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Correspondence and requests for materials should be addressed to K.F. (fkermen@olfac.univ-lyon1.fr) or B.M. (bensafi@olfac.univ-lyon1.fr)

* These authors contributed equally to this work.

Molecular complexity determines the number of olfactory notes and the pleasantness of smells

Kermen F.*, Chakirian A.*, Sezille C., Joussain P., Le Goff G., Ziessel A., Chastrette M., Mandairon N., Didier A., Rouby C. & Bensafi M.

INSERM, U1028, CNRS, UMR5292, Lyon Neuroscience Research Center, Neuroplasticity and Neuropathology of Olfactory Perception Team, Lyon, F-69000, France; University of Lyon, F-69000, France.

One major unresolved problem in olfaction research is to relate the percept to the molecular structure of stimuli. The present study examined this issue and showed for the first time a quantitative structure-odor relationship in which the more structurally complex a monomolecular odorant, the more numerous the olfactory notes it evokes. Low-complexity odorants were also rated as more aversive, reflecting the fact that low molecular complexity may serve as a warning cue for the olfactory system. Taken together, these findings suggest that molecular complexity provides a framework to explain the subjective experience of smells.

The wealth of our sensory world relies on the diversity of stimuli in our environment and on their manifold effects on behavior and cognition. The physical properties of stimuli are predictive of perception: perceived colors rely on the integration of frequencies of light waves in the visual system, and the pitch of a sound is perceived as high or low depending on its acoustic frequency. As regards smell, however, the relation between percept and stimulus properties remains unclear.

Olfactory perception is based on binding between ligands (odorant molecules) and olfactory receptors which are thought to recognize specific molecular features. An important rule governing this interaction is that a given odorant can activate one or several olfactory receptors[1]. This combinatorial coding is then processed by higher brain structures and gives rise to percepts that are difficult to name for novices but are sensed by experts in perfumery as olfactory "notes" (a smell being described as "green", "woody", "tobacco", etc). For example, whereas some odors are described by few olfactory notes (e.g., furan is described as smokey, cinnamon-like and spicy), others are described by multiple notes (e.g., coumarin is described as herbaceous, sweet, spicy, nut-like, tobacco-like and hay-like) (**Fig. 1a**). One major challenge in fundamental olfaction research, and which is also an important unresolved issue for perfumers, is to explain this complex perceptual processing on the basis of the structural features of the molecule. The present study hypothesized that an odorant which is structurally complex at the molecular level would also be described using multiple olfactory notes. To test this hypothesis, we examined the quantitative relationship between the structural complexity of odorants and the number of olfactory notes they evoked for experts and non-experts. The results from both sets of subjects revealed that the more complex the odorant's structure, the more numerous the olfactory notes it evoked. In non-experts, moreover, it was found that odorants of low structural complexity, evoking few olfactory notes, were also perceived as more unpleasant.

Results

Molecular complexity influences the number of olfactory notes. The relationship between the structural complexity of 411 odorants and the number of olfactory notes they evoked was examined. Odorant molecules were selected from the standardized Arctander atlas[2], which contains descriptions by experts referring to various chemosensory qualities: olfactory and trigeminal notes as well as flavors.

Firstly, to obtain a homogeneous measure of the number of olfactory notes across all odorants, a reference list was compiled, using a template developed by Chastrette and colleagues[3] which depicts the most relevant olfactory notes included in Arctander's book (see Methods). Secondly, the structural complexity of odorant molecules was measured, using a molecular complexity index initially developed by chemists to predict the probability of interaction between ligands (i.e., drugs) and receptors[4]. This index, which takes into account both the elements

