The Laryngoscope

Pronounced Olfactory Habituation with Age

Constantin A. Hintschich, MD; Cindy Ma, MD; Antje Hähner, MD; Thomas Hummel, MD

Objectives: Olfactory habituation is a transient decrease in olfactory sensitivity caused by prolonged odor exposure, aiding in the discernment of new olfactory stimuli against the background. We explored the impact of subclinical olfactory impairment on odor habituation using age as a proxy.

Methods: Before the actual experiment, the individual olfactory threshold for the rose-like odorant phenylethyl alcohol (PEA) was assessed separately for the left and right nostril using the "Sniffin' Sticks" test, and ratings for odor intensity and pleasantness were collected. After applying a nasal clip continuously delivering PEA odor to one nostril for 10 min and 2 h, respectively, threshold, intensity, and pleasantness were reassessed immediately after clip removal.

Results: In the group of 80 participants (younger adults-mean age 27.7 ± 4.5 years; older adults-mean age 61.5 ± 4.7 years), olfactory thresholds were already significantly elevated after just 10 min, and this habituation was even more pronounced after 2 h. This effect could be observed bilaterally even though significantly more distinct on the exposed side. Older participants generally exhibited a more pronounced habituation on the exposed side after 2 h compared to the younger participants.

Conclusion: The results indicate that older people experience more notable habituation after extended exposure to odors. This is most likely due to the compromised olfactory function in age. Although older and younger subjects scored in the normosmic range when tested with standardized olfactory tests, the stress on the system after exposure to an odor clearly revealed the lower functionality of the aging sense of smell.

Key Words: adaption, age, habituation, olfaction, smell.

Level of Evidence: 3

***Laryngoscope*, 00:1–4, 2024**

INTRODUCTION

Olfaction serves a multitude of functions. It enables us to detect potential dangers, such as spoiled food or toxic gases.[1] Moreover, olfaction plays a significant role in emotions, memory, and sexuality.[2] Additionally, retronasal olfaction during eating and drinking typically generates pleasurable sensations, contributing to reward and satisfaction.[3]

Despite our continuous perception of odors, prolonged or repeated exposure to an odor can temporarily decrease our olfactory sensitivity.[4,5] Similar adjustment mechanisms have been described in all sensory functions. They serve as highly important function of filtering new stimuli from the background.[4] The underlying mechanisms of this stimulus-derived decrement of a sensory function can be subdivided into adaptation and habituation[4]: Adaptation is an adjustment to the stimulus on a neuronal level. In the case of olfaction, this mechanism can occur peripherally at the level of the olfactory epithelium.[4] Central adaptation is due to processing of information at the levels of the olfactory bulb, the primary or the secondary olfactory cortex.[5] In contrast, habituation refers to a decrease in the perceptual or behavioral intensity.

While considerable research has been conducted in this field, the impact of olfactory dysfunction on lateralized adaptation and habituation in olfaction remains ambiguous. In this study, age was utilized as a proxy for subclinical olfactory impairment, given the age-related decline in the number of olfactory neurons.[6] The aim was to examine whether olfactory habituation is more pronounced on the ipsilateral side compared to the contralateral side, as evaluated through standardized olfactory threshold testing. Furthermore, we investigated whether older individuals exhibit a more pronounced olfactory habituation response compared to younger individuals.

MATERIALS AND METHODS

This prospective study was conducted following positive evaluation through the Institutional Review Board of the Technische Universität Dresden (EK 501112015). The study adhered to the Declaration of Helsinki and its latest amendment. Participants were provided with detailed information regarding the

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Editor's Note: This Manuscript was accepted for publication on March 18, 2024.

The study was supported by the Volkswagenstiftung.

The authors have no other funding, financial relationships, or conflicts of interest to disclose.

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DOI: 10.1002/lary.31442

study procedures and potential risks before giving their written consent to participate.

Normosmic individuals aged between 16 and 35 years, as well as those aged 55 years and older,[7] were enrolled in this study. Psychophysical confirmation of normosmia was required, and participation was limited only by the following exclusion criteria: side difference of psychophysically assessed olfactory function, smoking (>5 cigarettes per week), pregnancy or lactation, and preconditions which can be associated with olfactory dysfunction (e.g., major head trauma in the past, presence of neurodegenerative disease, acute or chronic rhinosinusitis).

