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Using a bio-inspired surface resonance plasmon electronic nose for fundamental research on human olfaction

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Abstract

Electronic noses are artificial devices designed to detect and classify odors, used for many industrial applications but they can also be a tool for fundamental research on the chemical senses. Indeed, one major issue in research on olfaction is that the relationship between the structure of volatile olfactory compounds and the perception they evoke is still little understood. Acknowledging the importance of biology in the equation, the present study offers a new way to approach to stimulus-percept problem in olfaction, 1/ by considering as stimulus the interaction between odorants and olfactory receptors and 2/ by extending the measure of percept and considering the issue of interindividual diversity. To this end, we used a bio-inspired surface resonance plasmon electronic nose (e-nose) and acquired response patterns for 20 representative odorants. We also collected perceptual ratings (on intensity, pleasantness, familiarity, edibility and irritation) and verbal description of the perceptual experience associated to these odorants in a sample of 74 individuals. Combining Principal Component Analysis and Dissimilarity Matrix Analysis, we showed a relationship between the e-nose space and both measures of perception, but only for odorants eliciting homogenous responses among the subjects. This study thus shows the relevance of a bio-inspired e-nose as a model of olfactory receptors interactions for the study of natural olfaction.

Keywords: stimulus-percept issue - olfaction - perception - electronic nose - interindividual differences

Contributions

Conceptualization: MM, MB; Formal Analysis: AF, MM; Funding acquisition: MB, Investigation: MM, IS, AO, JC; Methodology: MM, MB, AF; Resources and Software: RD, CH, TL, TH; Supervision: TH, MB, AH; Writing (Original Draft and Preparation): MM, MB; Writing (Review and Editing): All authors.

Introduction

Electronic noses are artificial systems designed to detect and/or classify volatile compounds. They were first conceptualized by Persaud and Dodd (1), who demonstrated that a matrix of electronic sensors with partial specificity can be used to discriminate simple from complex odors. Their work led to the development of several types of artificial noses, used in 5 main areas of applications: control of food and drinks quality (2–4), classification of aromas and perfumes (5–7), diagnosis of diseases (8–10), control of the environment (11–13), and security (14,15). Nonetheless, beyond these industrial applications, electronic noses may also constitute a relevant tool for more fundamental research about the chemical senses, especially olfaction.

Indeed, one of the major issues in olfactory research is that there is no clear relationship between the physico-chemical structure of an odorant and the perception it evokes. This has been formalized as the stimulus-percept issue. Although a lot of studies from chemists, biologists and psychologists have been conducted, very little is known nowadays (16). For example, it has been suggested that molecular complexity is associated with the hedonic tone of an odorant (17). Keller and colleagues (18) also related the number of sulfur atoms in a chemical compound to its semantic description of “sulfurous”. More recently, Licon and colleagues (19) described a number of physicochemical rules related to specific semantic descriptors. Nonetheless, there is still a large amount of perceptual experience of odors that cannot be explained by the sole chemical features of olfactory compounds.

The missing piece of the puzzle is the intermediary role of biology in the equation, through the interaction between the odorants and the olfactory receptors located in the nasal mucosa. Indeed, the human genome comprises around 400 functional genes for olfactory receptors, which can detect thousands of chemical compounds through differential patterns of activity (20). The importance of biology has been emphasized by Poivet and colleagues (21). In their study, the authors used a medicinal chemistry approach and investigated esters in light of the responses of mice olfactory receptors neurons. They were able to characterize chemical features biologically relevant for odor

perception, with better results than chemical-only machine learning algorithms such as presented in Keller and colleagues (18). This methodology combining chemistry and biology also allowed them to uncover key molecular features related to discrimination of acetophenone (22). More recently, a computational study using deorphanized human olfactory receptors demonstrated that their activation can accurately predict a large number of perceptual characteristics of odorants (23), with a better accuracy than chemical-based models.

However, the *in vivo* investigation of the interaction between odorants and olfactory receptors is practically limited in humans. To circumvent this issue, an interesting tool can be provided by technological advances. The progressive growth of electronic noses (e-noses) and especially bio-inspired ones allows for an artificial modeling of the organization of the olfactory receptors and their type of response. Electronic noses have proved their efficacy in several domains, including quality control of food (3,24) and assessment of pollutants (12). They have many advantages: they are portable, easy to use and avoid having recourse to costly human panels. In the field of olfactory research, bio-inspired devices offer a very interesting tool to study the interaction between chemicals and receptors. By using an electronic apparatus combined with machine learning, Haddad and colleagues (25) demonstrated that the hedonic value of odorants could be predicted by the response of an artificial nose. Since then, developers increasingly use peptides as receptors (26), as they are easy to assemble through chemical and biological means. More recently, Fournel and colleagues (27) used a bio-inspired surface plasmon resonance artificial nose and showed that the semantic properties of the odorants contributed to the organization of the e-nose responses.

In light of these results emphasizing the importance of accounting for interactions between chemicals and olfactory receptors to better understand the perception of odors, we reconsidered in our study what constitutes the “stimulus” part in the stimulus-percept problem, by replacing the physicochemical features of the odorants with the responses they evoke from their interaction with olfactory receptors. Given the difficulty to access such receptors in in-vivo investigations as it

requires biopsies (28), we used a bio-inspired artificial nose (29), whose combinatorial structure of peptides can be compared to what occurs in biological systems.

Regarding the “percept” element of the stimulus-percept equation, we also challenge what is considered as a measure of the perceptual experience evoked by an odorant. In Keller and colleagues (30), the data provided to machine learning algorithms was a set of semantic descriptors chosen from a list by a group of subjects, as well as ratings of intensity and pleasantness. Although this type of measure is commonly retrieved in studies aiming to relate chemical features and perception, it has several flaws. First, it does not cover all aspects of odor perception. Indeed, there are other dimensions important for the individuals, such as edibility, familiarity or trigeminal activation (31). Secondly, it does not allow the individuals to choose their own words to describe the odorants. The provided terms are often taken from professional characterizations of odors (32) and can be redundant and vague for novices (18,19,30). Keller and colleagues (18) themselves acknowledge a great diversity in the use of these descriptors among subjects, which can bias the measures that are then entered in algorithms. This issue of variability echoes the third, and probably the main issue in perception measure: the great diversity that is consistently observed in odor perception, especially in terms of pleasantness. It is due to many factors, such as age, sex, genetics, cultural background and life experiences (33). Nonetheless, it seems that for some odorants, the hedonic value is quite stable among individuals and comparable to other species (34). This could be related to the biological salience of such stimuli, as they indicate food or potential hazards for example (35). In sum, olfactory perception comprises a shared, homogenous part for some relevant odorants, but it also includes a highly variable, heterogenous dimension which is often let aside in algorithms relating chemistry with perception. In our study, we differentiate between these two aspects by investigating the relationship between artificial receptors responses for odorants evoking similar percepts among individuals and for odorants eliciting diverse experiences. We choose as a measure of perception both quantitative ratings for a larger set of perceptual dimensions (i.e.,

intensity, pleasantness, edibility, familiarity, irritation) and qualitative free descriptions of olfactory experience from the individuals.