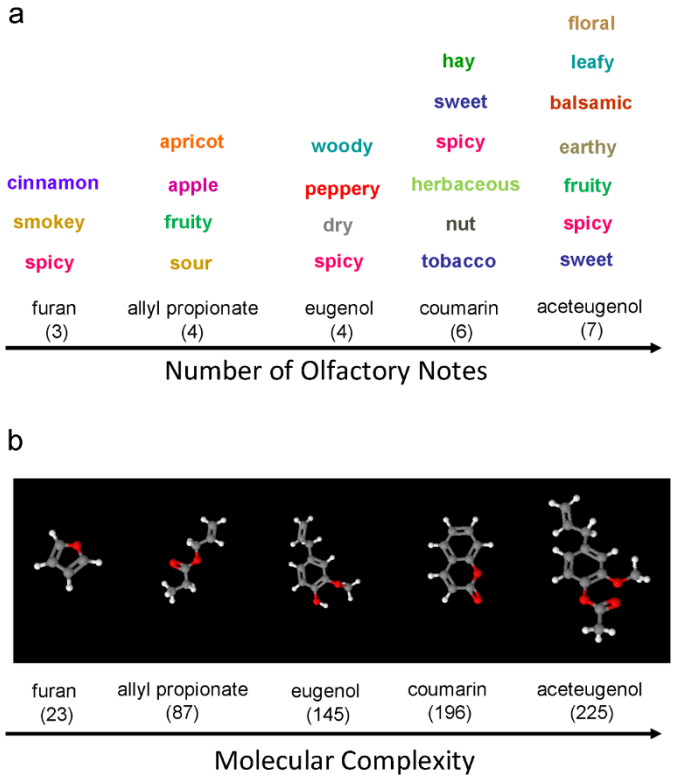

Figure 1 | Examples of odorants described by olfactory notes (a) and displaying various degrees of molecular complexity (b). (a) Odorants can be described by few or many olfactory notes. The number of olfactory notes evoked by each odorant is shown in brackets. (b) At the molecular level, odorant molecules display various degrees of complexity. The molecular complexity value for each odorant is shown in brackets. All odorants were selected from the Arctander atlas[2], which provides data regarding olfactory notes (see Methods). Molecular complexity values were obtained from the PubChem database and 3-dimensional molecular drawings were obtained from http://www.thegoodscentscompany.com/. (see Methods).

composing the molecule and structural features including symmetry[5] (see Methods), ranges from 0 (simple ions) to several thousand (complex natural products). In general, small and/or highly symmetrical molecules and compounds with few distinct atom types (or elements) have low complexity. For example, at the molecular level, coumarin (C9H6O2) is more complex than furan (C4H4O) because it contains more heavy atoms, has a greater number of double bonds and, unlike furan, is not symmetric (**Fig. 1b**).

To examine the relationship between molecular complexity and the number of olfactory notes, a linear regression analysis was first performed on the dataset and showed a significant positive relationship between variables ($r=0.28$, $p<0.0001$). However, this relationship was best described by a logarithmic function (logarithmic regression: $r=0.35$, $p<0.0001$), reflecting saturation of the number of olfactory notes above a certain threshold of molecular complexity (**Fig. 2a**). A statistical analysis performed on the same data set, splitting odorants into three classes of molecular complexity (low, medium and high: see Methods), confirmed this saturation effect ($F[2,408]=15.373$, $p<0.0001$): low complexity odorants evoked fewer olfactory notes than medium ($t(261)=4.522$, $p<0.0001$) or high ($t(284)=4.924$, $p<0.0001$) complexity odorants, while no difference was seen between medium and high complexity odorants ($t(271)=0.241$, $p=0.810$) (**Fig. 2b**). To ensure that this finding was not restricted to the main descriptors listed by Chastrette, used in the first analysis, a second analysis was performed using all the olfactory notes found in the odorant description (see Methods); the same quantitative relationship was found ($F[2,408]=11.629$, $p<0.0001$) (see **SI, Supp. Fig. 1**).

To further examine the specificity of the effect of molecular complexity on smell perception, we investigated whether the trigeminal component of an odorant depended on molecular complexity. Trigeminal notes were collected for all odorants (see Methods). No effect of molecular complexity on the number of trigeminal notes was found ($F[2,408]=0.763$, $p=0.467$; **Fig. 2c**). Thus, we show here for the first time that odorant molecular complexity itself influences the way humans perceive smells. However, since this result was based on descriptions by experts – who represent a very small portion of the population – it was important to know if the above effect would persist in non-experts.