Olfactory thresholds were psychophysically assessed separately for the left and right side before olfactory exposure. The subtest for the phenylethyl alcohol (PEA) threshold (T) of the "Sniffin' Sticks" test (order number 77861, Sigma-Aldrich, Deisenhofen, Germany)[8] was used, as described in detail elsewhere.[9] Ratings for intensity and pleasantness for the odor of rose, pineapple, and coffee were collected using a visual analog scale (horizontal scale, 10 cm long, ranging between 0 [no odor perceived] and 10 [extremely strong intensity]). Odor exposure was facilitated through a nasal clip (Aspura Clip, Schönefeld, Germany), delivering undiluted PEA odor unilaterally to one nostril, with the side randomized. The two experiments were carried out during separate appointments. During the initial experiment, patients were exposed for 10 min, while in the second experiment, the exposure duration was extended to 2 h. Both olfactory thresholds and intensity/pleasantness ratings were determined immediately after the removal of the clips after 10 min and 2 h, respectively.

Data were analyzed using SPSS Statistics software (version 26, IBM, Armonk, NY, USA), while graphs were generated using Prism software (version 9, GraphPad Software, San Diego, CA, USA). Unless stated differently, the findings are presented as mean ± standard deviation (SD), and statistical significance was set at $p < 0.05$. Continuous data were tested for statistical significance using paired Student's *t*-tests or ANOVA for repeated measures. Intergroup comparisons were performed using unpaired Student's *t*-tests. Categorical data were compared between groups using Fisher's exact test.

RESULTS

A total of 80 participants were included in this study, with 74% of them being female. The mean age of the participants was 44.6 ± 17.6 years. Based on a previous study,[7] participants were divided into two subcohorts: subcohort of 40 younger adults with a mean age of 27.7 ± 4.5 years ("younger") and an older subcohort of 40 participants with a mean age of 61.5 ± 4.7 years ("older"). The sex ratio did not differ between these subcohorts ($p = 1.00$).

At baseline and over the entire cohort, the mean olfactory threshold score for the exposed and non-exposed sides was 10.0 ± 3.7 and 10.2 ± 3.4, respectively, and did not differ significantly ($p = 0.48$; Fig. 1). At baseline, in neither age group, a significant difference in T scores was observed between the right and left nostril. T scores of the to be exposed side were approximately the same between both subcohorts (younger: 9.9 ± 4.0; older: 10.0 ± 3.3; $p = 0.88$). However, on the contralateral side, olfactory threshold was higher in younger subjects than in the older group (11.0 ± 3.6 vs. 9.4 ± 3.1; $p = 0.033$).

During the olfactory exposure, a notable decline in the T score was observed on both sides, as illustrated in Figure 1. Remarkably, the decrement was already evident after just 10 min of exposure, both ipsilaterally and contralaterally (10.0 ± 3.7 vs. 8.0 ± 4.2; $p < 0.0001$; 10.2 ± 3.4 vs. 8.8 ± 3.7; $p < 0.0001$). Furthermore, after 2 h of exposure the T scores decreased further on both sides (ipsilateral: 8.0 ± 4.2 vs. 5.8 ± 3.4; $p < 0.0001$; contralateral: 8.8 ± 3.7 vs. 7.8 ± 4.0; $p < 0.0001$). The loss of sensitivity was significantly more pronounced on the exposed side compared to the non-exposed side ($\Delta T_{10min/2h}$: −4.2 ± 3.5 vs. −2.4 ± 3.5; $p < 0.0001$; Fig. 1).