In summary, the present study aims to tackle the stimulus-percept issue in a new, original manner. We chose to investigate the relationship between ligand-receptors interactions and perception, by combining odorant measurements from a bio-inspired e-nose with the perceptual ratings and verbal description of individuals. To this end, we used a surface resonance imaging-based artificial e-nose, identical to the one used in Fournel and colleagues (27). We hypothesize that the relationship between the response of the e-nose and the perceptual ratings would be more important for odorants that elicit little variability among individuals compared to odorants evoking very diverse perceptions. The latter would be less related to the e-nose response, since the individual perceptual trajectories due to genetic, cultural and personal experience would be more apart from the standard response of the device.

Methods

Odorants

A total of 20 odorants were used in this study. They were chosen to best represent the physicochemical, perceptual, psychophysiological and phenomenal space of odorants. They were selected from Licon et al (31) and the results of a previous pilot study, in which the subjects were invited to rate 55 odorants on their propension to evoke different elements: visual images, sounds, textures, tastes, memories, irritation, freshness, warmth, well-being, stimulation, disgust, sensuality and relaxation. They also rated these same odorants on pleasantness and intensity, as well as to what degree the characterization of the odorants was difficult, and the certitude in their identification if they proposed one. An experiential space of the 55 odorants was constructed with the answers of the participants. From this space, we selected the 20 most representative odorants, while accounting for the diversity in chemical features of the molecules. The selected odorants are described in **Table I**, with common associated semantic descriptors. Each odorant (obtained from Sigma-Aldrich) was

diluted in mineral oil to obtain a total volume of 1mL, and then conditioned in a 15mL opaque vial. The concentrations are identical to those used in a previous study in the team (Licon et al, 2018) and correspond to the concentrations necessary to get 1Pa (10ppmv) of pressure in the air. For the testing with the e-nose, odorants were presented in 60mL transparent flasks, each containing 1mL of pure odorant. The concentrations used for the electronic nose were different from the ones used with the participants because humans have greater sensitivity compared to electronic nose and pure odorants would be too intense for the subjects. The electronic nose needs a higher concentration in order to maximize the signal to obtain reliable responses and choosing to include pure odorants allowed to make the odorant preparation reproducible.

Physicochemical characteristics

The twenty odorants can be characterized by thousands of physical and chemical descriptors, available through the Dragon software (Talete®). Here, we first extracted 82 relevant descriptors, that were easily interpretable by the experimenters. From this selection, descriptors for which the variance was null between the odorants was further removed, leaving a total of 59 descriptors for each of the 20 selected molecules.

Opto-electronic nose

In this study, we used an opto-electronic nose (NeOse Pro, #310 model, Aryballe Technologies SA, Grenoble, France) that is based on Surface Plasmon Resonance Imaging. It is composed of 64 cross-reactive peptide sensors that reversibly bind to volatile odorants. These peptides have no specific interaction properties, and each has different physicochemical properties. The air intake element consists of a constant airflow in a tube of 7cm length and 3mm diameter, with an inner diameter of 1mm (around 100mL/minute) injects the air containing odorants into the sensor chamber and the gold coated prism containing the sensor array. The sensors are immobilized onto the surface with thiol groups. Then, a collimated polarized light beam of 632 nm is sent through the prism onto the sensor array surface. When the odorants react with the sensor spots on

the gold surface, each spot lightens up with different intensities depending on the ligand-sensor integration. The gradual change in reflectivity is recorded by a video camera and processed into relative variations of reflectivity for each sensor.

Code	Odorant	Purity	Concentration	CID	Chemical class	Molecular weight	Common semantic descriptors
ACE	Acetic acid	99%	0.01%	176	Carboxylic Acid	60.06	Sharp, pungent, sour, vinegar
BCAR	Beta-caryophyllene	91%	33.64 %	5281515	Terpene	204.39	Sweet, woody, spicy, clove, dry
BENZ	Benzaldehyde	99.5%	2 %	240	Aldehyde	106.13	Sharp, sweet, bitter, almond, cherry
BUT	Butanoic acid	99%	0.11 %	264	Carboxylic Acid	88.12	Sharp, acetic, cheesy, buttery, fruity
BUTB	Butyl butanoate	98%	0.18 %	7983	Ester	144.24	Fruity, banana, pineapple, green, cherry
CAR	L-carvone	96%	1.93 %	439570	Terpene	150.24	Sweet, spearmint, herbal, minty
CIN	Cineole	99%	1 %	2758	Terpene	154.28	Eucalyptus, herbal, camphoreous, medicinal
CIS	Cis-3-hexenol	98%	0.24 %	5281167	Alcohol	100.18	Fresh, green, grassy, foliage, vegetable, herbal, oily
EOCT	Ethyl octanoate	99%	1.71 %	7799	Ester	172.3	Fruity, winey, waxy, sweet, apricot, banana, brandy
ESAL	Ethyl salicylate	99%	5.49 %	8365	Ester	166.19	Sweet, wintergreen, minty, floral, spicy, balsamic
EUG	Eugenol	98	13.45 %	3314	Benzene	164.22	Sweet, spicy, clove, woody
GER	Geraniol	98%	11.29 %	637566	Terpene Alcohol	154.28	Sweet, floral, fruity, rose, waxy, citrus
GUA	Guaiacol	98%	2.09 %	460	Alcool	124.15	Phenolic, smoky, spicy, vanilla, woody
IAA	Isoamyl acetate	95%	0.03 %	31276	Ester	130.21	Sweet, fruity, banana, solvent
LIN	(+)-Linalool	97%	2.17 %	6549	Terpene Alcohol	154.28	Citrus, floral, sweet, bois de rose, woody, green
MYR	Myrcene	75%	0.15 %	31253	Terpene	136.26	Peppery, terpenic, spicy, balsamic, plastic
OCTN	1-Octen-3-one	45-55%	0.27 %	61346	Ketone	126.22	Herbal, mushroom, earthy, musty, dirty
PROP	Propanoic acid	99%	0.04 %	1032	Carboxylic Acid	74.09	Pungent, acidic, cheesy, tropical
SAN	Alpha-santalol	NA	Pure	5368797	Terpene	220.39	Woody, santalol
VAL	Isovaleric acid	99%	0.48 %	10430	Carboxylic Acid	102.15	Sour, sweaty, cheesy, tropical