Molecular complexity influences the number of olfactory notes, even for non-experts. To examine this question, in a first psychophysical experiment, 24 non-expert healthy subjects were asked to sniff 54 odorants selected from the Arctander atlas (Experiment 1, see Methods) and to freely describe them verbally. To equalize final concentrations in inhaled air, the 54 pure odorants were diluted according to their respective vapor pressure value (see Methods). The non-expert responses once again showed a significant effect of molecular complexity on the number of olfactory notes ($F[2,51]=3.542$, $p=0.036$; **Fig. 3a**). Paired comparison showed that low complexity odorants evoked fewer olfactory notes than medium ($t(34)=2.442$, $p=0.020$) or high ($t(34)=2.313$, $p=0.027$) complexity odorants, while no difference was seen between the latter ($t(34)=0.327$, $p=0.746$), thus replicating the relationship between molecular

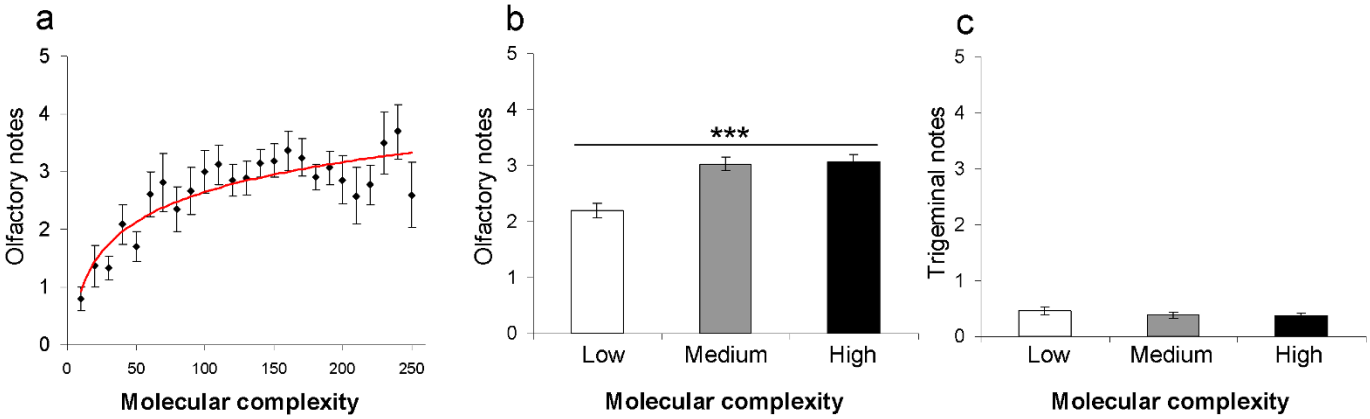

Figure 2 | Molecular complexity of monomolecular odorants influences the number of perceived olfactory (but not trigeminal) notes. A significant logarithmic relationship is observed between molecular complexity and the number of olfactory notes (a). Molecular complexity of odorants influences the number of olfactory notes (b) but not the number of trigeminal notes (c) evoked by odorants. Error bars represent s.e.m. *** $p<0.0001$.

