Is the Age-Related Loss in Olfactory Sensitivity Similar for Light and Heavy Molecules?

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Abstract

The process of aging affects olfaction quite early and can lead to a major handicap. One may ask whether olfactory loss is general or if it affects some odors more specifically? We investigated whether an age-related increase in olfactory threshold could be more or less specific to heavy or light molecules, based on the idea that these odors would bind differently to olfactory receptors. One group of 30 older subjects (50–70 years) and one group of 30 young adults (18–30 years) were tested for their threshold to 4 odors. Two odorants were light molecules (<150 g/mol) and the 2 others were heavy molecules (>150 g/mol). Both sets contained a single molecule and a binary mixture. Older subjects performed worse than young adults in an odor identification task, confirming a decline in the olfactory function. As a major result, young adults were as sensitive to light and heavy molecules; on the contrary, older subjects were less sensitive to heavy molecules (single molecule and binary mixture). The results suggest that older people present a heterogeneous olfactory loss more specific to heavier molecules.

Key words: aging, molecular weight, olfaction, threshold, receptor

Introduction

In older people, olfactory function—as in vision or in audition—declines and thus changes the perception of the world: food becomes less tasty, flowers become less odorant, and fragrances become less distinct. As odors are closely linked to affect, this decline is likely to impact on well-being. It has been shown that a panel of older subjects (age range: 72–78 years) was less able to discriminate different foods than young adults (age range: 16–25 years) (Schiffman and Pasternak 1979). A study on 2800 subjects revealed that between 53 and 59 years old, prevalence of olfactory dysfunction reached 6.1%, whereas in 80- to 97-year-old people, it reached 62.5% (Murphy et al. 2002). In 3400 patients with idiopathic olfactory loss, the mean age for olfactory function decline has been defined at 57 years (Fark and Hummel 2013). As a more severe consequence, olfactory loss linked to aging may impair perception of danger. Stevens et al. (1987) showed that 45% of older subjects—versus 10% of young adults—failed to detect the odor put in commercially available liquefied petroleum. Reasons for decline in olfactory functions are numerous, even when neurodegenerative disorders such as Parkinson's or Alzheimer's disease are not considered.

Modifications of the olfactory network due to aging could appear at the peripheral level. In rats, it has been shown that the apoptosis of olfactory sensory neurons drastically increased in old rats (24 months) compared with young rats (12 weeks) (Robinson et al. 2002). We could suppose that same processes are involved in humans. A histological study in humans (Paik et al. 1992) revealed that, due to aging, there was a replacement of some patches of the olfactory epithelium by respiratory epithelium, likely decreasing the exchange surface between air and olfactory receptors (OR). In mice, the olfactory bulb presented a decrease in neurogenesis (Enwere et al. 2004) and in humans, a reduction in the number of mitral cells was found (Bhatnagar et al. 1987; Meisami et al. 1998; Buschhüter et al. 2008). Twenty-four-month-old mice had less neurogenesis of interneurons in the olfactory bulb even if they had as many or even more interneurons in total than 2 months’ young mice (Enwere et al. 2004). The authors correlated this decrease in neurogenesis of interneurons with impairment in discrimination between pairs of odors. In humans, a study on 8 pairs of olfactory bulbs of women aged between 25 and 102 years...
showed a reduction of the volume of olfactory bulbs; specifically, a reduction of about 520 cells per year was observed in the layer of mitral cells (Bhatnagar et al. 1987). Some effects of aging on olfactory processing have also been observed at the level of the central nervous system. When an odor is presented, older people exhibit decreased brain activity and longer latency in olfactory event–related potentials, which indicates prolonged olfactory processing (Murphy et al. 1994, 1998; Hummel et al. 1998). Finally, fMRI studies showed that older subjects display decreased activity in certain olfactory regions, such as the orbitofrontal cortex, the cingulum, and the hippocampus (Yousem et al. 1999; Suzuki et al. 2001) as well as in the entorhinal cortex, the piriform cortex, or the amygdala (Cerf-Ducastel and Murphy 2003) when they are stimulated with different odors.

