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No Oral-Cavity–Only Discrimination of Purely Olfactory Odorants

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Abstract

The purely olfactory odorants coumarin, octanoic acid, phenylethyl alcohol, and vanillin had been found to be consistently identified when presented retronasally but could not be identified when presented oral-cavity only (OCO). However, OCO discrimination of these odorants was not tested. Consequently, it remained possible that the oral cavity trigeminal system might provide sufficient information to differentiate these purely olfactory odorants. To evaluate this, 20 participants attempted to discriminate vapor-phase coumarin, octanoic acid, phenylethyl alcohol, and vanillin and, as a control, the trigeminal stimulus peppermint extract, from their glycerin solvent, all presented OCO. None of the purely olfactory odorants could be discriminated OCO, but, as expected, peppermint extract was consistently discriminated. This inability to discriminate clarifies and expands the previous report of lack of OCO identification of purely olfactory odorants. Taken together with prior data, these results suggest that the oral cavity trigeminal system is fully unresponsive to these odorants in vapor phase and that coumarin, octanoic acid, phenylethyl alcohol, and vanillin are indeed purely olfactory stimuli. The OCO discrimination of peppermint extract demonstrated that the absence of discrimination for the purely olfactory odorants was odorant dependent and confirmed that the oral cavity trigeminal system will provide differential response information to some vapor-phase stimuli.

Key words: human, olfaction, oral cavity, purely olfactory odorants, trigeminal

Introduction

One useful approach to characterizing sensory systems is to elucidate those environmental states or changes that do not serve as effective stimuli, as well as those that do. For human smelling, 2 sensory systems require such characterization: the olfactory and the trigeminal systems (see Silver and Finger 1991; Cometto-Muñiz et al. 1998; Rawson 2000; Doty and Cometto-Muñiz 2003). If certain potential stimuli could be shown to activate only one of these systems, valuable tools would be provided to analyze the functional properties of both systems. A series of studies had resulted in the designation of a set of chemicals as purely olfactory odorants. That is, it was proposed that the olfactory system but not the trigeminal system could be stimulated by these chemicals. The empirical bases for this designation as purely olfactory odorants were the observations of little or no detection by anosmics upon vapor-phase orthonasal presentation and a general lack of nasal lateralization (Doty et al. 1978, Radil and Wysocki 1998; Wysocki and Wise 2004; Cometto-Muñiz et al. 2005). The underlying logic was that the anosmics could detect trigeminal stimuli and that trigeminal stimuli were regularly lateralized nasally. More recently, these purely olfactory chemicals were found to be sufficient retronasal olfactory stimuli for linguistic descriptions by normosmics (Chen and Halpern 2008). The same odorants did not permit oral cavity, trigeminal system–based, descriptive responses (Chen and Halpern 2008), but ability to discriminate them upon vapor-phase oral-cavity–only (OCO) presentation is unknown. However, other vapor-phase stimuli, for example, orange and strawberry extracts, although they were not effective for oral cavity trigeminal system–based descriptive responses, did support trigeminal system–based discrimination of these vapor-phase odorants from their solvents (Dragich and Halpern 2008). Consequently, it is possible that the putative purely olfactory odorants might also support trigeminal system–based, oral cavity discrimination from their solvents. If this were the case, the designation purely olfactory would require qualification because it would be limited to linguistic descriptions but would not preclude discriminative trigeminal responses.

The goal of the present research was to examine OCO discrimination of vapor-phase purely olfactory odorants that had previously been orthonasally and retronasally studied in investigations that required linguistic descriptions as responses. The hypothesis was that OCO discrimination of

vapor-phase purely olfactory odorants would not occur. To serve as a positive control, vapor-phase presentations of peppermint extract were included. Based upon previous data, it was expected that OCO discrimination of the peppermint extract would occur (Dragich and Halpern 2008). If the nondiscrimination hypotheses were confirmed, this result would indicate that the trigeminal system, at least the oral cavity component, cannot provide meaningful information on the purely olfactory odorants coumarin, octanoic acid, phenylethyl alcohol, and vanillin. This finding would substantiate limits on the responsiveness of the trigeminal sensory system. On the other hand, the OCO discrimination of peppermint extract would both demonstrate that the absence of discrimination for the purely olfactory odorants was odorant dependent and would confirm that the oral cavity trigeminal system will provide differential response information to some vapor-phase stimuli.