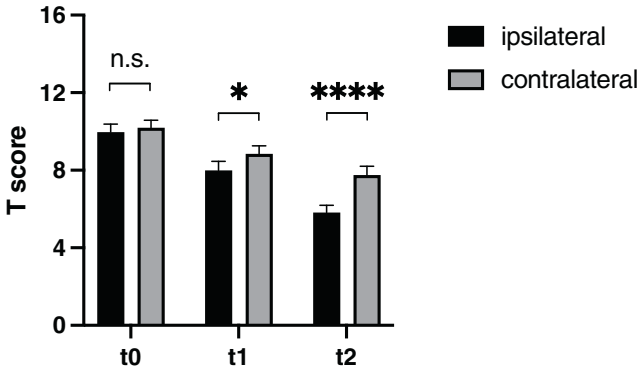

Fig. 1. Threshold (T) scores at baseline and after 10 min and 2 h of unilateral odorant exposure, respectively. Significance levels are indicated between the exposed and non-exposed sides (mean ± standard error of the mean (SED); n.s. not significant; *$p < 0.05$; ****$p < 0.0001$). Significance levels for both ipsilateral and contralateral between baseline, 10 min, and 2 h are not indicated ($p < 0.01$).

In terms of age-related differences (Fig. 2), after 2 h of exposure older participants showed a more pronounced ipsilateral habituation in comparison to the younger group (ΔT_{2h}: −4.9 ± 2.6 vs. −3.4 ± 4.1; $p = 0.053$). For the contralateral nostril, no such differences were observed (ΔT_{2h}: −2.8 ± 4.1 vs. −2.1 ± 2.8; $p = 0.35$). There were no significant differences related to gender.

Over all subject's ratings of intensity for "rose" showed bilaterally a significant decrease between baseline and 2 h (ipsilateral: $p = 0.013$ and contralateral: $p = 0.002$; Fig. 3), while the pleasantness rating decreased significantly on the exposed side but not contralaterally (ipsilateral: $p = 0.038$ and contralateral: $p = 0.93$). No significant effect was observed for intensity or pleasantness ratings for either pineapple or coffee odor.

DISCUSSION

Our results confirm that olfactory exposure to PEA leads to a significant decrement in the olfactory sensitivity for phenyl ethanol, which confirms previous findings.[10,11]

Interestingly, in this study, the effect is observable not only on the exposed side but also, albeit to a lesser extent, contralaterally. The contralateral change in sensitivity can partially be attributed to retronasal olfaction during exhalation, or passive diffusion of the odor to the contralateral side, especially during the long-term

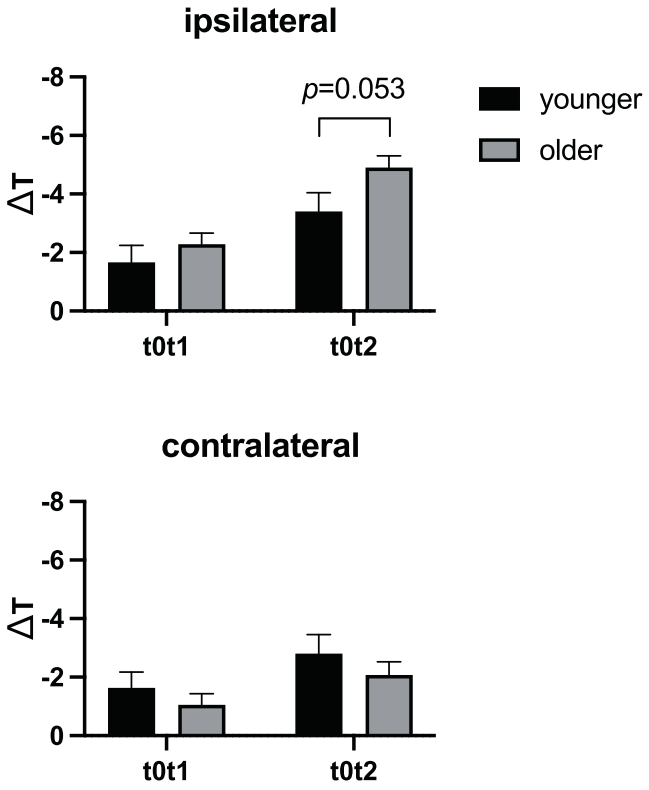

Fig. 2. Changes in ipsi- (A) and contralateral (B) threshold (ΔT) for the younger and older cohort. Note that no significant differences were observed. (mean ± standard error of the mean (SED)).