Table 1. Characteristics of the 20 tested odorants

There are three steps in signal acquisition: first, unodorized air is measured to record a baseline. Then, reflectivity increases as the odorants bind to the sensor peptides, in the adsorption phase, until it reaches an equilibrium in which there are as many odorants binding to the sensors as odorants detaching from the sensors. Finally, in the desorption phase, as the odorants progressively detach from the sensors, reflectivity decreases. The difference between the equilibrium and the baseline provides a 64 dimensions vector that is further normalized and represents the e-nose response to the odorant in further analyses. Note that the electronic nose gives a response when presented with odorless mineral oil only, but that the intensity of the response is about 0.02 at its maximum compared to a mean of 13.5 ± 2.6 for the different odors tested here.

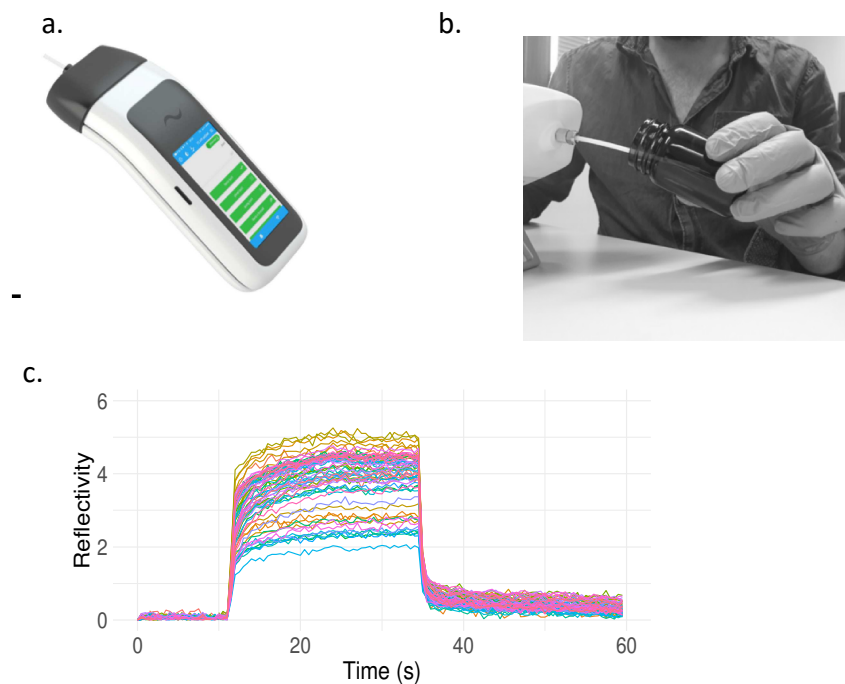


Figure 1. Experimental Design for the e-nose acquisitions. a. Aspect of the e-nose device. b. Example of presentation of an odorant to the e-nose. c. Snapshot of the data that can be visualized with the Neose Pro App software v1.8.0. Each color corresponds to a specific sensor.

In this study, each of the 20 odorants was presented six times to the e-nose, following a randomized order and with two different experimenters (three times for each of them). The

acquisitions were all made in two days, respecting a time interval of 5 minutes between each trial. The experimental design is presented in *Figure 1*.

Ethics Statement

This study followed the statement of the Declaration of Helsinki. It was approved by the Comite de Protection des Personnes in France (CPP 2017/55) and by the ethical committee at the Medical Faculty of the Technical University of Dresden in Germany. Formal verbal and written consent were obtained from all the participants.

Human ratings and verbal description of odors

In total, 74 participants were involved in the experiment. The subjects were recruited from the Technical University of Dresden, Germany (37 participants), as well as in Lyon, France (37 participants). The inclusion criteria were the following: no olfactory-related disorders, no neurological or psychiatric disorders, fluency in German or in French, age 18 to 50. The mean age was 24 +/- 6.1 years old (53 women).

For each of the 20 odorants used in the e-nose session, the participants smelled a vial and described their subjective experience of the odorant within 2 minutes, according to a short semi-guided interview conducted by the experimenter. The questions asked by the experimenter were aimed to stimulate verbalization and could be of the following sort: “*What does this odor evokes for you?*”, “*What do you think when you smell this odor?*”, “*If you had to describe this odor to a friend who has never experienced it, what would you say?*”. Finally, the subjects rated each of the odorants on a quantitative scale on the following dimensions: intensity (1 to 9), familiarity (1 to 9), edibility (1 to 9), pleasantness (-4 to 4) and irritation (1 to 9).

In a second step, the verbalizations of the subjects were transcribed and categorized into five descriptive categories, according to the type of references that were made. They were the following:

- *Impact*: references to the impact of the odor on the individual (including emotions, effect, intensity, behavior and pleasantness)

- *Source*: references to the source of the odor (including food, manufactured products, natural environment, places, people and other sources)
- *Characterization*: qualitative description of the odor (including expertise terms, olfactory, gustatory, trigeminal, sensory and other descriptors, and naturalness)
- *Memory*: references to previous experiences with the odor (including novelty, context, recognition and recollection)
- *Difficulty*: references to the difficulty for the subject to verbalize, describe or associate something to his/her experience
- *Function*: references to the function of the odor (e.g. medicinal, danger signaling...)