Materials and methods

Participants

Participants were 20 paid volunteers, 13 females and 7 males. Ages ranged from 18 to 55 years (median age ± semi-interquartile range [SIR] = 21 ± 1.75 years). They were nonsmoking, nonpregnant, and nonlactating individuals associated with Cornell University, over the age of 18, who could communicate in American English, recruited using posters. These were the only exclusion and inclusion criteria used. No chemosensory screening of participants was done. The protocol was reviewed and approved by Cornell's University Committee on Human Subjects (UCHS)/Institutional Review Board for Human Participants. Each potential participant read and signed an informed consent form approved by the UCHS before participating in the experiment. Participants were asked not to eat or drink anything except water, for 1 h before a scheduled session.

Odorants

The 4 purely olfactory odorants were 1) CAS# 91-64-5, high-performance liquid chromatography ≥99% coumarin, 2) CAS# 124-07-2, ≥98% octanoic acid, 3) CAS# 60-12-8, 99% Food Chemicals Codex phenylethyl alcohol, and 4) CAS# 121-33-5, 99% ReagentPlus vanillin, all from Sigma-Aldrich, Inc. (St Louis, MO). These 4 chemicals were selected as nontrigeminal odorants on the basis of previous data indicating little or no detection by anosmics upon vapor-phase orthonasal presentation, a general lack of nasal lateralization (Doty et al. 1978; Radil and Wysocki 1998; Wysocki and Wise 2004; Cometto-Muñiz et al. 2005), and no OCO identifications but consistent retronasal identifications (Chen and Halpern 2008). However, it should be noted that Kobal and Hummel (1991) found some orthonasal lateralization with phenylethyl alcohol.

The peppermint extract was an alcohol-free food grade liquid extract of plant material, identified as a flavor, sold for inclusion in human foods and beverages, and purchased at retail. This extract was produced by Frontier Natural Products Co-op (Norway, IA). The peppermint extract was selected as the positive control stimulus because it had been discriminated in a previous study of OCO responses to vapor-phase stimuli (Dragich and Halpern 2008).

Each presentation of an odorant or its solvent in an odorant delivery container (ODC) (see odorant delivery containers) had a total of 5 mL of the liquid odorant including diluent or of the odorant's solvent. The solvent used for dilution was CAS# 56-81-5, United States Pharmacopeia–Food Chemicals Codex glycerin. The concentration of the presented odorants was 10%, in reference to the undiluted odorants, which would be 100%. The concentration that was used was based upon previous studies (Chen and Halpern 2008; Dragich and Halpern 2008). For the purely olfactory odorants, the 10% concentration had been sufficient to permit consistent retronasal identification of the vapor-phase odorants, but had not allowed OCO identifications. Fresh dilutions were made every 2 days, allowed to equilibrate with the vapor phase at least 30 min before use, and kept at room temperature, 22 °C.

Odorant delivery containers

Odorants were presented using clean (washed and air-dried) ODCs as described by Chen and Halpern (2008). Briefly, the ODCs were 118 mL, 5.1 cm high, black homopolymer containers with the shape of a frustum of an ellipsoid (Figure 1). The 5-mL volumes of diluted odorants, or their solvent, just

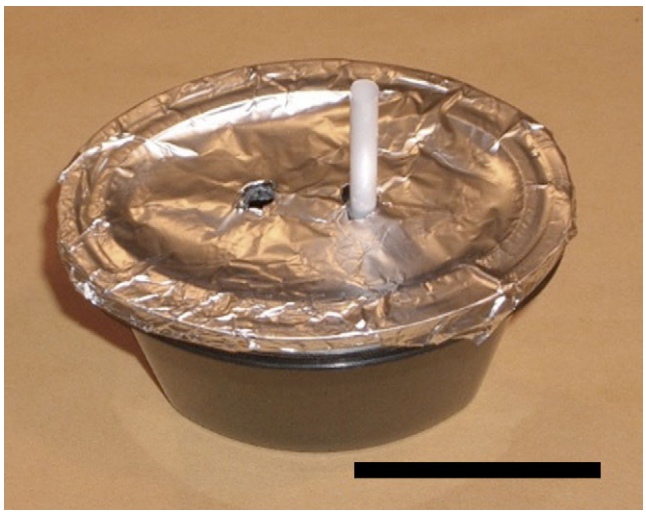

Figure 1 Photograph of an ODC. A straw through which vapor-phase stimuli were inhaled into the oral cavity is in place in 1 of the 2 holes in the tight-fitting lid. Aluminum foil covered the lid, except for the 2 holes. The total volume of the ODC was 118 mL. Five milliliters of stimuli were contained in an ODC during identification trials. The horizontal calibration line represents 4 cm.