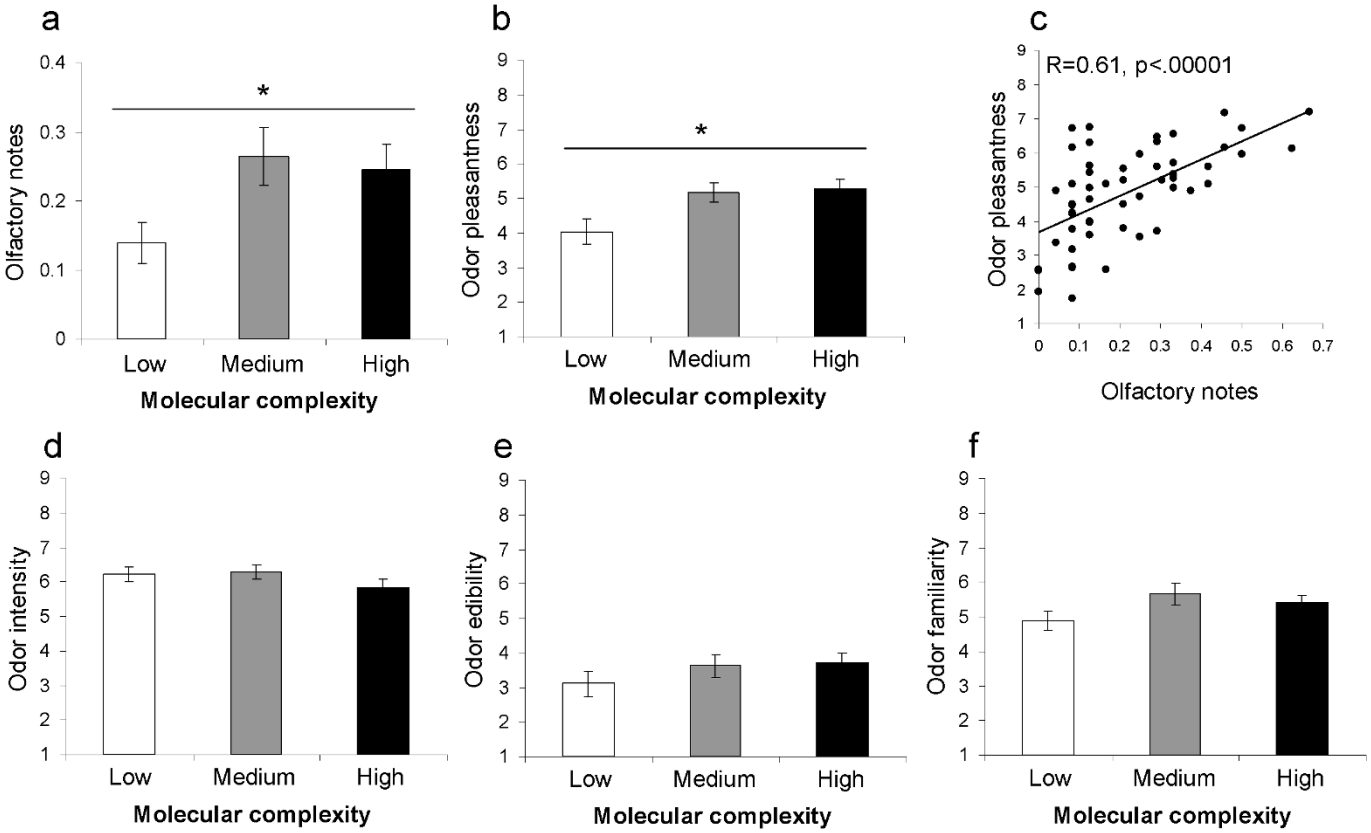

Figure 3 | Molecular complexity of odorants influences the number of olfactory notes and pleasantness of odors. Subjects (n=24) were asked to rate the pleasantness, edibility, intensity and familiarity of a set of odorants on a 9-point scale (see Methods) and to freely describe the odors. Odorants of low molecular complexity were verbally described using fewer olfactory notes (a), and rated as more unpleasant (b). A significant positive relationship was observed between the number of olfactory notes and odor pleasantness (c). No effect of molecular complexity on an odorant's perceived intensity, edibility or familiarity was observed (d–f) Error bars represent s.e.m. *$p<0.05$.

complexity and the number of olfactory notes found in expert subjects.