Data analysis

In the sample of 74 participants, 7 individuals were smokers (9.5%). As smoking is known to impair olfactory performance (36), we performed a non-parametric Wilcoxon test to compare their judgements and verbalizations, although this analysis should be taken with caution as the two subgroups were clearly unbalanced. There was no significant difference on each measured variable except for a tendency between non-smokers and smokers regarding intensity ($M_{\text{Smokers}} = 5.8 \pm 0.8$, $M_{\text{Non-Smokers}} = 6.5 \pm 0.8$, $W = 334$, $p = .07$). Secondly, we compared responses between the two language groups with a series of Wilcoxon tests as well. Germans used more references to Characterization compared to the French ($M_{\text{Germans}} = 2.6 \pm 1.1$, $M_{\text{French}} = 2.0 \pm 1.1$, $W = 430$, $p = .006$) and more references overall ($M_{\text{Germans}} = 10.0 \pm 2.3$, $M_{\text{French}} = 8.7 \pm 2.5$, $W = 498$, $p = .04$). However, this effect may be due to the effect of exposure to odors, as Germans were significantly more exposed to odors in their work compared to French (25 Germans sometimes or often exposed vs 9 French, $X^2(2) = 15$, $p = .0006$). To eliminate the effect of exposure, we filtered the data to extract individuals who were not exposed to odors, which corresponded to 28 French and 12 Germans. In order to have equivalent groups, we then randomly selected 12 Germans in this sample. A Kruskal-Wallis test was conducted to compare verbalizations in the 6 main categories according to language. There were 99 replications in order to get a stable p-value. The mean p-value

was used to interpret the test. In this case, there was no longer a difference between Germans and French for the number of references to Characterization ($M_{\text{French}} = 1.9 \mp 0.9$, $M_{\text{Germans}} = 1.9 \mp 1.2$, $t = 0.26$, $p = .69$), suggesting that the interindividual variability that was observed is more likely due to diverse exposure to smells rather than to language per se.

Then, the twenty odorants were organized in four different spaces of representation, with the construction of Euclidean distance matrices:

- A *Chemical* space, with 59 dimensions (see **Supplementary Table 1** for further description)
- A *E-nose* space, with 64 dimensions (corresponding to the normalized activation for each sensor)
- A *Ratings* space, with 5 dimensions (Intensity, Pleasantness, Edibility, Familiarity and Irritation)
- A *Descriptions* space, with 6 dimensions (Difficulty, Function, Memory, Characterization, Impact and Source)

Then, a Principal Component Analysis (PCA) was conducted on these matrices and the first extracted principal components were correlated to each other to determine if the different spaces shared similar organization. Finally, to compare the different spaces, we used Dissimilarity Matrix Analysis (Mantel tests, 9999 permutations). All the statistical analysis were performed with R software (version 3.5.0), with the packages *FactomineR* for the PCA, and *ade4* for the Mantel tests. In the results, p-values are presented by default without correction for multiple comparisons, excepted when they are significant with Holm correction.

Results

E-nose Space

To characterize the responses of the electronic nose, a PCA conducted on the e-nose space revealed that the first three principal components explained 82% of the variance (see **Figure 2**). PC1 was correlated the most with Sensors 1 ($r = .98$, $p_{\text{Holm}} < .001$), 6 ($r = .97$, $p_{\text{Holm}} < .001$), 12 ($r = .98$, p

$p_{Holm} < .001$), 20 ($r = .98$, $p_{Holm} < .001$), 32 ($r = .97$, $p_{Holm} < .001$) and 45 ($r = .97$, $p_{Holm} < .001$). PC2 was correlated the most with Sensors 43 ($r = .91$, $p_{Holm} < .001$) and 44 ($r = .90$, $p_{Holm} < .001$). PC3 was correlated to none of the e-nose sensors activity. **Supplementary Figure 1** represents the results of the PCA with all the trials for each odorant and shows relative stability in the activity of the receptors, with the exception of the odor SAN. This can be explained by the weak relative activity of the e-nose sensors compared to the other odorants ($M_{SAN} = 1.4 \pm 0.4$, $M_{OtherOdors} = 13.5 \pm 2.6$), which results in a less specific and interpretable response.