More generally, an investigation of 18 odorants showed that 15 of them were perceived at higher threshold (6-fold changes) in older subjects (older than 40 years) compared with young adults (Venstrom and Amoore 1968). However, an interesting point in this latter study is that not all odorants showed the same decrease in sensitivity. Similarly, Konstantinidis et al. (2006) showed that impairment in odor identification due to aging was odor specific, with some odors being equally identified in all age cohorts and some others showing sensitivity to the process of aging. The authors found that this disparity between odors of the “Sniffin’ Sticks” test in response to aging was correlated to pleasantness. That is, unpleasant odors were age invariant, whereas pleasant odors exhibited sensitivity to aging. Because this study deals mostly with mixtures of odors, there is no possibility to correlate the observed results with the chemical structure of molecules. However, it was shown that hedonicity of a molecule could be predicted by the different chemical parameters referring more or less to the weight/size of the molecule (Khan et al. 2007).

The specific question in the present study was as follows: Is the olfactory loss in older people chemically heterogeneous in relation to the molecular weight of the odorant molecules? It appears in the literature that the loss of OR is disparate due to a patchy destruction of the olfactory epithelium, as it was shown in rodents. The olfactory epithelium in old mice or rats (24–27 months) was destroyed especially in the anterior part, which is more exposed to environmental injury (Loo et al. 1996; Lee et al. 2009). However, this topographic heterogeneity does not mean that mainly OR responding to heavy or light molecules would be destroyed. Indeed, to our knowledge, it has not been proven that the olfactory epithelium presented a chemotopy based on the size of the odorants although other topographies have been found to be related to genetics in animals (Ressler et al. 1993; Vassar et al. 1993; Strotmann et al. 1994) and possibly to pleasantness in humans (Lapid et al. 2011). We suppose that OR responding to heavy or light molecules can be dispersed across the entire epithelium. Thus, we are more inclined to base our hypotheses on a differential specificity of light and heavy molecules and not on the differential topography of OR binding light or heavy molecules. Indeed, it has been proven that animal OR and probably also human OR could bind a large range of molecules (Zhao et al. 1998; Duchamp-Viret et al. 1999; Malnic et al. 1999; Saito et al. 2009). Our assumption is that light and heavy molecules would differ in the size of the set of OR they could bind, in other words, in their specificity. The idea behind this is the more specific the odorant molecule, the narrower the set of receptors activated and in turn the higher loss of sensitivity toward these molecules in the older population. Let us take a practical but hypothetic example: we suppose that heavier molecules are more generalist than lighter ones. In young and healthy adults, heavy odorants (H) would be able to activate 50–100 different OR, whereas light ones (L) would only activate 6–10 OR. However, in older people, the destruction of the olfactory epithelium would reduce the number of potential OR to bind to half of the number, resulting in 50 OR for H and only 5 for L. As the detection of each molecule would be elicited by at least 6 activated OR, older subjects would not detect the lighter molecules, whereas they would still detect the heavier ones. From the literature, 2 hypotheses emerged with regard to the varying specificity due to molecular weight: 1) heavy molecules activate a more restricted panel of OR as they do not fit easily into the binding pocket (Amoore 1964) or 2) as heavy molecules would show more binding sites, they may activate a wider panel of OR, as suggested in studies looking to the carbon chain length (Araneda et al. 2000; Gaillard et al. 2002; Xu et al. 2003). One study gives a first insight to this issue; molecules with a higher complexity index—based on bond connectivity, diversity of nonhydrogen atoms, and symmetry—were given a higher number of olfactory notes compared with less complex odors (Kermen et al. 2011). The authors suggested that complex molecules would activate a higher number of receptors. The hypothesis 2 appeared more plausible regarding the study of Kermen et al. (2011); however, it would be worthwhile to determine the correlation between odorant molecular complexity and molecular weight. In the end, we evaluated whether older subjects would be either 1) less sensitive to heavy molecules or 2) less sensitive to light ones.

Materials and methods

Subjects

Sixty subjects participated in the experiment. The pool of subjects was constituted of a group of 30 older people (E) (age range: 50–70 years; mean age: 59 ± 7 years; 15 women and 15 men) and a group of 30 young adults (Y) (age range: 18–30 years; mean age: 25 ± 3 years; 15 women and 15 men).

Detailed medical history combined with an odor identification assessment by the “Sniffin’ Sticks” test (Hummel et al. 1997) ascertained that subjects had no detected pregnancy,
no major health impairment, and a normal sense of smell. They also performed a “mini mental state” test in order to exclude any major cognitive problems. They were asked not to smoke and eat or drink at least 1 h before the testing, in order to not distort olfaction. They received a moderate financial reward for the time spent in the laboratory. The recording procedure was explained in detail to the subjects, who provided written consent prior to participation. The study was conducted according to the Declaration of Helsinki and was approved by the Ethics Committee of the Technical University of Dresden (EK84032011).

