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Olfactory training for patients with olfactory loss after upper respiratory tract infections

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Abstract Olfactory training consisting of daily suprathreshold odor exposure over 12 weeks seems to improve olfactory function. It is unknown if a longer period of training might be more effective. A prospective non-randomized clinical study was performed including 39 patients with olfactory loss after an upper respiratory tract infection (URTI) of less than 24 months duration. Patients exposed themselves with suprathreshold concentrations of four odors (rose, eucalyptus, lemon, cloves) applied in ''Sniffin' Sticks'' felt-tip pens over 32 weeks. Olfactory function was performed before (T1), after 16 weeks (T2), and 32 weeks of training (T3) using the 'the Sniffin' Sticks test kit calculating the TDI score (Threshold, Discrimination, Identification). The mean TDI score showed a non-significant trend of improvement at T2, and was significantly increased at T3 ($p = 0.021$). Overall, 31 patients (79 %) showed an increased TDI score at T3. The increase of TDI from T1 to T3 was 4.6 ± 5.1. Age, gender, duration and initial severity of olfactory loss had no influence on the improvement (all $p > 0.05$). Only patients with a D score lower than the median value of 8 showed a significantly higher increase of the D score at T3 ($p = 0.004$). The present study confirmed that olfactory training improves olfactory function in patients with olfactory loss after URTI. A longer duration of training over 32 weeks seems to increase the effectiveness in comparison to a 12-week period. This was tested in a completed German multicenter trial to be published soon containing a control group to include the effect of a spontaneous recovery after URTI.

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Introduction

An acquired loss of olfactory function as decreased sense of smell (hyposmia) and absent sense of smell (anosmia) has a major impact on the quality of life of the [1]. Olfactory dysfunction after an upper respiratory tract infection (URTI) is an important etiology [2]. No standard therapy has yet been established to treat effectively olfactory disorders. The results of a treatment with prednisolone are controversial [3, 4]. Other medical treatment like with minocycline, Vitamin A, or herbal drug combinations did not appear to be useful [4–6]. On the other hand, it has been shown experimentally in animals and also in clinical studies that olfactory training can improve olfactory functions [7–11]. Hummel et al. used Sniffin' Sticks for their suprathreshold olfactory training in patients with olfactory loss caused by URTI, trauma, Parkinson's disease, or idiopathic etiology [9, 11]. Sniffin' Sticks are felt-tip pens and well known for the Sniffin' Sticks olfactory test kit [12]. To use them also for olfactory training is effective, as the results from the olfactory testing can directly be transferred to the training program. Furthermore, the sticks are easy to handle and allow a training at home with high patient's compliance. Using a 12-week olfactory training course, 20 % of the patients with Parkinson's disease and about 28 % of the other patients exhibited an improvement of olfactory function [9, 11].

We asked now the question if it might be possible to increase the effect of olfactory training by extending the period of training. Therefore, we performed a prospective single-center study to investigate the change of olfactory

function in patients with olfactory loss after URTI following olfactory training for 32 weeks consisting of frequent short-term exposure to various odors.

Materials and methods

Patients

The prospective cohort study was approved by the local ethics committee. Informed consent was obtained from all participants. Patients of the Department of Otorhinolaryngology, University Hospital Jena, Germany, with olfactory dysfunction after URTI were included. The age range was limited to 18–70 years. The interval between observation of the olfactory loss and the URTI did not exceed 30 days. Only patients with a permanent olfactory loss of <24 months were included. Inclusion was restricted to patients with anosmia and hyposmia (definitions see below). Exclusion criteria were other reasons for olfactory dysfunction than URTI (e.g., olfactory dysfunction after traumatic brain injury, chronic rhinosinusitis, and neurodegenerative diseases), respiratory allergies, pregnancy, malignant tumors or tumor therapy with influence on olfactory ability, other severe chronic disease, prior paranasal sinus surgery or surgery of the nose. Most patients had been treated with systemic or topical corticosteroids, but without success. Some patients were not treated with corticosteroid in advance. In case of corticosteroid treatment, it was stopped at least 3 months before starting the olfactory training.