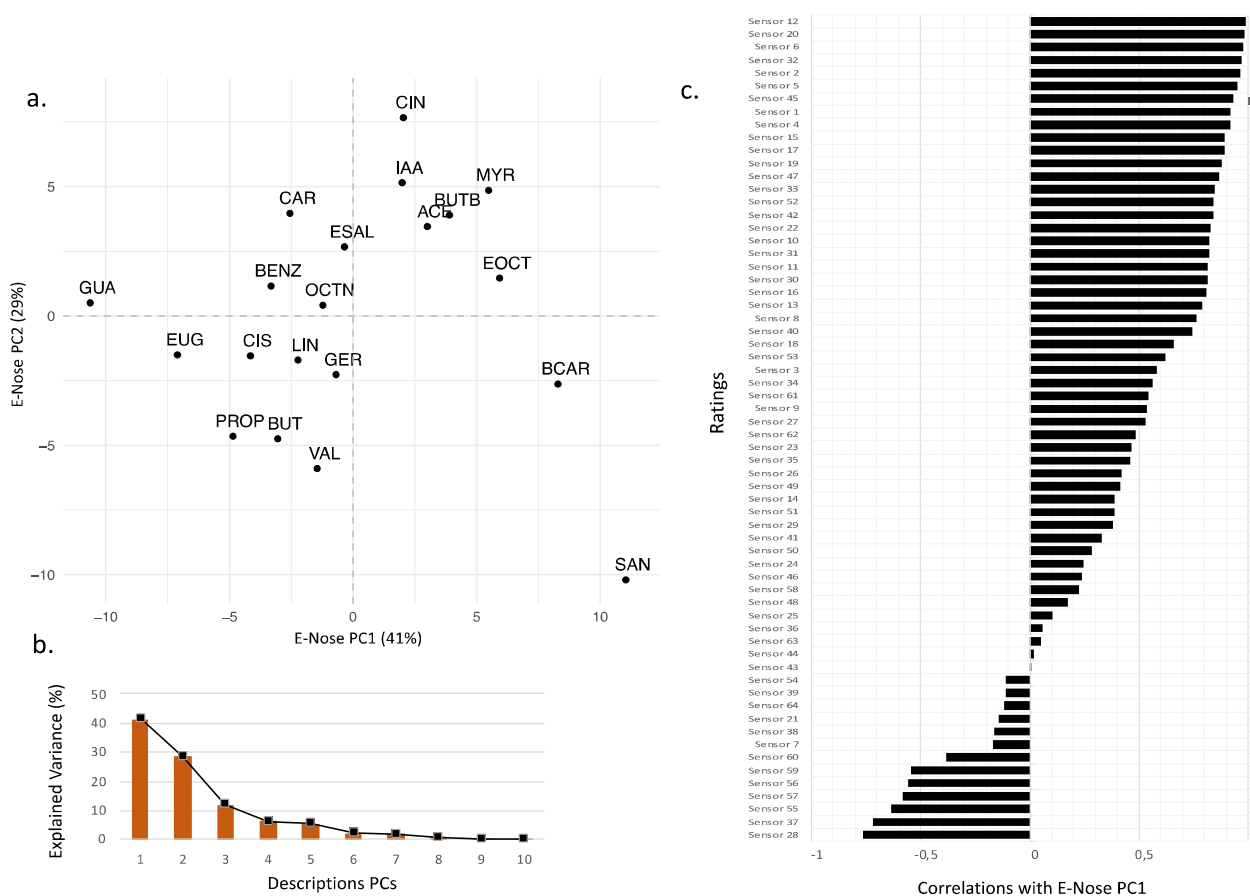


Figure 2. Results of the Principal Components Analysis for the E-Nose space.

a) Representation of the e-nose space showing the 20 odorants in a 2D space with $PC1_{E-Nose}$ on the x-axis and $PC2_{E-Nose}$ on the y-axis. b) Histogram of the percentage of explained variance for each principal component extracted from the PCA analysis. c) Correlations between each of the 64 E-Nose sensors with $PC1_{E-Nose}$.

Ratings Space

Next, to characterize the ratings given for the tested odorants, a PCA conducted on the ratings space revealed that the first three principal components explained 99% of the variance (see **Figure 2**). PC1 was correlated the most with Edibility ratings ($r = .97$, $p_{\text{Holm}} < .001$), Pleasantness ($r = .96$, $p_{\text{Holm}} < .001$) and Familiarity ($r = .77$, $p_{\text{Holm}} < .01$). PC2 was correlated the most with Intensity ratings ($r = .96$, $p_{\text{Holm}} < .001$). PC3 was correlated to none of the ratings.

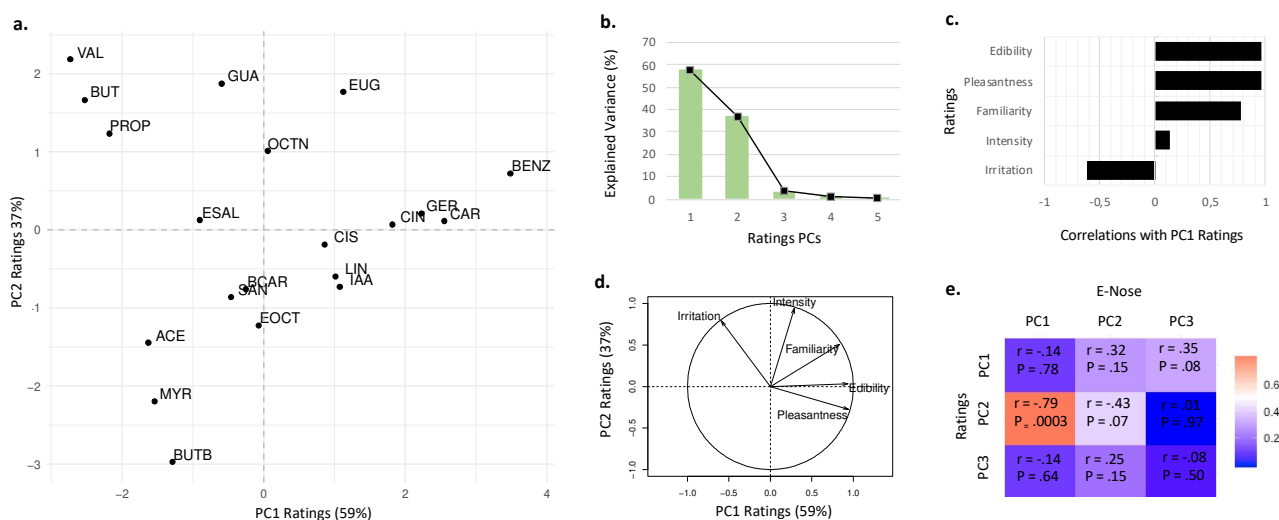


Figure 3. Characterization of the ratings space

a) Representation of the ratings space showing the 20 odorants in a 2D space with $PC1_{\text{Ratings}}$ on the x-axis and $PC2_{\text{Ratings}}$ on the y-axis. b) Histogram of the percentage of explained variance for each principal component extracted from the PCA analysis. c) Correlations between each of the 5 ratings with $PC1_{\text{Ratings}}$. d) Circle of correlations for each rating. e) Correlation map between the first 3 PCs of the ratings space and the first 3 PCs of the e-nose space.

Descriptions Space

Then, to characterize the verbal descriptions given for the tested odorants, a PCA conducted on the 6 dimensions of the descriptions space revealed that the first three principal components explained 77% of the variance (see **Figure 3**). PC1 was correlated with references to Source ($r =$

.84, $p_{\text{Holm}} < .001$) and to Memory ($r = .70$, $p_{\text{Holm}} = .056$). PC2 was correlated with Characterization of the odors ($r = .77$, $p_{\text{Holm}} < .01$). PC3 was not significantly correlated with any variables.