covered the bottom of the ODC, providing an odorant surface area of 11.45 cm^2. In the tight-fitting lids for the containers, two 5-mm diameter holes were made. In one of the holes, a 6.5 cm long section of a 5-mm outer diameter, 4.8 mm inner diameter homopolymer polypropylene straw was inserted perpendicular to the lid, such that 3.25 cm of the straw was inside the container and was fixed in position. This allowed each straw to sample the headspace over a liquid odorant but precluded contact with the odorant. Aluminum foil rectangles, with holes corresponding to the 2 holes in the lids, were positioned over the lids to prevent visual observations of the odorants. Each ODC, including lid and straw, was used for 1 odorant and was discarded after use with 1 participant.

Noseclip

Each odorant presentation began with the participant putting on a noseclip (Spirometrics Disposable Noseclip—Latex Free, D1060-2, Spirometrics, Gray, ME) prior to receiving any ODCs containing a diluted odorant or solvent. Each noseclip was used for 1 participant and then discarded. The noseclip remained in place for all OCO odorant and solvent presentations.

Odorant discrimination testing

Before discrimination testing began, an experimenter provided a detailed explanation of how to use the straw to inhale vapor-phase odorant from an ODC into the participant's oral cavity. Next, the participant put his or her noseclip in place and then received 10 successive sets of 5 ODCs, each set of 5 arranged in 2 rows on a 32×42–cm tray. All stimuli were at 22 °C. One ODC of each set of 5 contained a diluted odorant; the other 4, solvent. The location of the odorant-containing ODC on each tray was determined by a fixed random order. A unique 3-digit code on each ODC, not prepared by the experimenter conducting the testing, indicated which one of the 5 ODCs of each set contained diluted odorant. This permitted the discrimination response to be recorded but allowed the testing to be done double blind. Within the 10 successive sets of ODCs, each of the 5 odorants was presented twice in a fixed random order.

For each ODC in a 5 ODC set, the participant, with his or her noseclip in place, first exhaled from his or her mouth, second holding the ODC with the straw upright and between his or her lips, inhaled deeply into their oral cavity using the ODC's straw, and third exhaled from his or her mouth after removing the straw from between his or her lips (see "For OCO presentations" in Chen and Halpern 2008). The participant was permitted to repeat this sequence up to 3 times for any or all the 5 ODCs in each set and then was required to indicate that, by pointing at one of the ODC, which one was different from the others. That is, a forced-choice discrimination was made for each set of 5 ODCs. If the participant said that he or she did not know which ODC was different, he or she was told to do his or her best and to pick one.

After the different ODC had been indicated by the participant, the participant was required to drink a sip of water from a provided disposable container and then, within approximately 10 s, was presented with the next set of 5 ODCs.

It should be noted that the discrimination response tested in this study is the ability to detect that one sample differs from several others. Specifically, the difference consists of the presence of a single component that is absent from most of the samples but is present in only one. This type of discrimination measure has been used in a number of previous studies (see Cain et al. 1990, 2008; Laska and Teubner 1999).

Statistical analyses

Because each diluted odorant was present twice within the 10 presentations of 5 ODC sets, each participant could select the ODC containing a particular diluted odorant a total of 0, 1, or 2 times across these trials. The number of times that each of the 20 participants correctly selected the ODC containing the diluted odorant, for each of the 5 odorants, is shown in Table 1. These numbers are the raw data of this study. Central tendencies and variability of correct selections were obtained by calculating medians and SIRs for each odorant across all 20 participants (Table 1).

