, studies that either overexpressed a particular olfactory receptor subtype (32) or used electrical stimulation of the olfactory system (33) together implied that wide olfactory activation results in no percept at all. Thus, it is unlikely that our white was the result of activating the entire sensory apparatus at any level. Our

white was a percept, and it is this notion of a convergent percept induced by mixtures that differ in their individual components that is common to white light, white noise, and white smell.

One may question whether white smell exists in nature. We speculate that a naturally occurring olfactory white would constitute an extremely rare event. Nevertheless, both white light and white noise also are rare in nature, but they have served significantly in the neurobiological study of vision and audition. We hope olfactory white can serve similarly in the study of olfaction. With this hope in mind, we conclude by stating that olfactory mixtures of ~ 30 components with a good distribution of components in olfactory space and equated component intensity will mostly smell similar, having a quality we call “olfactory white.” In this respect, olfaction shares a fundamental psychophysical property with vision and audition.

Materials and Methods

After providing written informed consent to procedures approved by the Ethics Committee at the Weizmann Institute of Science, 208 participants (110 women) with no history of olfactory dysfunction (ages ranging from 21–40 y, mean age 26.7 ± 2.9 y) participated in the intensity-rating ($n = 24$), similarity-scoring ($n = 59$), discrimination ($n = 20$), identification ($n = 25$), delayed match-to-sample ($n = 60$), and pleasantness and edibility-rating ($n = 20$) experiments. All experiments were conducted in stainless steel-coated odorant-nonadherent rooms. All interactions with participants during the experiments were via computer interface only. All experiments used ~ 40 -s intertrial intervals, and trial order was counterbalanced across participants. Fresh odorant mixtures were prepared every 2 d. *SI Appendix, Table S7* provides the recipes for the mixtures of the similarity tests. For all statistical comparisons, we first tested normality of distribution. For normal distributions we tested correlations using the Pearson statistic and group differences using Student's paired *t* distributions. For non-normal distributions, we tested correlations using the Kendall correlation and group differences using Wilcoxon sign test.

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