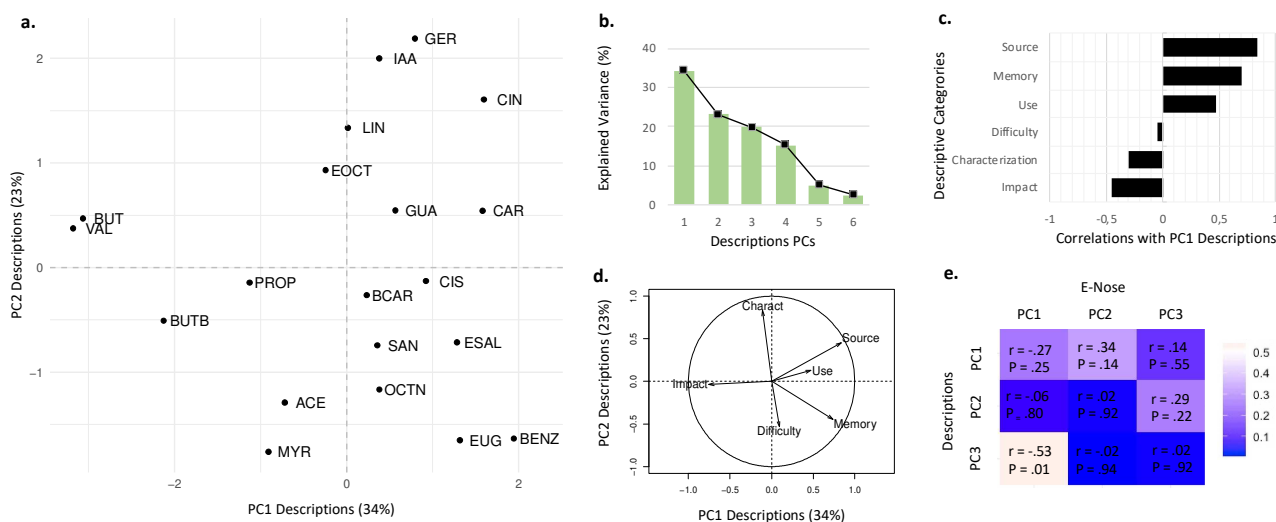


Figure 4. Results of the Principal Components Analysis for the Descriptions space.

a) Representation of the descriptions space showing the 20 odorants in a 2D space with $PC1_{\text{Descriptions}}$ on the x-axis and $PC2_{\text{Descriptions}}$ on the y-axis. b) Histogram of the percentage of explained variance for each principal component extracted from the PCA analysis. c) Correlations between each of the 5 ratings with $PC1_{\text{Descriptions}}$. d) Circle of correlations for each description category. e) Correlation map between the first 3 PCs of the descriptions space and the first 3 PCs of the e-nose space.

Comparison between the spaces

First, we compared the perceptual ratings and the perceptual descriptions to determine if these two aspects of perception were associated. To this end, we built Euclidean distance matrices between the odorants and computed a Mantel test with 9999 permutations. It showed that the ratings and descriptions spaces of odorants were significantly correlated ($r = .66$, $p_{\text{Holm}} < .001$). Moreover,

the first three main components extracted from the PCA analysis were also correlated with each other: PC1_{Descriptions} was associated with PC1_{Ratings} ($r = .84$, $p_{\text{Holm}} < .001$).

Then, we compared the space of the electronic nose responses to each aspect of perception. Using Dissimilarity Matrix Analysis, we found no association between the e-nose space and the ratings space ($r = .14$, $p = .11$, see **Figure 3e**), nor between the e-nose and the descriptions space ($r = .02$, $p = .37$, see **Figure 4e**). However, there was a significant relationship between PC1_{E-nose} and PC2_{Ratings} ($r = -.79$, $p_{\text{Holm}} < .01$).

Dissociating homogenous and heterogenous perception

Finally, we wanted to test our hypothesis that odorants eliciting homogenous perception between the individuals will be closer to the responses of the bio-inspired electronic nose, as they are less influenced by learning and different trajectories of the individuals. To this end, we divided the group of 20 odorants in two groups along a variability scale corresponding to their distribution of pleasantness ratings. The ten odorants with the highest kurtosis value (i.e., the tailedness of the density distribution) were assigned to the “Low Variability” group, and the others were assigned to the “High Variability” group (see **Figure 5**). The criterion of pleasantness rating was chosen as it has been consistently shown that it is the main dimension of odor perception and drives behavior.

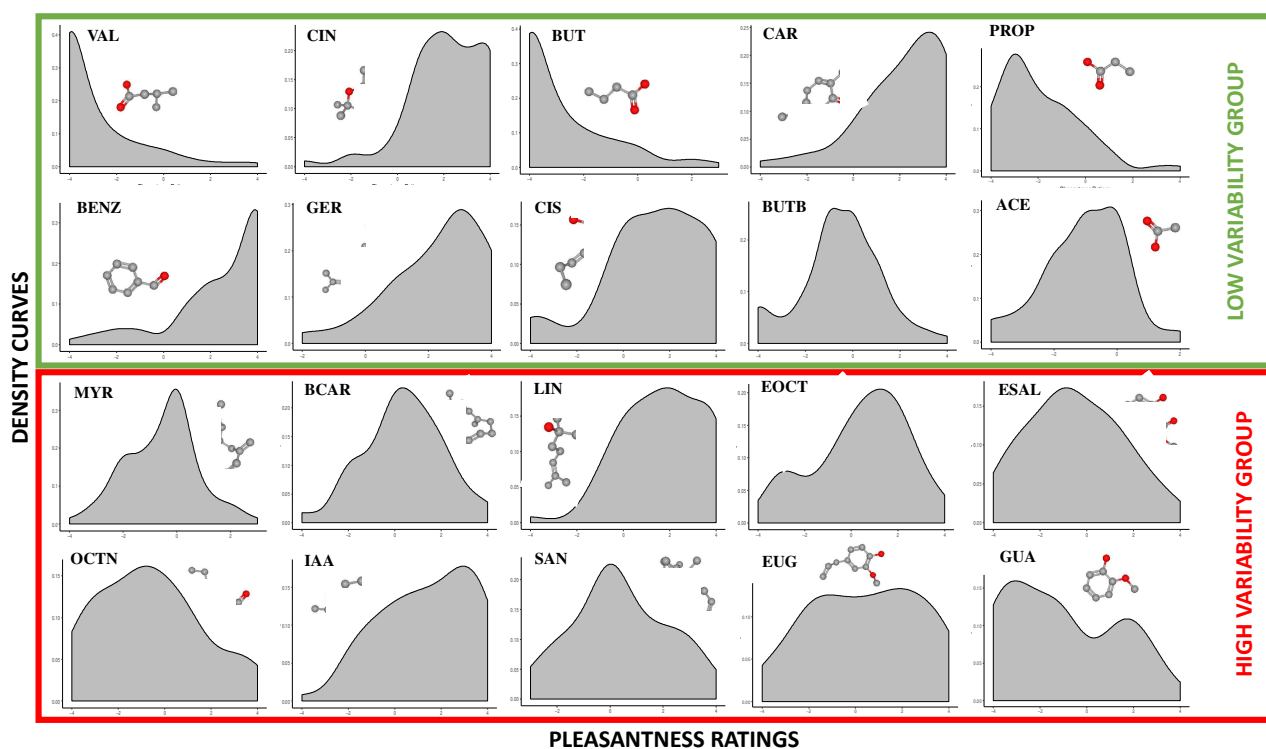


Figure 5. Distribution of pleasantness ratings for each odorant. The low variability and high variability groups are separated according to a variability scale corresponding to the kurtosis of the density distribution of the ratings. The x-axis represents the range of the ratings (from -4 to 4) and the y-axis represents the density.