**Odors**

Two sets of odors were used (Table 1). One set was composed of light molecules (Lm, molecular weight < 150 g/mol) and the other set of heavy molecules (Hm, molecular weight > 150 g/mol). Both sets contained a single molecule and a binary mixture. In the Lm set, the single molecule was cis-3-hexenol (Lm1, molecular weight = 100.16 g/mol), quality: cut-grass, CAS#928-96-1), the binary mixture was composed of γ-valerolacton and γ-heptalacton (Lm2, molecular weight: 100.12:128.17 g/mol, ratio: 1:1, quality: herbal:coconut, CAS#108-29-2;CAS#105-21-5). In the Hm set, the single molecule was β-ionone (Hm1, molecular weight = 192.30 g/mol, floral, CAS#79-77-6), the binary mixture was composed of γ-decalacton and γ-dodecalacton (Hm2, molecular weight: 170.25:198.31 g/mol, 1:1, peach creamy:peach metallic, CAS#107797-27-3;CAS#2305-05-7). The odor was presented at 4 dilution steps: 1:10, 1:10², 1:10³, and 1:10⁴, in order to roughly determine thresholds. Odors were prepared in brown glass bottles of 60 mL. In each bottle, 10 mL were put on an odorless cotton pad to prevent incidental spilling and bottles were let to equilibrate at least during 2 h before testing. After approximately 50 assays, the bottles were changed. For each level of concentration, 2 blank bottles were filled only with 10 mL of propylene glycol. Fragrance Resources Hamburg GmbH provided odors and solvent.

**Experimental procedure**

**Identification test**

The identification test consisted in evaluating the basal olfactory abilities of the subject. To that end, an identification test was used as described in Hummel et al. (1997). Sixteen “Sniffin’ Sticks” were presented to the subject together with a list of 4 verbal descriptors; subjects were asked to select the descriptor which corresponded to the odor. The test result was the number of correct answers.

**Threshold test**

A method of three-alternative forced choice test was used to determine threshold to each odor, based on the single staircase method (Doty 1991). In the successive trials, 3 bottles were presented in a randomized order; one was odorized and the others contained only solvent. Subjects had to identify the odorized bottle, among bottle 1, 2, or 3. They were blinded and could rely only on olfaction for the identification. They had just 1 assay to smell the bottles, presented by the experimenter during 3 s, and were forced to answer even if they did not seem to smell any difference between the 3 bottles. The highest level of dilution (1:10⁴, i.e., the weakest concentration of odorant) was presented first; each incorrect response induced the presentation of a lower dilution level (higher concentration), until a correct answer was given, which induced a second trial at the same dilution step. Two correct identifications of the odorized bottle allowed to test a lower dilution level. If the identification was correct, the level at which the 2 answers were correct was defined as the threshold. If the identification was wrong, the lower dilution

<table>
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<tr>
<th>Table 1</th>
<th>Set of odors used during the experiment</th>
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<tr>
<td><strong>Component 1</strong></td>
<td><strong>Component 2</strong></td>
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<tr>
<td>Light, Mw &lt; 150 g/mol</td>
<td>cis-3-hexenol, Mw = 100.16 g/mol</td>
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<td></td>
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<tr>
<td>Heavy, Mw &gt; 150 g/mol</td>
<td>β-ionone, Mw = 192.30 g/mol</td>
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Half of the set was composed of light molecules (molecular weight < 150 g/mol) and the other part was composed of heavy molecules (molecular weight > 150 g/mol). Each set of light and heavy molecules was composed of 2 odors, a single molecule and a binary mixture. Current name of each molecule and their molecular weight (Mw) are given in the table.
step was retested. The order in which each odor was tested was counterbalanced between subjects.

Intensity and hedonicity tests

Then subjects evaluated intensity and hedonicity of each odor presented at the highest concentration (supraliminal level for every subject). For intensity, subjects had to answer on unipolar scales with 4 labeled levels ranging from (1) not intense, (2) little intense, (3) intense to (4) very intense and for hedonicity, from (1) very unpleasant, (2) unpleasant, (3) pleasant to (4) very pleasant.