Olfactory testing

All patients received a complete otorhinolaryngologic examination including nasal endoscopy. Assessment of their olfactory function was performed using the Sniffin' Sticks olfactory test kit (Burghart, Wedel, Germany) [12]. This kit is a validated instrument that contains three separate tests for odor threshold (T), discrimination (D), and identification (I), respectively. In addition, the results of the three tests are summarized as the TDI score. The TDI score allows for the differentiation of quantitative olfactory loss in terms of normosmia (TDI score $\geq$30 points), hyposmia (16 points $<$ TDI score $<$ 30 points), and functional anosmia (TDI score $\leq$ 16 points) [13]. Olfactory testing was performed before inclusion into the study, after the olfactory training period of 16 weeks and after 32 weeks of training. In brief, Sniffin' Sticks are felt-tip pens. The odorants of the pens were presented approximately 2 cm in front of both nostrils for 2 s. Beta-phenylethyl alcohol (PEA) odor threshold was assessed by a single-staircase, 3-alternative forced choice procedure. Three pens were presented to the patient in a randomized order, two contained odorless solvent (propylene glycol) and the other an odorant in 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 four of a total of seven reversal points was used as detection threshold (T), 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 (D). 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 odor identification (I), 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 with a maximum of 48 points. TDI was measured at baseline (T1), after 16 weeks (T2) and finally after 32 weeks of olfactory training (T3). An improvement of olfactory function was arbitrarily defined as an increase of the TDI of $\geq$2 points.

Olfactory training

Olfactory training was performed in accordance with Hummel et al., but using Sniffin' sticks instead of glass bottles as odor material [9]. As distinguished from this study, the olfactory training in the present study was performed over a longer period of 32 weeks. Patients exposed themselves twice daily to four odors (PEA = rose, eucalyptol = eucalyptus, citronellal = lemon, and eugenol = cloves) prepared in the same way as the Sniffin' Sticks as felt-tip pens. The patients were instructed to sniff every morning and evening after the meal at the four sticks in a random order. The sticks were held in a distance of approximately 2–3 cm under the nostrils. The patients were advised to sniff on every stick approximately 10–20 s, i.e., it took about 40–80 s to sniff on all four sticks. One hour before olfactory training, the patients were not allowed to smoke to exclude an influence on the olfaction.

Statistical analysis

For statistical analysis, SPSS (Statistical Packages of Social Sciences, Version 20.0, SPSS Inc., Chicago, IL) was used. If not indicated otherwise, data are presented with mean values ± standard deviation (SD). Analyses of variance (ANOVA) were used for comparisons of the results

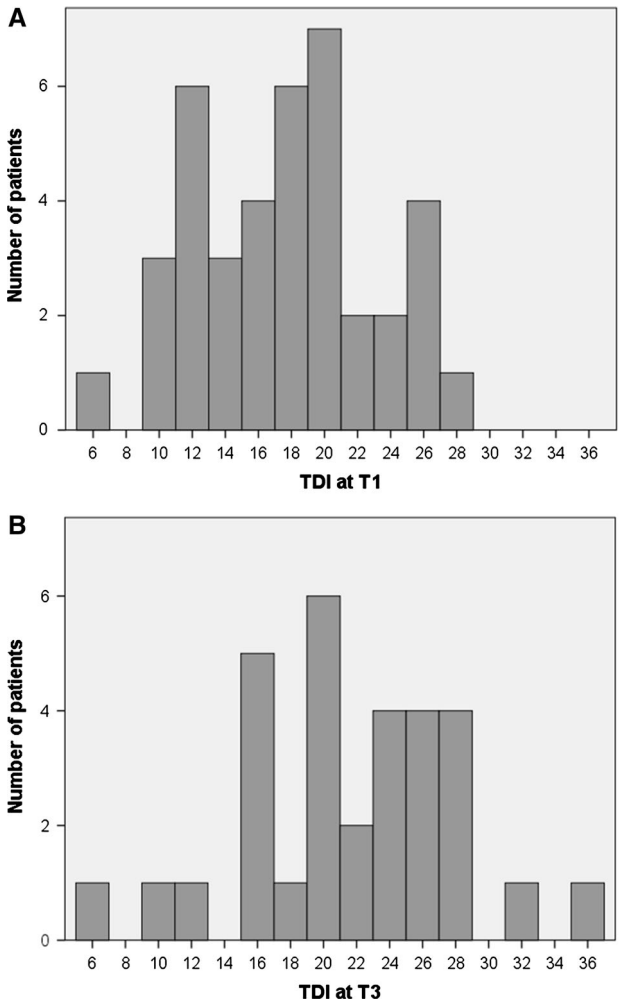

Fig. 1 Effect of olfactory training on TDI scores. **a** at T1 (baseline), **b** at T3 (after 32 weeks of training)

of olfactory testing (TDI values at T1, T2, and T3) with Bonferroni correction for multiple testing. The Mann–Whitney test was used to compare the influence of dichotomous continuous variables (e.g., gender, <>median age) on the TDI results at T1 and on the changes between T1 and T3 (T3 − T1 = ΔT3T1). Nominal p values of two-tailed tests are reported. The significance level was set at $p < 0.05$.