Low complexity odorants are perceived as more unpleasant. To investigate whether the effect of molecular complexity could be related to other perceptual dimensions, participants were asked to rate odor pleasantness, intensity, familiarity and edibility (see Methods). A significant effect of molecular complexity on odor pleasantness was found ($F[2,51]=5.128$, $p=0.009$; **Fig. 3b**): low complexity odorants were rated as more unpleasant than medium ($t(34)=2.524$, $p=0.016$) or high ($t(34)=2.716$, $p=0.010$) complexity odorants, while no difference was seen between the latter ($t(34)=0.264$, $p=0.793$). Interestingly, there was a positive correlation between the number of olfactory notes and odor pleasantness: odorants that evoked few olfactory notes were also perceived as more unpleasant ($r=0.61$, $p<0.0001$; **Fig. 3c**). No significant difference in edibility rating ($F[2,51]=1.012$, $p=0.370$; **Fig. 3e**), perceived intensity ($F[2,51]=1.227$, $p=0.302$; **Fig. 3d**) or familiarity ($F[2,51]=1.937$, $p=0.154$; **Fig. 3f**) was observed between the three groups of odorants.

The number of olfactory notes does not depend on perceptual certainty. Although it is tempting to conclude that the number of olfactory notes evoked by an odorant directly reflects its molecular complexity, it might also depend on perceptual certainty: perception of structurally complex odorants might be associated with uncertainty in verbal description, inclining subjects to come up with more notes in an effort to describe them. To address this, a second experiment was performed, using the same set of 54 stimuli. Participants were asked to smell the stimuli, to rate odor pleasantness and perceived intensity, to freely describe them verbally and finally to rate the certainty of their verbal description (Experiment 2, see Methods). However, since the number of olfactory notes evoked was relatively low in Experiment 1, the description task was slightly modified so as to encourage participants to use more olfactory descriptions in defining the odorants (see Methods); consequently, the number of olfactory notes evoked was greater in Experiment 2 than in Experiment 1 (mean=0.22 notes/odorant in Experiment 1 vs. 0.71 in Experiment 2). Interestingly, even with this greater overall number of reported olfactory notes, the results again showed an effect of molecular complexity on the number of olfactory notes ($F[2,51]=5.287$, $p=0.008$) and odor pleasantness ($F[2,51]=6.512$, $p=0.003$), but not on certainty ($F[2,51]=1.185$, $p=0.314$) or perceived intensity ($F[2,51]=0.489$, $p=0.616$) (see **SI, Supp. Fig. 2**).

Discussion

The present study showed for the first time that major dimensions of odor perception, namely pleasantness and the number of reported olfactory notes, are influenced by an odorant's molecular complexity. We first showed that, in experts, structurally complex odorants evoke more olfactory notes than less complex odorants, and then replicated this finding in naïve subjects. We also demonstrated that, in naïve subjects, low complexity odorants are evaluated as more aversive than high complexity odorants.

Like other sensory modalities, olfaction is a complex perceptual process involving both innate and learnt components. Human olfactory perception can be modulated by receptor polymorphism[6], physiological states[7], learning processes[8] and lexical knowledge[9–12], and these aspects, which were not under study here, are prominent parameters in odor perception. What is shown here, however, is that

a relationship between molecular structure and number of evoked olfactory notes exists not only in experts but also in non-expert subjects, meaning that it is maintained beyond differences in learning and experience and may reflect an intrinsic property of the human olfactory system. In line with other studies[13–17], this finding demonstrates that olfactory processing is partly driven by the odorant molecule itself, along with learnt components.

One concern that may be raised regarding our findings is that the influence of molecular complexity on the number of olfactory notes found here may have been due to a bias in the selection of odorants. To avoid this possibility, we controlled and verified several aspects in our design. First, since the volatility and vapor concentration of non-diluted odorants would be likely to correlate with molecular complexity, we diluted the odorants so as to equalize their vapor concentrations (see Methods). Using photo-ionization type gas-analysis, we showed that low and high molecular complexity odorants produced similar vapor concentrations in the inhaled air (**see Supp. Fig. 3**). Moreover, a complementary statistical analysis did not reveal any relationship between odorant boiling point on the one hand and number of olfactory notes ($r=0.16$, $p=0.236$) or odor pleasantness ($r=0.12$, $p=0.387$) on the other hand, again suggesting that volatility did not account for the observed effects (see **SI, Supp. Fig. 4**). Consequently, there was no difference in the perceived intensity of odorants of low, medium and high complexity (**Fig 3d**), rendering it unlikely that the effects observed on number of olfactory notes and pleasantness were due to differences in concentration. Secondly, it might be suggested that high molecular complexity odorants evoke more olfactory notes because they are more familiar and thus easier to describe. This possibility is, however, weakened by the fact that no difference in familiarity scores was found between low, medium and high complexity odorants (**Fig. 3f**).