Statistical analysis

Data were analyzed using R software (version 2.15.0; R Foundation for Statistical Computing). Type II ANOVAs were produced to identify the possible main effects of sex, smoking habits, and identification abilities on the threshold values. The identification scores ranged from 11 to 16, so 3 groups were formed: a “low” score group (11–12), a “middle” score group (13–14), and a “high” score group (15–16). Then type III ANOVAs were produced in order to highlight a possible interaction between factors group (older subjects and younger subjects) and odor (Lm1, Lm2, Hm1, and Hm2). When an interaction was observed, a post hoc Tukey multiple comparisons test was used to compare each level of the 2 factors (group and odor); these tests were based on type I ANOVA. Therefore, when necessary, the results of types I and III were compared. Concerning the psychophysical data, the same models of ANOVA were used. Finally, the correlation between the age of subjects and the threshold values to each odor was evaluated using a Pearson correlation test. The level of significance level was fixed at $P = 0.05$.

Results

Evaluation of the olfactory loss

Older subjects performed worse in the identification test ($M = 13.1$, standard deviation [SD] = 1.6) than young adults ($M = 14.8$, SD = 1.0; $F[1, 58] = 101.9$, $P < 0.0001$). Even if the identification score was lower in older subjects, none of them had a diagnosis of hyposmia (value = 9, 10, or 11) or anosmia (<8). There was no significant main effect of sex ($F[1, 58] = 2.91$, $P = 0.09$), smoking habits ($F[1, 58] = 0.25$, $P = 0.62$), or identification abilities ($F[1, 58] = 2.00$, $P = 0.16$) on the threshold values. No interactions were found between sex, smoking habits, or identification abilities and the group factor on the threshold values (sex × group: $F[1, 57] = 0.55$, $P = 0.65$; smoking habits × group: $F[1, 57] = 0.64$, $P = 0.59$; identification × group: $F[2, 57] = 0.44$, $P = 0.51$).

Thresholds measurement

First, the general threshold in older and younger subjects was compared using a type III ANOVA with 2 factors group and odor; there was no main effect of group on the thresholds, but an interaction appeared between the 2 factors ($F[3, 57] = 7.10$, $P = 0.001$, Figure 1). This means that older and younger subjects had different thresholds on some of the molecules but not similarly on all of them. In comparisons between groups for each stimuli, there was no difference between older subjects (Lm1: $M = 10.10$, SD = 2.30; Lm2:

![Figure 1](https://academic.oup.com/chemse/article-abstract/39/5/383/291861/104382073161) Threshold values ($M ± 95\% CI$), given in dilution step, of the single molecules—light (Lm1, cis-3-hexenol) and heavy (Hm1, β-ionone)—and of the binary mixtures composed of light (Lm2, γ-valerolacton and γ-heptalacton) or heavy molecules (Hm2, γ-decalacton and γ-dodecalacton) in the groups of older people (50–70 years old) and of young adults (18–30 years old). The highest value of the y axis (12) is the highest dilution step (lower threshold).
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M = 9.1, SD = 2.67) and younger subjects (Lm1: M = 8.70, SD = 2.77, Lm2: M = 7.40, SD = 3.59) for light molecules (P > 0.36). However, a difference appeared between the groups concerning the single heavy molecule, older subjects were less sensitive to the single heavy molecule (Hm1: M = 6.10, SD = 3.39) than young adults (Hm1: M = 8.50, SD = 2.85) (P = 0.048). This difference did not appear for the binary mixture of heavy molecules (Hm2, older subjects: M = 5.70, SD = 3.19; younger subjects: M = 7.30, SD = 3.22, P = 0.45). Regarding comparisons between stimuli in each group, older subjects were less sensitive to the single heavy molecule (Hm1) than to the light single molecule (Lm1) (P < 0.00002), whereas there was no difference for young adults (P = 1.0). Interestingly, the same pattern showed up for the binary mixtures. Older subjects were less sensitive to the mixture of heavy molecules than to the mixture of light ones (P = 0.0005). These results suggest that older subjects are less sensitive to the heavy molecules used here, in comparison to young adults or to the light molecules.

If we look to the effect of age on the thresholds of the different odors, we found out that the threshold to Hm1 was negatively correlated to age (P[60] = −0.36, P = 0.005, Figure 2A). Similarly, there was a negative correlation between age and threshold to Hm2 (P[60] = −0.28, P = 0.03, Figure 2B). It means that while getting older, people were less sensitive to both Hm1 and Hm2.

