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Effects of Olfactory Training in Patients with Olfactory Loss

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Objectives: Olfactory function is known to be modulated by repeated exposure to odors. The aim of this investigation was whether patients with olfactory loss would benefit from "Training" with odors in terms of an improvement of their general olfactory function. It was hypothesized that olfactory Training should produce both an improved sensitivity towards the odors used in the Training process and an overall increase of olfactory function.

Study Design: The prospective study was performed in patients with olfactory dysfunction.

Methods: One group of patients performed the Training (n = 40), whereas another part did not (n = 16). Exclusion criteria for patients were sinunasal disease. Olfactory training was performed over a period of 12 weeks. Patients exposed themselves twice daily to four intense odors (phenyl ethyl alcohol: rose, eucalyptol: eucalyptus, citronellal: lemon, and eugenol: cloves). Olfactory testing was performed before and after training using the "Sniffin' Sticks" (thresholds for phenyl ethyl alcohol, tests for odor discrimination and odor identification) in addition to threshold tests for the odors used in the training process.

Results: Compared to baseline, training patients experienced an increase in their olfactory function, which was observed for the Sniffin' Sticks test score and for thresholds for the odors used in the training process. In contrast, olfactory function was unchanged in patients who did not perform olfactory training. The present results indicate that the structured, short-term exposure to selected odors may increase olfactory sensitivity.

Key Words: Olfaction, anosmia, smell, regeneration.

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INTRODUCTION

Recent studies have shown that olfactory disorders occur at a much higher rate than previously assumed. The frequency of a decreased olfactory function was estimated as high as 16%, with approximately 5% of the general population being functionally anosmic.[1] In adults aged 50 years and above, the prevalence of impaired olfaction was found to be 25%,[2] indicating that aging is the most important factor in olfactory loss.[3] In addition, sinunasal disease, upper respiratory tract infections (URTIs), and trauma are among the most frequent causes of dysosmia.[4]

Olfactory loss has been shown to have a severe impact on the quality of life in some patents,[5] whereas other patients either suffer little or even remain undiagnosed.[6] Apart from the psychological strain in at least some of the patients, most patients experience hazardous events. No therapy has yet been proven to be effective in post-URTI and post-traumatic smell disorders, other than the possible treatment of olfactory loss associated with sinunasal disease,[7] despite the fact that numerous studies indicate that olfactory receptor neurons may regenerate.[8] More importantly, it has been shown that exposure to an odor may modulate this regenerative capacity.[9,10]

Olfactory training has been shown to improve olfactory function in humans.[11–13] The goal of this single-center, prospective, controlled, nonblinded study was to investigate the change of olfactory function following frequent short-term exposure to odors over a period of approximately 12 weeks.

MATERIAL AND METHODS

Patients

All participants were either self-referrals or referred from an outside institution to the Smell & Taste Clinic, Department of Otorhinolaryngology, University of Dresden Medical School. All participants provided written informed consent. The experimental design was approved by the ethics committee of the medical faculty of the Technical University of Dresden.

A total of 56 patients were included into the study (33 women, 23 men). Based on previous studies,[14,15] this

sample size appeared to be adequate to study potential effects of the training procedure. The mean age was 57.8 years (±12.0 SD, range 23–79 years). The patients were thoroughly examined by experienced otorhinolaryngologists, which included an endoscopic examination of the nasal cavities and an MRI scan of the head if deemed necessary. Exclusion criteria were pregnancy, age of less than 18 years, normosmia, sinunasal disease, or acute nasal diseases (e.g., acute viral infections). Depending on the clinical findings and past medical history, olfactory dysfunction was either classified as postinfectious (following an infection of the URT), post-traumatic (following head trauma), or idiopathic. The postinfectious group consisted of 35 patients (24 female, 11 male; mean age 59.1 years, ±12.1 SD), the post-traumatic group of seven patients (three female, four male; mean age 51.1 years, ±12.7 SD), and the idiopathic group of 14 patients (six female, eight male; mean age 58.0 years, ±10.9 SD).

Training With Odorants

Olfactory training was performed over a period of 12 weeks. Patients exposed themselves twice daily to four odors (phenyl ethyl alcohol (PEA): rose, eucalyptol: eucalyptus, citronellal: lemon, and eugenol: cloves). These four odorants were chosen to be representative of four odor categories claimed by Henning[16] in his work on the "odor prism" (*Geruchsprisma*), where he tried to identify primary odors (compare[17]). These categories are flowery: *blumig* (e.g., rose), foul: *faulig*, fruity: *fruchtig* (e.g., lemon), aromatic: *würzig* (e.g., cloves), burnt: *brenzlich*, and resinous: *harzig* (e.g., eucalyptus). Training patients received four brown glass jars (total volume 50 mL) with one of the four odors in each (1 mL each, soaked in cotton pads to prevent spilling). All jars were labelled with the odor name.