Previous studies attempted to relate odor quality to the odorant's physicochemical parameters[18]. Perfumers and chemists noticed that the presence of certain chemical groups in a given odorant molecule was often associated with specific olfactory notes[19]. For example, whereas molecules that contain a sulfur atom tend to induce a typically unpleasant odor of rotten eggs, other chemical groups such as esters confer a pleasant fruity character to the odor. A number of theories were formulated in the past concerning this relationship between molecules and odor percepts, such as the steric theory[20], the vibrational theory[21] or the chromatography analogy[22]. However, these theories still failed to fully predict odor quality from molecular structure. In the present study, we opted for a different approach: we did not attempt to determine any specific quality of an odorant on the basis of structural complexity. Indeed, the molecular complexity index does not distinguish between functional groups. For example, it cannot differentiate between a thiol (butanethiol, C4H10S) and an alcohol (butanol, C4H10O), both of which have a complexity value of 13. However, while butanol and butanethiol elicit qualitatively different olfactory perceptions (according to the Arctander atlas, butanol smells "winey" and butanethiol "sulfuraceous"), they evoke the same number of olfactory notes. Rather, the present findings provide new insight into the "molecule to percept" issue by explaining the number of notes of an odorant on the basis of its molecular complexity.

Whether the influence of molecular complexity on the number of olfactory notes and on odor pleasantness respectively involves separate and/or specific neural mechanisms for each dimension remains unclear. The strong positive correlation found between the two variables is in favor of the hypothesis that they do not represent independent dimensions. Previous psychophysical studies relating odor labeling to odor pleasantness strengthen this hypothesis: for example, it was shown that jury members gave higher pleasantness ratings for the odor of substances presented with their brand label than for the same odors presented without a label[23]. Likewise, pleasantness judgment was enhanced when participants were able to identify the odorant source[24] or when the experimenter provided a name for the odorant object[25].

The neural mechanisms by which molecular complexity determines the number of olfactory notes evoked by an odorant and its pleasantness remain unknown and different hypotheses may be suggested. Firstly, odorants with lower molecular complexity may activate more receptor types, since they would tend to be smaller and thus able to fit into a larger variety of receptor binding sites. However, the mechanism by which this would entail fewer olfactory notes for low complexity odorants is unclear. In line with the present findings, we hypothesize that complex odorants (with a large variety of molecular features) will activate more olfactory receptors than low complexity odorants, and hence evoke a greater number of olfactory notes and greater pleasantness. We tested this hypothesis using data available on the activation of mammalian odorant receptors by a set of odorants[26] (see **SI, Table 5**). The analysis supported the hypothesis, showing that high complexity odorants activate more types of olfactory receptor than low complexity odorants ($r=0.34$, $p=0.006$) (see **SI, Supp. Fig. 5**). The fact that odors that are attractive for animals and pleasant for humans induce a larger total neural response at various levels of the olfactory system than repulsive or unpleasant odorants[27,28] further strengthens this hypothesis.

In conclusion, our finding that molecular complexity influences the way we perceive odors could lead to a better understanding of the neural mechanisms of olfactory perception by providing a new framework to explain neural activation at receptor level, in the olfactory bulb or cortex.

Methods

Odorant selection from Arctander's book. Odorant information was obtained from the book "Perfume and Flavor Chemicals", published in 1969 by Steffen Arctander[2]. In this book, Arctander gives a complete description, including olfactory and trigeminal notes as well as flavors, of more than 3,000 odorants. 411 monomolecular odorants were pseudo-randomly selected from this book (excluding molecules described as odorless, which usually have larger molecular weight and greater molecular complexity) (**SI, Table 1**).