Using Dissimilarity Matrix Analysis (see **Figure 6**), we found a tendency for a relationship between the e-nose space and the ratings space ($r = .32$, $p = .06$) for the group of High Variability odorants, and no relationship between the e-nose and the descriptions space ($r = .01$, $p = .46$). Regarding the main components of the spaces, $PC1_{E-nose}$ was correlated with $PC1_{Ratings}$ ($r = -.89$, $p_{Holm} = .04$) and with $PC1_{Descriptions}$ ($r = -.89$, $p_{Holm} = .04$).

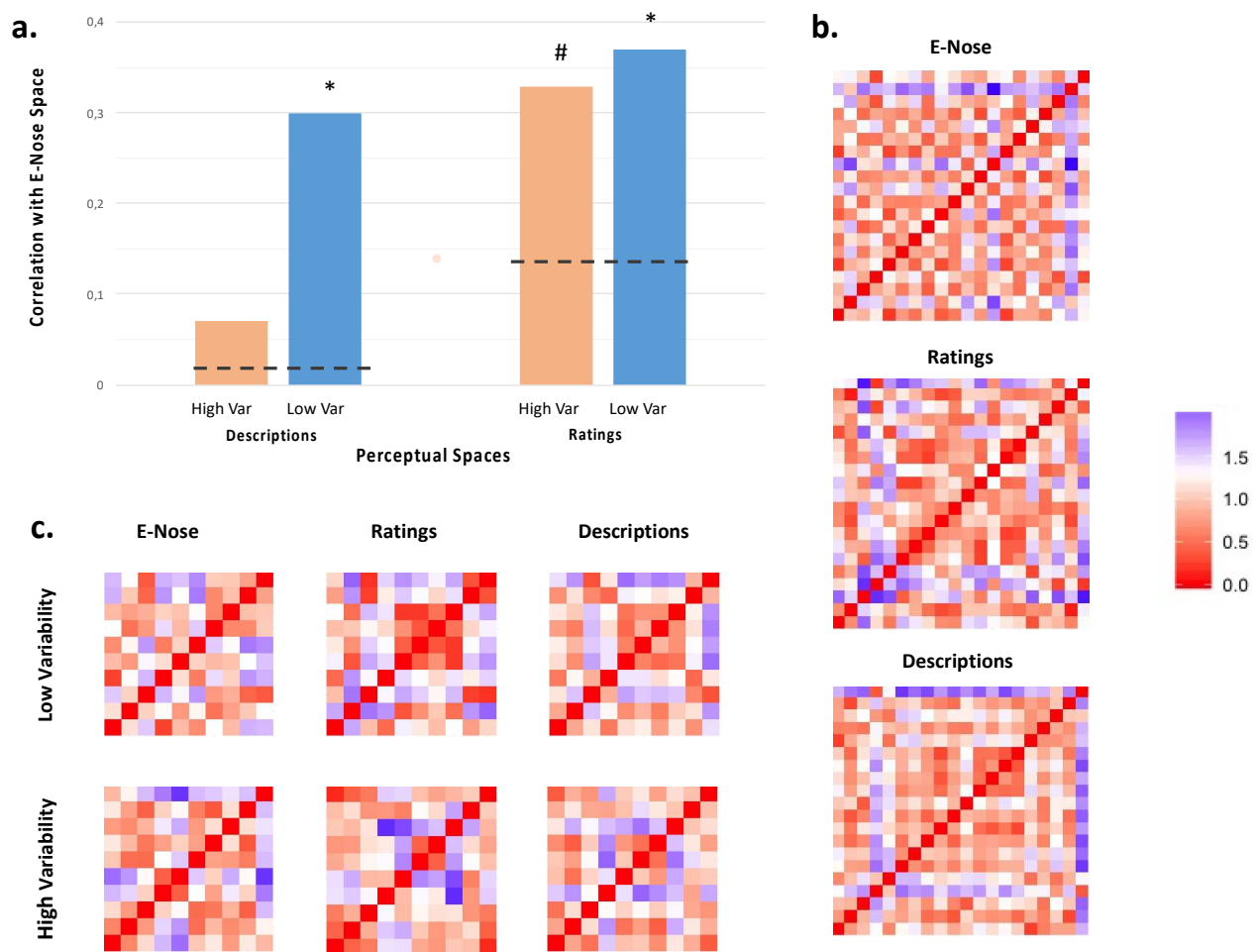


Figure 6. Correlation between the e-nose space and the perceptual spaces. a) Correlation between the e-nose and the two perceptual spaces for the odorants eliciting high variability in hedonic ratings and the ones eliciting low variability. The dashed line indicates the correlation for all odorants combined. *: $p < .05$, #: $p < .10$. b) Matrices of normalized Euclidian distances between the 20 odorants for the e-nose, ratings and descriptions space. c) Matrices of normalized Euclidian distances between the odorants for the e-nose, ratings and descriptions space, differentiated for the 10 odorants eliciting low variability in hedonic ratings and for the 10 odorants eliciting high variability. The scale indicates the Euclidian distance values divided by the mean for each matrix.

For the Low Variability group, we found this time a significant association between both the e-nose and the ratings space ($r = .37$, $p = .03$) and between the e-nose and the descriptions space ($r = .30$, $p = .04$). For the main components of the spaces, there was a correlation between: $PC1_{E-Nose}$ and

PC2_{Ratings} ($r = -.76$, $p = .01$), PC2_{E-Nose} and PC1_{Ratings} ($r = -.67$, $p = .03$), PC2_{E-Nose} and PC1_{Descriptions} ($r = -.87$, $p < .01$) and PC3_{E-Nose} and PC3_{Descriptions} ($r = .73$, $p = .01$).

Additionally, as it has been shown that e-nose responses can be associated with pleasantness (25,27) we compared the first three Principal Components of the e-nose space and the pleasantness ratings. There was a statistical trend between PC2_{E-Nose} and Pleasantness ($r = -.57$, $p = .08$) only for the Low Variability group of odorants.