Patients were advised to sniff the odors in the morning and in the evening for approximately 10 seconds each. To focus their attention on the training, they were asked to keep a diary in which they rated their overall olfactory abilities each Sunday (data not analyzed). Further, patients received a phone call by one of the experimenters (KR) every 3 weeks into the training period to ask 1) about the patients' olfactory function and 2) to maintain compliance with the training procedure. Patients in the nontraining group were advised to wait and see how the olfactory function would spontaneously recover.

Olfactory Testing

Olfactory testing was performed before and after the training period of 12 weeks using the Sniffin' Sticks test kit,[18] which involves tests for odor threshold, odor discrimination, and odor identification. Using commercially available felt-tip pens, the odorants were presented approximately 2 cm in front of both nostrils for 2 seconds. PEA odor threshold was assessed by a single-staircase, 3-alternative forced choice (3-AFC) procedure. Three pens were presented to the patient in a randomized order, two contained odorless solvent (propylene glycol) and the other an odorant in a certain dilution. The patient's task was to indicate the pen with the odorant. Concentration was increased if one of the blanks was chosen and decreased if the correct pen was identified twice in a row. The mean of the last 4 of a total of 7 reversal points was used as detection threshold (ranging from 1 to 16).

A total of 16 odor concentrations were tested starting from a 4% stock solution (dilution ratio 1:2; solvent propylene glycol). The second subtest assessed the ability of the patient to discriminate different odors. Again, 16 triplets of pens were offered, each including two identical odors and a different one. The patient's task was to indicate the pen which had a different smell. The score was the sum of correct responses ranging from 0 to 16. Both threshold and discrimination testing was performed with the patient being blindfolded. For testing of odor identification, 16 pens containing common odors were offered. The patient had to identify each of the odorants from a list of four descriptors. The sum of the scores from the three subtests resulted in the TDI-score (Threshold, Discrimination, Identification) with a maximum of 48 points. As defined in,[19] a score of 30.5 points or more indicates normosmia, a score between 16.5 and 30 points indicates reduced olfactory function in terms of hyposmia, and a score of less than 16.5 points indicates functional anosmia.

Threshold Measures

While thresholds for PEA were measured using the single-staircase paradigm within the Sniffin' Sticks test kit (see previously discussed data), thresholds for the other odorants used for training (eucalyptus, eugenol, and citronellal) were assessed by means of the method of ascending limits,[20] using a 3-AFC procedure. This procedure was chosen because it is slightly faster than the staircase procedure, although it maybe somewhat less reliable.[21]

Odors were presented in brown glass jars, similar to the presentation of PEA using the Sniffin' Sticks. Two of the jars contained odorless solvent (propylene glycol), the other an odorant in a certain concentration. The patient's task was to indicate the jar with the odorant. Correct identification was assumed when the patient correctly identified the same odor concentration three times in a row. A total of eight odor concentrations for each odor were tested starting from 4% stock solutions (dilution ratio 1:4; solvent propylene glycol). Between tests of the odorants, subjects rested for approximately 5 minutes to minimize adaptation.

Statistical Analysis

For statistical analyses, SPSS (Statistical Packages for Social Sciences, version 14.0, SPSS Inc., Chicago, IL) was used. Comparisons between the two groups were performed using t tests for independent samples and χ^2 tests. Analyses of variance (repeated measures design: rm-ANOVA) were used for comparisons of olfactory function (within-subject-factor: Sniffin' Sticks subtest [PEA

TABLE I.
Descriptive Characteristics (Means, Standard Deviations [SD]) of Patients Who Underwent Training (n = 40) and Those Who Did Not Use Training (n = 16) Plus Results From *t* Tests for Independent Samples.

Parameter	Group	Mean	Standard Deviation	Results From *t* Tests
Age (in years)	No training	62.3	13.4	$t = 1.82$
	Training	56.0	11.0	$P = .07$
Duration of disease	No training	53.3	85.4	$t = 0.16$
(in months)	Training	49.2	83.1	$P = .87$
TDI score	No training	18.7	6.4	$t = 0.26$
(in units)	Training	19.2	6.4	$P = .80$
PEA odor threshold	No training	3.2	3.0	$t = 0.74$
(in dilution steps)	Training	2.7	2.2	$P = .46$
Odor discrimination	No training	9.0	2.8	$t = 0.32$
(number correctly identified)	Training	8.7	3.0	$P = .75$
Odor identification	No training	6.5	2.8	$t = 1.43$
(number correctly identified)	Training	7.7	3.0	$P = .16$
Eucalyptus odor threshold	No training	4.4	2.3	$t = 0.33$
(in dilution steps)	Training	4.7	2.2	$P = .75$
Citronellal odor threshold	No training	4.4	2.4	$t = 0.55$
(in dilution steps)	Training	4.7	2.1	$P = .58$
Eugenol odor threshold	No training	4.0	2.6	$t = 1.42$
(in dilution steps)	Training	5.0	2.2	$P = .16$

threshold, odor discrimination, and odor identification]) between the groups (between-subject-factor: group [training, no training]) obtained before and after a period during which some of the subjects trained while others did not (session: before, after). Correlation analyses were performed according to Pearson. The alpha level was set at .05.