Firstly, to measure the number of olfactory notes evoked by each odorant, the 74 olfactory notes selected by Chastrette and colleagues[3] were used as a reference list. These notes were selected in a study of the whole of Arctander's book by excluding those which did not provide qualitative olfactory information and also the least frequent ones (**SI, Table 2**). In line with Chastrette and colleagues, odorants in our selection are described on average by around 2.7 olfactory notes. We also performed a complementary analysis taking into account all the olfactory notes present in the odorant description (this did not include words related to intensity, flavor or trigeminality of odorants). Using this method, the odorants in our selection were described on average by around 3.6 olfactory notes. Secondly, another analysis took account only of the trigeminal notes (**SI, Table 3**) found in the odorant description.

To examine the nature of the psychophysical function that best defines the relationship between molecular complexity and the number of olfactory notes, we compared different types of regression analysis (simple or logarithmic), with molecular complexity as the independent variable and number of olfactory notes as the dependent variable. For purposes of graphical representation (**Fig 2a**), odorants were categorized according to molecular complexity on a path of 10 ($0<x\leq10$, $10<x\leq20$, …, $240<x\leq250$).

The molecular complexity values in our dataset ranged from 2 to 249. To further examine the influence of molecular complexity on 1) the number of olfactory notes 2) the number of trigeminal notes, we categorized molecules by low (molecular complexity value between 2 and 99.7, $n=138$), medium (molecular complexity value between 100 and 150, $n=125$) or high molecular complexity (molecular complexity value between 151 and 249, $n=148$), so as to have approximately the same number of molecules in each category.

Analysis of Variance (ANOVA), with molecular complexity (low, medium and high) as the independent factor and number of olfactory notes, pleasantness rating or number of trigeminal notes as the dependent variables, was performed to test the effect of molecular complexity on these perceptual parameters. Statistical significance was set at $p< 0.05$.

Odorant molecular complexity. Molecular complexity is an index of how complicated a molecular structure is, based on bond connectivity, diversity of non-hydrogen atoms and symmetry. In general, larger compounds exhibit greater complexity than smaller ones, but large symmetrical compounds and large compounds with low diversity of atom kinds are downgraded. The molecular complexity of the odorants used in the present study was collected from PubChem, one of the largest databases of chemical molecules (http://pubchem.ncbi.nlm.nih.gov/). The value was computed using the Bertz/Hendrickson/Ihlenfeldt formula[5]:

$$C = Cn + Ce$$

where C is molecular complexity, Cn skeletal complexity (as a function of n, which is bond connectivity) and Ce a function of element diversity or kinds of atoms. Cn and Ce are in turn composed of 2 terms: an overall complexity term and a symmetry term subtracted from it, so as to reduce skeletal complexity (Cn) or element diversity (Ce) when the molecule is symmetric or atoms of the same kind are present.

Psychophysical experiments. The studies were conducted according to the Declaration of Helsinki and were approved by the local ethics committee "CPP Lyon Sud Est 2". Testing was performed in an experimental room designed specifically for olfactory experiments.

Odorant concentrations were equalized by dilution in mineral oil so as to achieve an approximate gas-phase partial pressure of 1 Pa[15]. Vapor pressure values for the 54 odorants used in Experiments 1 and 2 were collected from a specialized website (http://www.thegoodscentscompany.com/) and are referenced for each odorant with the volume/volume dilution values in Supp. Table 4 (**SI**). Odorants were presented in 15 ml vials (opening diameter: 1.7 cm; height: 5.8 cm; filled with 5 ml solution) and absorbed on scentless polypropylene fabric (3×7 cm; 3 M, Valley, NE, USA) to optimize evaporation and air/oil partitioning. Moreover, to further ensure that the resulting vapor concentrations did not differ according to molecular complexity, concentrations were measured for a subset of 10 representative odorants (5 low complexity odorants: butanol-1, butyric acid, ethyl butyrate, benzaldehyde and isoamyl acetate; 5 high complexity odorants: citral, geraniol, R-(+)-limonene, terpinenol and carvone-l). Measurements were performed using an olfactometer[29] connected to a gas analyzer (photo-ionization type, PID, RAE Systems, Sunnyvale, CA, USA). The output odorous air was fed by a 4 mm tube (20 cm length) into the gas analyzer. Each odorant was presented 5 times (duration: 3 sec; interstimulus interval: 2 min) in the gas analyzer. As expected, there was no significant difference in vapor concentration between low and high complexity odorants (see **Supp. Fig. 3**).