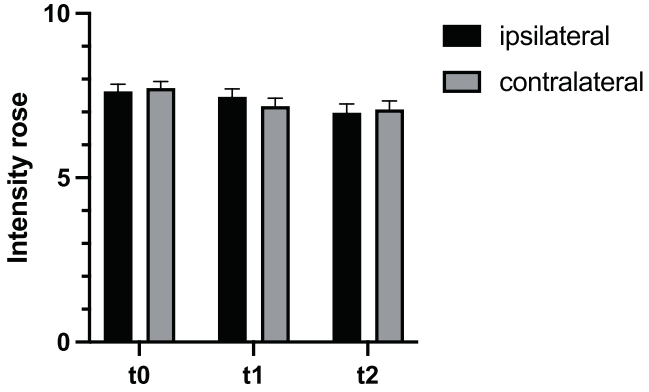

Fig. 3. Intensity scoring for PEA odor (rose). Significance levels between baseline, 10 min, and 2 h are not indicated (mean ± standard error of the mean (SED); ipsilaterally between baseline and 10 min and contralaterally between 10 min and 2 h not significant; others $p < 0.05$).

stimulation of 2 h. Still, the present results for the contralateral side are hypothesized to be also due to central nervous system mechanisms.[12,13] Although effects at a receptor level are important, it is generally assumed that habituation is largely brought about by more general central nervous effects as shown, for example, by Cain[13] or also Hummel et al.[14]

In the older subcohort, ipsilateral habituation was more pronounced compared to the younger participants. Hence, when relating this to the integrity of the olfactory system, it can be assumed that more fragile olfactory systems like in older participants habituate faster than more robust systems as found in younger participants. Similar findings have been observed in older people after a much shorter exposure duration of only 30 s[15] and in hyposmic patients.[16,17] The disparity between the age groups may be attributed to the difference in olfactory sensory neuron density. Studies have indicated a decline in the number of olfactory sensory neurons within the olfactory mucosa of both aged mice[18] and humans,[6,19] probably due to impaired regeneration from a dormant stem cell population, the horizontal basal cells.[20] Therefore, it is plausible that in older individuals, the reduced number of remaining olfactory sensory receptors could become saturated more rapidly by an odorant, leading to a more pronounced habituation response. Additionally, age-related alterations in the olfactory fila[21] and decreased olfactory bulbs[22] might also account for the intergroup difference.

Still, the present results diverge from the findings of Mignot et al.[23] in which both older and younger subjects were exposed to odors at their homes for a period of 2 weeks. This study did not reveal any significant sensitivity differences toward the exposed odors between both age groups. The disparities between our study and the research conducted by Mignot et al. may stem not only from differences in experimental design but also from their bilateral assessment of olfactory function compared to our focus on lateralized olfactory sensitivity. Reduced olfactory sensitivity might potentially be compensated for by bilateral nasal function, which plays an important role in overall olfactory capacity.[24,25] In fact, olfactory side differences have been shown to be an indicator of a bad prognosis of olfactory function.[26]

However, the present results might be limited by methodical difficulties. (1) The olfactory exposure was not performed strictly unilaterally. Olfactory exposure might have led to an orthonasal or retronasal (via the nasopharynx) exposure and subsequently a direct habituation of the contralateral side. (2) The age difference between the two subcohorts might have been too little, as suggested by the comparable T scores between subcohorts at baseline. This could have potentially limited the effect of age on olfactory habituation. On the other hand, the present results emphasize that, even when there was no difference at baseline, obviously age took its toll on olfactory sensitivity.

CONCLUSION

In conclusion, the present results indicate that older people experience more notable habituation when subjected to extended exposure to odors. It can be assumed that the background of this response is the compromised olfactory function in older people. Although older and younger subjects scored in the normosmic range when tested with standardized olfactory tests, the stress on the system after exposure to an odorant clearly revealed the lower functionality of the aging sense of smell. This also helps to explain parts of the complaints of patients reporting olfactory loss although scoring in the normal range.

ACKNOWLEDGMENT

Open Access funding enabled and organized by Projekt DEAL.

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