Finally, in an exploratory analysis, we examined whether comparing the odorants located at the extreme ends of the variability scale could provide better associations between the e-nose responses and the perceptual and verbalization spaces. Results revealed indeed that comparing the more extreme olfactory stimuli on the variability scale led to the highest correlations between the e-nose space and the perceptual and verbalization spaces (see *Supplementary Table 2*).

Relationship with the chemical space

Finally, we compared the chemical space of odorants to the responses of the electronic nose and to individual perception. Using Dissimilarity Matrix Analysis, we found a significant relationship between the chemical space and the e-nose space ($r = .33$, $p_{\text{Holm}} < .01$), but no relationship with any of the perceptual spaces (for the ratings, $r = .09$, $p_{\text{Holm}} = .20$, and for the descriptions, $r = .02$, $p_{\text{Holm}} = .38$).

As it has been shown that chemical features of odorants are associated with pleasantness (36), we compared the first three Principal components of the chemical space with the rated pleasantness of the 20 odorants. We found a correlation between PC1_{Chemical} and Pleasantness ($r = .50$, $p = .02$). When differentiating between odorants eliciting low and high perceptual variability, then we found again a relationship between pleasantness ratings and PC1_{Chemical} for the Low Variability group ($r = .69$, $p = .02$), but not for the High Variability group ($r = .37$, $p = .29$).

Discussion

The present experiment offers a new way to approach the stimulus-percept problem in olfaction, 1/ by considering as stimulus the interaction between odorants and olfactory receptors and 2/ by extending the measure of percept and considering the issue of interindividual diversity.

First, we found that the ratings and verbal descriptions of the odorants shared a similar structure, as both their distance matrices and their first principal components were highly correlated. The dimensions that were associated the most with these components were in the one hand pleasantness, edibility and familiarity ratings, and in the other hand references to the source and memory of the odor on the subject. It is consistent with previous findings on the main driving factors of the organization of perception that showed the importance of the hedonic tone of the odors and their edibility (31).

Second, there was no relationship between the e-nose response and both measures of perception when we considered the odorants altogether. However, when separating them into two groups according to the degree of inter-individual variability in the perception they evoked, we found a relationship between the e-nose distance matrix and both ratings and descriptions matrices, only for the odorants eliciting low variability in hedonic ratings among the subjects. If we look at the typical source or associations of these 10 odorants in *PubChem* (molecular database) and atlases for perfumers, four of them are typically associated with rot or decaying food (valeric acid, butyric acid, propanoic acid, acetic acid), four are typically associated with food (L-carvone as mint, geraniol as citrus, benzaldehyde as almond, and butyl butyrate as fruit), and one is associated with medicinal use (cineole as eucalyptus). Interestingly, almost all of these odors are associated with the main biological functions of smell in humans, namely detection of food and of potential hazards (35). For the odorants with high perceptual variability, there is more ambiguity in the sources attributed to them. Indeed, most of them can be described as several types of sources (e.g., guaiacol as smoke or vanilla, isoamyl acetate as banana or solvent, ethyl octanoate as fruit or chemical,

eugenol as clove or dental product, 1-octen-3-one as mushroom, forest or rot), which is associated with more variability in individuals' experiences.

In sum, this study brought some arguments in favor of the hypothesis that there is a link between artificial and natural olfaction especially for odorants prone to low inter-individual variability and more likely to evoke a standard response related to their biological salience.

Regarding the chemical features of odorants per se, we retrieved a similar organization between the chemical and e-nose spaces, with a correlation between both their distance matrices and their first principal components as well. As the artificial nose is supposed to represent the ligand-receptors interactions, the association between its pattern of response and the chemical structure of the odorants is consistent and was retrieved in Fournel and colleagues (27). Here, we retrieved a correlation between the chemical space and pleasantness, but when separating odorants eliciting high or low variability in their ratings, the correlation was found only for odorants with homogenous hedonic ratings. Although it has been shown that pleasantness of sulfuraceous descriptors can be predicted by the chemical features of the odorants (18,36,37), even the best algorithms proposed to predict perception from chemistry have low performance for most of perceptual dimensions (30). Here, we characterized perception as a whole, with many facets not limited to pleasantness. Although chemical structure of odorants can be related to pleasantness ratings, it is not associated with a more complete image of perception whereas electronic nose responses share a similar organization with the perceptual space. This shows that integrating biology, even in an artificial manner, is an asset to better understand the stimulus-percept issue in olfaction.

One of the limitations of this experiment is the relative weak association retrieved between the tested variables. It can be assumed that with a larger sample, the correlations would be strengthened. We acknowledge that the present experiment involved a small number of molecules compared to larger studies (19,30). However, in this experiment, we aimed for a complete, reliable assessment of the perception evoked by the odorants. To this end, participants were invited to freely

describe their olfactory experience of the molecules for two minutes, as well as rating them on several dimensions. This task can be quickly exhausting for the subjects, given the difficulty of the task, the olfactory habituation phenomenon, and the decrease in motivation and focus over time. In order to limit these pitfalls, we chose to include less stimuli in a session. Another issue of this study is the fact that we used an artificial system to model the interaction between odorants and olfactory receptors. Integrating biology is essential to better understand the stimulus-percept issue, and we are aware that an electronic nose cannot be directly compared with the performance of a natural system. Further research is needed in this area to improve sampling methods and ways to study human olfactory receptors *in vivo*, but the use of a biology-inspired, 64 peptides electronic nose is a first step towards this goal. Another potential avenue of research is the possibility of predicting perception in its diversity with the artificial nose. To this end, one may need very large sets of molecules as stated above, rated by a large number of participants, so that machine learning algorithms could be used to generate predictive models. Moreover, it would be interesting in such analyses to compare the performance of predictive models using either an artificial response as in the present study or using *in vitro* biological responses. For the latter, one may collect all available data on orphanized receptors and use their ligands as stimuli in the analysis. Today, such databases do exist (38–40) but are likely not large enough yet to generate datasets that machine learning techniques can include in their algorithms. In this context, it is important to set up interdisciplinary projects combining chemistry, biology, computational sciences and psychology.

In summary, as our study and Poivet and colleagues (21) point out, if biology is not accounted for in computational models, one cannot achieve accurate and meaningful understanding of the stimulus percept issue. Artificial noses can be a way to study it by circumventing the difficulty to observe *in vivo* responses of the human olfactory receptors, but future experiments should tend to include natural systems' biology in their investigation. Also, we need a better understanding of the percept associated with olfactory compounds to solve the equation, and this entails accounting for perceptual heterogeneity.

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