Intensity and hedonicity evaluations

The psychophysical tests consisted in measuring intensity and hedonicity of each odor (Lm1, Hm1, Lm2, and Hm2). Concerning intensity, no significant interaction was found between group and odor factors using type III ANOVAs (F[3, 57] = 2.52, P = 0.06). Consequently type II ANOVAs were made to look for main effects. There was a significant effect of odor on the intensity (F[3, 57] = 22.17, P < 0.00001). Indeed, all subjects perceived Hm1 (M = 2.25, SD = 0.93) as less intense than all other odors (Lm1: M = 3.28, SD = 0.64; Lm2: M = 3.08, SD = 0.74; Hm2: M = 2.70, SD = 0.67) (Tukey post hoc test: P < 0.007 for all comparisons). Similarly, Hm2 was perceived as less intense than Lm1 and Lm2 odors by all subjects (P < 0.03 for all comparisons). As we did not find any interactions between factors group and odor, it is likely that difference in intensity did not account for differences in thresholds between older and younger subjects. Moreover, in the control group (young adults), such difference of intensity did not relate to difference in threshold.

Concerning hedonicity, type III ANOVA showed an interaction between factors group and odor (F[3, 57] = 2.82, P = 0.04). Indeed, young adults found Hm2 (M = 2.4, SD = 0.68) more pleasant than Lm2 (M = 1.73, SD = 0.58) (P = 0.0008), whereas this pattern was not found in older subjects (Hm2: M = 2.17, SD = 0.53; Lm2: M = 2.10, SD = 0.66; P = 1.00).

Discussion

A first result is that older subjects performed worse than younger subjects in an olfactory identification task, which underscores a decline in the olfactory function. The objective of this study was to investigate whether this olfactory loss due to aging was differential regarding the molecular weight of the odorants. Our hypotheses were that either 1) older subjects would be less sensitive to heavy molecules because they would activate a more restricted range of OR as, with their large shape, they would not fit easily

Figure 2 Distribution of threshold values of heavy molecules presented (A) as a single molecule (Hm1, β-ionone) or (B) as a binary mixture (Hm2, γ-decalacton and γ-dodecalacton) as a function of age. Each cross represents the threshold value of 1 subject. The highest value of the y axis (12) is the highest dilution step (lower threshold). The black line represents an Excel linear regression to inform on the direction of the correlation between the 2 variables. The correlations are given in the text.
into different binding pockets (i.e., different OR types) or 2) older subjects would be more sensitive to heavy molecules because they would activate a broader range of OR as they would present a larger number of binding sites. As a major result, older subjects (50–70 years old), with some degrees of olfactory loss, are less sensitive to heavy molecules than young adults (18–30 years old). Interestingly, this pattern has been observed for a single molecule and a binary mixture. More precisely, concerning the binary mixture, older subjects were less sensitive to the binary mixture of heavy molecules compared with the light ones, which was not the case in young adults. We also found a negative correlation between age and threshold of heavy molecules, whenever the odor was a single molecule or a binary mixture. Our results would thus confirm the first hypothesis where older subjects would be less sensitive to heavy molecules.

As a minor result, it has to be noticed that the higher pleasantness of the heavy mixture compared with the light one in young adults was not observed in older subjects. Several studies also showed a decreased pleasantness in older subjects, at least for odors initially pleasant (Konstantinidis et al. 2006; Joussain et al. 2013). Joussain et al. (2013) showed that in a set of 25 odorants, the pleasant ones were rated as less pleasant by a group of older subjects compared with young adults. Moreover, they confirmed this effect with an electroencephalogram showing a decrease in event-related synchronization of the beta band in older individuals. Actually, it may exist a correlation between molecular weight and pleasantness as Schiﬀman (1974) underscored. Indeed, a second analysis of a multidimensional scaling of 50 odors revealed that in a group of pleasant molecules, the more pleasant molecules were more on the right side of an olfactory space, whereas the less pleasant molecules were more on the left side and these less pleasant molecules were also the lighter ones. Therefore, one could say that an olfactory loss affecting the sensitivity to heavy molecules could also modify the pleasantness of these molecules.

A few explanations could be given to the decline of sensitivity more speciﬁc to heavy molecules in older people. This phenomenon could take place at the OR level and therefore would ﬁt with the steric theory of molecules (Amoore 1964). This theory stipulates that each OR has a speciﬁc shape that would correspond to the shape of one or several molecules. Then each ligand presents a speciﬁc afﬁnity to this OR depending on its shape. Some OR are thus broadly tuned and some others are very speciﬁc (Saito et al. 2009).