Experiment 1. Twenty-four participants (9 male and 15 female, mean age = 22.79 +/− 4.45 yrs) without neurological disease or olfactory disorder were tested. Olfactory screening on the European Test of Olfactory Capabilities (ETOC[30]) checked normal sense of smell. Subjects were asked to smell 54 odorants grouped into the same molecular complexity categories as in the Arctander analysis: low (n=18; molecular complexity value between 7.2 and 86.9), medium (n=18; molecular complexity value between 99.3 and 150) and high molecular complexity (n=18; molecular complexity value above 154) (see **SI, Table 4**). The instructions given to the subjects were as follows: "You are going to smell several odors one after the other. Your task will be to sniff each vial and then to estimate how intense, pleasant, familiar and edible the smell was. To give your estimates, you will rate each odorant on a scale from 1 (not at all intense, pleasant, familiar or edible) to 9 (very intense, pleasant, familiar or edible). Then, after each of these odor ratings, you will have to explain "what that smell makes you think of". It is important to note that, whereas for experts the notion of olfactory notes is well defined, this is not the case for naïve subjects. This is why we chose a very open question, to capture as many as possible of the semantic associations or terms that could be considered as an olfactory "note".

Once the instructions had been read and the consent form signed, the experiment started. To habituate the subjects to the experimental setting, a training session using a sequence of 1 to 3 empty vials was carried out. The experimenter then presented the odorant vial 1 cm below the subject's nose and subjects were instructed to sniff at each vial presentation and to rate odor intensity, pleasantness, familiarity and edibility. Odorants were presented every 45 sec. Once odor ratings were completed, participants were asked to verbalize on each odor by answering the question "What does that smell make you think of?". Here, for each subject and each odorant, the olfactory notes that fitted the Chastrette descriptor list were counted. As in the Arctander analysis, an ANOVA was used to examine whether molecular complexity influenced the number of olfactory notes and odor intensity, pleasantness, familiarity and edibility ratings.

Experiment 2. Six participants (1 male and 5 female, mean age = 27.83 +/− 8.70 yrs) without neurological disease or olfactory disorder were tested. Subjects were asked to smell the 54 odorants used in Experiment 1. The instructions given to the subjects were as follows: "You are going to smell several odors one after the other. Your task will be to sniff each vial and then to estimate how intense and pleasant the smell was. To give your estimates, you will rate each odorant on a scale from 1 (not at all intense or pleasant) to 9 (very intense or pleasant)". Then, after each of these odor ratings, subjects had to describe the smell. However, since the number of olfactory notes evoked in Experiment 1 was relatively low, to encourage participants to evoke more notes, they were instructed to "identify and/or describe the smell using one or several words" (in contrast with Experiment 1, where participants were asked to explain "what that smell makes you think of?"). Finally, they were asked to rate the certainty of their description on a scale from 1 (not at all certain) to 9 (very certain). As in Experiment 1, an ANOVA was used to examine whether molecular complexity influenced the number of olfactory notes and odor intensity, pleasantness and certainty ratings.

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Author contributions

FK, AC, NM, MC, BM designed the study; FK, AC, PJ, GLG, AZ, CS, BM performed the experiments and data analyses; FK, AC, AD, CR, BM wrote the manuscript; BM supervised the study.

Additional information

Supplementary information accompanies this paper at http://www.nature.com/scientificreports

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F. Kermen, A. Chakirian, C. Sezille, P. Joussain, G. Le Goff, A. Ziessel, M. Chastrette, N. Mandairon, A. Didier, C. Rouby & M. Bensafi

Due to a typesetting error, the first author's name is spelled incorrectly in the "How to Cite" section of the PDF. The correct citation appears below.

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