Results

Patients' characteristics

Thirty-nine (39) patients were included into the study (29 women, 10 men). The mean age was 56 ± 8 years (median 57 years; range 40–69 years). The average duration of olfactory loss was 10 ± 7 months (median 8 months; range 1–25 months). The mean TDI score at T1 was 17 ± 5 (median 17; range 6–28.25; Fig. 1a).

Table 1 Results of olfactory testing at baseline (T1), after 16 weeks (T2), and after 32 weeks of olfactory training (T3)

Parameter	T1	T2	T3	T1–T2 p*	T1–T3 p*	T2–T3 p*
TDI	17 ± 5	19 ± 6	21 ± 7	0.308	**0.021**	0.732
T	1 ± 2	2 ± 2	2 ± 3	0.501	1.000	0.242
D	8 ± 2	9 ± 3	10 ± 3	0.388	**0.004**	0.221
I	8 ± 3	8 ± 3	9 ± 3	0.959	0.431	1.000

* ANOVA with multiple comparisons

Improvement of olfactory function under olfactory training

Already after 16 weeks of olfactory training (T2), the mean TDI scores showed a non-significant trend of improvement (Table 1). After 32 weeks of training (T3), the mean TDI score and the mean D score were significantly increased ($p = 0.021$; $p = 0.004$, respectively), i.e., olfactory function was improved (Fig. 1b). The other subscores, the T score and the I score did not improve significantly. Overall, eight patients (21 %) did not show an improvement during the olfactory testing at T3. The other 31 patients (79 %) showed an increased TDI score at T3 compared to T1. 22 patients (56 %) improved by ≥6 points. The absolute mean of increase of TDI from T1 to T3 was 4.6 ± 5.1 (median: 4.5; range −5.5 to 16.25) and for the D score 2.2 ± 2.7 (median: 2; range −2 to 10).

Factors with association to TDI at baseline and to TDI changes between T1 and T3

Age, duration of the olfactory loss prior to the start of the olfactory training, and gender had no influence on the initial TDI score or on the initial D score at T1 (Table 2, Fig. 2). Furthermore, these parameters had also no significant influence on the improvement of the TDI score or the D score at T3. The initial severity of the olfactory loss expressed by the TDI score showed no association on the absolute changes between T1 and T3. Patients with a D score at T1 lower than the median value of 8 showed a significantly higher increase of the D score after 32 weeks (T3) of olfactory training ($p = 0.004$).

Discussion

The present study provided the following major results: 1) An olfactory training improved olfactory function in patients with olfactory loss after URTI. After a training period of 32 weeks, the olfactory function increased in 79 % of all patients and an improvement ≥6 points was

Table 2 Influence of baseline parameters on initial TDI at T1 and on the changes of the TDI at T3

Parameter	TDI				D			
	T1	*p*	ΔT3T1	*p*	T1	*p*	ΔT3T1	*p*
Age at T1		0.766		0.921		0.407		0.765
<median 57 years	17 ± 6		5 ± 5		8 ± 3		2 ± 2	
≥median 57 years	17 ± 5		5 ± 5		8 ± 2		2 ± 3	
Duration of olfactory loss		0.629		0.540		0.678		0.395
<median 8 months	17 ± 5		6 ± 6		8 ± 2		3 ± 4	
≥median 8 months	17 ± 6		4 ± 5		8 ± 3		2 ± 2	
Gender		0.558		0.611		0.400		1.000
Female	17 ± 6		5 ± 5		8 ± 3		2 ± 3	
Male	18 ± 5		4 ± 6		8 ± 2		2 ± 3	
TDI at T1	N.A.			0.446	N.A.			0.119
<median 17			5 ± 6				3 ± 3	
≥median 17			4 ± 5				1 ± 2	
D at T1	N.A.			0.064	N.A.			**0.004**
<median 8			7 ± 5				4 ± 3	
≥median 8			3 ± 5				1 ± 2	

N.A. not applicable

seen in 56 % of the patients. 2) Olfactory training seems to be useful independent of age (≤70 years), gender, duration and severity of olfactory dysfunction. 3) A longer duration of training over 32 weeks could increase the effectiveness of training in comparison to a shorter training period.