The criterion for discrimination of an odorant by a participant was established as correct selection of the ODC containing a particular diluted odorant a total of 2 times across the 2 presentations of that odorant. This criterion was selected because the probability of selecting by chance the 1 ODC containing diluted odorant from the 5 ODCs presented in each set was 0.2; for both presentations of that odorant, the probability of selecting by chance the correct ODC was $0.2 \times 0.2 = 0.04$. Overall percent discriminations for each odorant across all participants were calculated by counting the number of participants who discriminated that odorant (Table 1), dividing by the number of participants and multiplying by 100 (Figure 2). This provided an overall indication of the degree of discrimination for each odorant.

For inferential statistics, because of the relatively small sample size and in order to avoid unnecessary assumptions, nonparametric statistics were used, with $P \leq 0.05$ taken as an indication of statistical significance. The Friedman nonparametric analysis of variance (ANOVA) by ranks analyzed the number of correct selections across all odorants, and Wilcoxon signed-rank tests (WILCOXON) analyzed the number of correct selections for pairs of odorants. Bonferroni corrections were applied to the probability values obtained from the WILCOXON tests.

Results

There was a significant difference in the number of correct selections of the ODC with odorant across the 5 odorants, $P < 0.0001$ (ANOVA, Friedman statistics = 31.25, degrees of freedom = 4, 76). This ANOVA outcome indicated that one or more differences in the numbers of correct selections

Table 1 The number of correct selections of the 1 ODC that contained diluted odorant from the 5 ODCs that were presented on each of the 2 trials for each odorant, for each participant and odorant, and the median number of correct selections, and SIR, for each odorant

Odorants					
Participant	Coumarin	Octanoic acid	PEA	Peppermint extract	Vanillin
1	0	0	0	1	1
2	0	0	0	**2**	1
3	0	0	1	**2**	0
4	0	0	1	**2**	1
5	0	**2**	1	1	0
6	0	0	1	1	0
7	0	0	**2**	1	0
8	1	0	1	**2**	0
9	0	0	1	**2**	0
10	1	1	0	1	0
11	1	1	1	1	1
12	1	0	0	**2**	0
13	1	1	0	1	0
14	0	0	**2**	**2**	0
15	1	0	1	**2**	0
16	0	0	1	0	1
17	0	0	0	**2**	1
18	1	0	0	**2**	1
19	0	0	1	**2**	1
20	0	0	0	1	0
Median	0	0	1	2	0
SIR	0.5	0	0.5	0.5	0.5

PEA, phenylethyl alcohol. Bold-faced, underlined numbers denote selection of the ODC containing that odorant by that participant on both of the possible instances. Such correct selection has a probability of 0.04 and was taken as the criterion for discrimination.

existed and that pairwise comparisons between odorants were justified. For the 4 purely olfactory odorants, pairwise comparisons between odorants found that there were no significant differences between these odorants in the number of correct selections of the ODC containing odorant $P \geq 0.25$ (WILCOXON), Bonferroni corrected. Pairwise comparisons between the number of correct selections for peppermint extract and all other odorants found that the number of correct selections of the ODC containing odorant differed between those for peppermint extract and those for all other odorants, $P \leq 0.02$ (WILCOXON), Bonferroni corrected.

Zero percent participants discriminated coumarin or vanillin; 5% (1 participant) discriminated octanoic acid, and 10% (2 participants) discriminated phenylethyl alcohol (Figure 2, Table 1). In contrast, 55% of the participants, that is, 11, discriminated peppermint extract, selecting the correct ODC on both of the available presentations (Figure 1, Table 1). The median number of correct selections across the 20 participants was 0 for coumarin, octanoic acid, and vanillin; 1, for phenylethyl alcohol; and 2, the maximum possible, for peppermint extract (Table 1).