RESULTS

At baseline the two groups were not significantly different in terms of age, sex distribution (training: 26 women and 14 men; no training: seven women and nine men; $\chi^2 = 2.13$, $P = .23$), and causes of olfactory deficits (training: URTI, n = 24; trauma, n = 5; idiopathic, n = 11; no training: URTI, n = 11; trauma, n = 2; idiopathic, n = 3; $\chi^2 = .49$, $P = .78$). Also, before training the two groups did not differ significantly with regard to measures of olfactory sensitivity (Table I).

In terms of general olfactory sensitivity as measured by means of the Sniffin Sticks kit,[19] patients undergoing training exhibited significantly higher scores than patients who did not train (interaction between factors "session" and "group": $F[1,51] = 4.91$, $P = .031$). When using *t* tests for comparison, differences between results before and after training across the entire groups were very pronounced for PEA odor thresholds ($t = 3.20$, $P = .002$), but not significant for odor discrimination and identification. Similarly, odor thresholds improved during training for citronellal ($t = 2.82$, $P = .007$) and eugenol ($t = 2.95$, $P = .005$), but not for eucalyptol ($P = .07$).

With regard to improvement on an individual level, only one of 16 subjects from the no training group (6%) exhibited improvement of more than 6 points in the TDI score, whereas 10 of 36 subjects exhibited improvement in the training group (28%). Patients from the training group exhibiting improvement had a TDI score that was, on average, 10.3 points higher than before the training. With regard to PEA thresholds, odor discrimination, and odor identification these numbers were at 4.6, 2.4, and 3.3 respectively. When looking at the cause of the olfactory disorder of those patients exhibiting improvement, it was URTI in five cases (all hyposmic), trauma in two cases (both functionally anosmic), and idiopathic olfactory loss in three cases (1 functionally anosmic, 2 hyposmic). Improvement resulted in URTI patients in hyposmia (n = 3) and normosmia (n = 2), in patients with post-traumatic olfactory loss in hyposmia, and in patients with idiopathic olfactory loss in hyposmia (n = 1) and also normosmia (n = 2).

DISCUSSION

The present study provided the following major results: 1) olfactory training appears to increase olfactory function in approximately 30% of the subjects over a period of 12 weeks only compared to subjects who had no olfactory training; and 2) improvement is not only found in patients with olfactory loss due to URTI and idiopathic olfactory loss, but also in patients with functional anosmia following head trauma.

This clinical study is consistent with previous studies suggesting that the olfactory sense has to ability to change and recover. Such plasticity has been shown not only in animals,[22] but also after repeated exposure of human subjects to androstenone,[23] which has been shown by means of psychophysical and electrophysiological techniques, meaning recordings from the olfactory epithelium. Together with data from animal research,[9,10] these findings suggest that repeated short-term

exposure to odors may result in an increased growth of olfactory receptor neurons and an increased expression of olfactory receptor in response to the exposure.

Olfactory training has been known to have a beneficial effect on the olfactory sense. For example, Henning[16] described the superior sensitivity of wine traders in terms of wine odors,[24] and his own sensitivity for coumarin that he acquired during 11 years of frequent exposure during his experimental work on the sense of smell.[11,12,25] The positive influence of exposure to odors on odor sensitivity may not only relate to changes at the level of the olfactory epithelium, but may also relate to changes at the level of the olfactory bulb, or at even higher levels of processing.[13]

However, recent data also indicate that more continuous exposure to odors does not necessarily result in an increased olfactory function. A practical example for this loss of sensitivity relates to the odor of a smoker or a person having eaten garlic, who often is unable to tell whether they carry this specific smell or not, simply because they have become used to it over time. As a consequence, when trying to use training with odors in a clinical context, exposure to the training odors should be restricted.

Although results from the present study seem to suggest that olfactory training may be helpful in patients with olfactory loss, they also raise numerous questions. Future studies need to determine 1) whether the observed increase of olfactory sensitivity is temporary or would stay even after the training period is over; 2) whether training with odors increases the responsiveness to odors at the level of the olfactory epithelium using recordings of the electro-olfactogram; 3) whether training leads to an increase of the volume of the olfactory bulb; and 4) whether patients need to train with odors, or whether sniffing alone leads to the same results. Compared to the present work, these future studies will also have to use more balanced control groups in terms of the number of subjects. To investigate parts of these questions, a multicentric study is currently underway under the auspices of the Working Group on Smell and Taste in Austria, Switzerland, and Germany.

CONCLUSION

The present study's results indicate that the structured, short-term exposure to odors may increase olfactory sensitivity.

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