In the context of aging, as the olfactory epithelium becomes patchier, the loss of OR could be disastrous for molecules that are selectively recognized, whereas molecules that bind to various types of OR would activate different OR more easily. Because older subjects in our study do not present a reduced sensitivity to light molecules, we can make the hypothesis that these small molecules can connect to a various set of OR. If humans have an actual loss of OR as it has been found in rodents (Apfelbach et al. 1991; Loo et al. 1996; Lee et al. 2009), then with their light weight and probably small size, the small molecules would ﬁt into various binding pockets and would be still well detected by older people, whereas the heavier molecules would not be able to activate a sufﬁcient number of more OR supposedly more speciﬁc.

These explanatory hypotheses are partly derived from preliminary data, which highlight that the rates of speciﬁc anosmia are higher for heavy molecules than for light ones (Hummel T, Hatt H, Gisselmann G, unpublished data). In this study, 20 molecules ranging from 85 to 252 g/mol were screened for anosmia in a healthy population of 1000 volunteers (616 women, age range: 19–55 years). There was a positive correlation between the molecular weight of molecules and the percentage of subjects presenting an anosmia. These last results are in accordance with the hypothesis that heavier molecules activate more speciﬁc OR than smaller molecules.

A second hypothesis is that OR can be submitted to conformational or chemical modiﬁcations that decrease their speciﬁcity. Indeed, Rawson et al. (1998) have shown that OR in older subjects are less speciﬁc than OR in younger subjects. The authors suggested that aging induced a loss of control on the OR expression in each olfactory sensory neuron (OSN), inducing the expression of multiple OR types per OSN, resulting in a loss of olfactory sensitivity in older subjects (Rawson et al. 2012). Together with our results, these effects of aging would reduce the olfactory sensitivity more speciﬁcally to certain odorants as the heavier ones modifying the resulting perceptions involved, for example, in discrimination or identiﬁcation tasks.

However, our results are in contradiction to results and resulting hypotheses of Kermen et al. (2011) that complex molecules would induce more olfactory notes than less complex odors because they would activate a larger set of OR. Thus, it is likely that the OR level is not the only site that could cause a higher threshold in response to contact with heavier molecules. Indeed, with aging, the composition of the mucus of all the nasal cavities becomes denser because of dehydration (Janzen 1986; Rawson 2006), and even if direct proof is not yet available, it is likely that the olfactory mucus would also change similarly. An effect of this could be that the passing of molecules toward the olfactory epithelium might be speciﬁcally affected to the detriment of larger/heavier molecules; however, this is unlikely with the odors used in this study. Actually, a differential solubility was found but tend toward heavier molecules being more hydrophobic and thus more prone to pass through olfactory mucus containing a lower partition of water. Indeed, the molecules have different solubilities (Lm1: \( \log P = 1.697 \); Lm2: \( \log P_{\text{y}-\text{methylalacton}} = -0.270, \log P_{\text{y}-\text{heptalacton}} = 0.923; \) Hm1: \( \log P = 3.995 \); Hm2: \( \log P_{\gamma\text{-decalacton}} = 2.390, \log P_{\gamma\text{-dodecalacton}} = 3.470 \)), which appeared positively correlated \( (r = 0.89, P < 0.02) \) with the molecular weight of the molecules. After the OR level, there are also some disparities in the processing of the olfactory information in older subjects compared with young adults, like an atrophy of the olfactory glomeruli (Smith 1942), a reduction in the number of mitral...
cells (Bhatnagar et al. 1987), or a reduced activity in some olfactory regions, like orbitofrontal cortex and hippocampus (Suzuki et al. 2001) as well as in entorhinal cortex, piriform, or amygdala (Cerf-Ducastel and Murphy 2003). In the end, at all of these various stages, the perception of odors could be affected differentially regarding the molecular weight of the detected molecule.

In conclusion, due to the lack of research in the domain of OR in older people, we felt forced to produce hypotheses with regard to the observed results. To confirm those hypotheses, interdisciplinary studies are necessary in order to link up the psychophysical part and the proteomic, structural, and physiological part to explain the functioning of OR. However, the present study brings a new perspective to the general problem of olfactory loss in older subjects and gives some insights in improving the everyday life of older people, for example, in creating dedicated fragrances with molecules more able to bind on a wide spectrum of OR.

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**Conflict of interest**

None of the authors reports a potential conflict of interest.

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