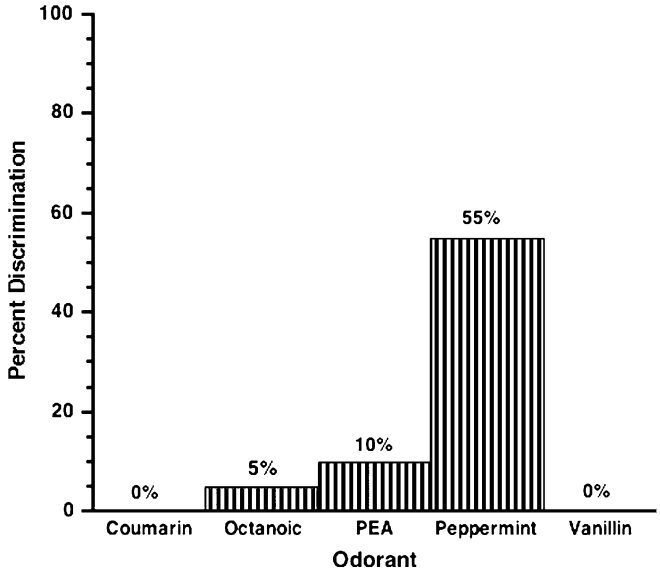

Figure 2 Percent discrimination (selection of the 1 ODC containing diluted odorant on both instances in which 5 ODCs were presented) across 20 participants for coumarin, octanoic acid (octanoic), phenylethyl alcohol (PEA), peppermint extract (peppermint), and vanillin.

Discussion

Across participants, the purely olfactory odorants did not differ among themselves in the number of correct selections of the ODC containing odorant during OCO presentations and did not support discrimination between themselves and their solvents. These observations are in agreement with the hypothesis that discrimination of purely olfactory odorants would not occur. The concentrations that were used had been sufficient for retronasal identification of the same odorants (Chen and Halpern 2008), and the present study used the same type of ODC. This indicated that these factors did not account for the absence of OCO discrimination between purely olfactory odorants and their solvents.

However, failure to observe OCO discrimination in the present study could have been due to a stimulus delivery, response, or analysis procedure that was inappropriate for the tested OCO discrimination responses. This possibility was evaluated by including as a positive control an odorant, peppermint extract, which had previously been shown to be discriminated from its solvent when presented OCO, albeit using a different vapor-phase stimulus delivery procedure (Dragich and Halpern 2008). The present study found that,

for peppermint extract, selection of the 1 ODC containing odorant from among a set of 5 presented ODC differed from, and exceeded, correct selection for any of the purely olfactory odorants. Peppermint extract was discriminated from the solvent, using the same OCO stimulus delivery, response, and analysis procedures that had been utilized for the purely olfactory odorants. This expected positive outcome for one odorant permits the absence of OCO discrimination for the purely olfactory odorants to be accepted with confidence.

Consequently, it may be proposed that vapor-phase coumarin, octanoic acid, phenylethyl alcohol, and vanillin are totally ineffective as oral cavity trigeminal stimuli and, perhaps, as stimuli for the trigeminal system in general. These 4 truly purely olfactory odorants are likely to be a subset of a larger group of chemicals that also do not stimulate the trigeminal sensory system. This set probably includes octane (Cometto-Muñiz et al. 2005) and, no doubt, other chemicals. Because the trigeminal system does respond to other vapor-phase stimuli, permitting not only discrimination but also in some cases identification (Dragich and Halpern 2008), understanding the characteristics of those stimuli that cannot activate the trigeminal system would help to specify the sensory properties of the trigeminal system.

It might be argued that the discrimination criterion of correctly selecting the ODC containing odorant on both presentations was too demanding. The criterion of 2 correct selections for discrimination, corresponding to $P = 0.04$, was employed because a single correct selection, 1 ODC out of 5, could occur by chance with a probability of 0.2. If only 1 correct selection was taken as discrimination, 7 participants would have discriminated coumarin; 4, octanoic acid; 12, phenylethyl alcohol; 19, peppermint extract, and 8, vanillin. A large disparity between the purely olfactory odorants and peppermint extracts would remain. However, because correctly selecting 1 ODC with odorant out of 2 sets of 5 could occur by chance at a 0.2 probability level, it seems prudent to employ the present discrimination criterion of correctly selecting both ODCs with odorant out of 2 sets of 5 that corresponds to probability level <0.05.

It could be proposed that using Bonferroni corrections of the WILXOCON P values was too conservative (see Perneger 1998; Nakagawa 2004). If Bonferroni corrections had not been applied, across all participants, the total number of correct selections of the ODC containing phenylethyl alcohol, 14, would have been significantly different from the total number of correct selections of the ODC containing octanoic acid, 5, $P = 0.043$, but there would have been no other significant differences between the purely olfactory odorants. Because Kobal and Hummel (1991) had found some orthonasal lateralization with phenylethyl alcohol, the non-Bonferroni-corrected significant difference between phenylethyl alcohol and other purely olfactory odorants is interesting. In the present study, 10% of the participants, that is, 2, met the discrimination criterion for phenylethyl alcohol, more than for the other purely olfactory odorants. Discrimination by 2 participants, although quite small and much less than the 11 participants (55%) who discriminated peppermint extract, is more than 1 participants of 20 who could be expected to discriminate by chance alone. Phenylethyl alcohol had been reported to have very low detectability by anosmics when presented orthonasally, comparable to coumarin, octanoic acid, and vanillin (Cometto-Muñiz et al. 2005), indicating little or no nasal cavity trigeminal stimulation. None of the latter 3 odorants were discriminated in the present OCO study. Nonetheless, it may be that phenylethyl alcohol, which can be classified as an irritant (MSDS PEA 2007), is a trigeminal stimulus for some participants. A subset of participants with greater OCO discrimination ability for some odorants had been observed in a previous study (Dragich and Halpern 2008). Not surprisingly, without Bonferroni correction, the total number of correct selections of ODC containing peppermint extract, 30, differed from all other odorants, $P \leq 0.003$.

The observed OCO discrimination response to vapor-phase peppermint, together with the absence of discrimination responses to the purely olfactory odorants, may be relevant to judgments of flavor. This is the case because, during normal eating and drinking, oral cavity stimulation can be the initial component of retronasal smelling (see Halpern 2008a, 2008b). Consequently, dysfunctions of the oral cavity trigeminal system, or of the retronasal smelling system in general, can have clinical significance (e.g., Halpern 2008b). It follows that evaluations of retronasal smelling should be considered when reports of difficulties in flavor appreciation occur.

Any assertion that something does not occur must be approached with skepticism. At a psychophysical level, the claim that certain chemicals are purely olfactory odorants is an assertion that these chemicals do not stimulate the trigeminal system sufficiently to produce behavioral responses that differ from those that may be attributed to chance, but do stimulate the olfactory system. To support this claim, the chemicals, at reasonable concentrations, must either be: 1) for detection, discrimination, or identification measures, delivered to portions of sensory surfaces that provide trigeminal, but not olfactory, receptor neurons, or 2) for nasal lateralization measures, delivered to sensory surfaces that have not only olfactory but also trigeminal receptor neurons. In both instances, it would not be very convincing to provide only negative data. That is, detection, discrimination, or identification of the purely olfactory odorants must be found when they are delivered to the nasal cavity of normosmics, where sensory surfaces exist that do have olfactory receptor neurons. In addition, when trigeminal stimulatory chemicals are used, at least detection or discrimination, as well as lateralization, should be observed upon delivery to sensory surfaces with trigeminal or olfactory receptor neurons.

The purely olfactory odorants met both the negative and the positive criteria. The purely olfactory odorants had not been detected by anosmics when delivered orthonasally as

the vapor-phase version of the undiluted chemicals, but, under the same circumstances, trigeminal stimuli such as linalool, nonanal, or valeric acid were detected (Doty et al. 1978; Cometto-Muñiz et al. 2005). The inability of anosmics to detect coumarin, octanoic acid, phenylethyl alcohol, and vanillin continued to be the case even when the vapor-phase concentrations of the chemicals were increased by factors of 1.6–8.5 by heating the liquid odorants to 37 °C. Moreover, normosmics could not do nasal lateralization of purely olfactory odorants such as octanoic acid or phenyethyl alcohol but could lateralize trigeminal stimuli (e.g., butanol above its trigeminal threshold; Wysocki et al 2003). Finally, normosmics had been able to identify purely olfactory odorants when presented retronasally to their nasal cavities but could not identify these chemicals when restricted to their oral cavities, which have trigeminal but not olfactory receptor neurons (Chen and Halpern 2008).

In conclusion, across participants, the vapor-phase purely olfactory odorants were not discriminated when presented OCO and did not differ from each other in number of correct selection of the ODC containing odorant. Under the same testing and analysis conditions, peppermint extract was discriminated and differed from all purely olfactory odorants in the number of correct selection of the ODC containing odorant. This outcome for the purely olfactory odorants extends the previously reported nasal cavity ineffectiveness as trigeminal stimuli of coumarin, octanoic acid, phenylethyl alcohol, and vanillin to the oral cavity as well. At the level of individuals, the possibility remains that phenylethyl alcohol may be a trigeminal stimulus for some persons.

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