The present study is not without limitations. A control group without olfactory training was not analyzed. Furthermore, although patients with known neurodegenerative disease were excluded, it cannot be ruled out that patients with unknown neurodegenerative disease were included, as screening tests were not performed. The median duration of olfactory loss after URTI in our study sample was 8 months, i.e., the probability of a further spontaneous improvement of olfactory function was very low. Nevertheless, it is necessary to compare the presented rates of improvement to data from the literature on the spontaneous recovery of olfactory function after URTI: A spontaneous recovery rate of 31–48 % (TDI change >6 points within about 5–6 months is reported [4–6]. In the present study, 56 % of patients had a TDI change >6 points after the olfactory training. This suggests that the observed improvement of olfactory function after olfactory training is better than an expected spontaneous recovery rate. Furthermore, the effectiveness of such a longer training including a control group was the subject of an ongoing multicenter trial initiated by working group on Olfaction and Gustation of the German Academy of Otorhinolaryngology, Head and Neck Surgery. First results will be published soon.

This clinical study is consistent with previous studies. Recent investigations proposed that the olfactory function has the ability to change and recover and they suggested that repeated short-term exposure to odors may result in an increased growth of olfactory receptor neurons and an increased expression of olfactory receptors in response to the exposure. Therefore, an olfactory training should produce an overall increase of olfactory function [11]. The present study confirms this hypothesis for patients with olfactory loss after URTI. Haehner et al. described same effect, an increase of olfactory function, in patients with Parkinson disease [11]. In their study, the patients increased their olfactory function after a training period of 12 weeks. We may speculate that a longer training period, like in the present study, would have had an even better effect. Furthermore, we showed in accordance with the study of Haehner et al. that odor discrimination but not distinct odor threshold changes after the olfactory training [11]. Probably, the type of training that applies different odors at each training setting can explain the predominant effect on the improvement of odor discriminations. Recently, another study used a quite similar olfactory training paradigm: Hummel et al. characterized patients with olfactory loss and increasing their olfactory function after a training period of 12 weeks also using glass bottles as odor training material [9]. Unlike the present study including only patients with olfactory function after URTI, a heterogeneous group of patients with different reasons of olfactory loss were tested. Nevertheless, the olfactory function increased in 10 out of 36 patients (28 %) regardless of the reason of olfactory dysfunction and using a much shorter training period. In the present study, we saw only a trend of improvement after 16 weeks, and finally 31

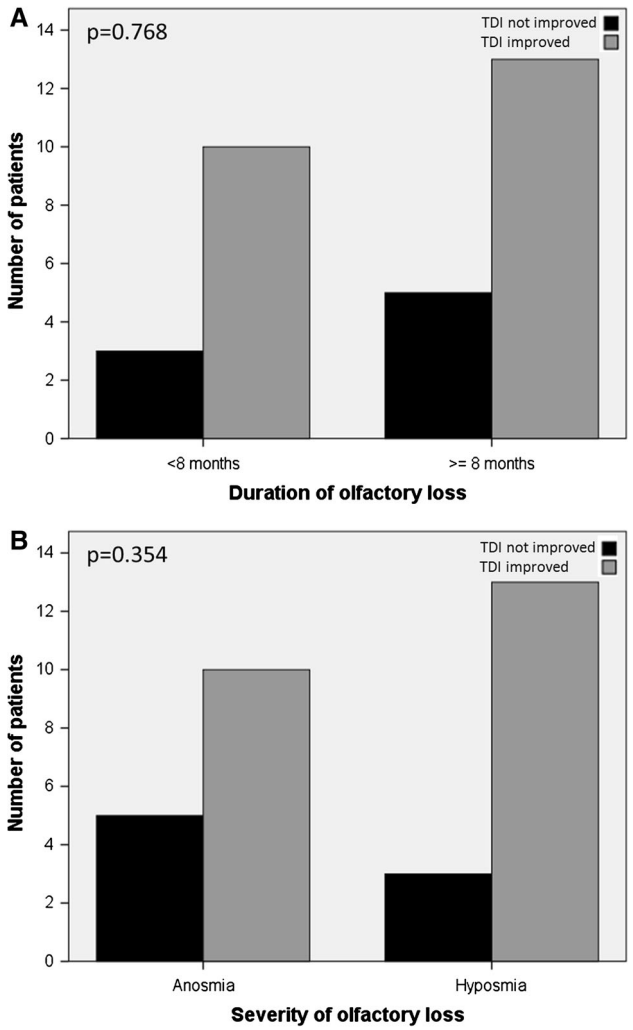

Fig. 2 Relation between duration of olfactory loss after URTI (**a**) and of severity of olfactory loss (**b**) on the improvement rates. Neither the duration (<> median of 8 months) nor the severity (anosmia versus hyposmia) had an influence on the improvement rates after the olfactory training (Chi square test)

out of 39 patients (79 %) showed an improvement in olfactory function. There is another study also using a long training period of 8 months in patients with olfactory dysfunction and a variety of etiologies [14]. Twenty-eight of 46 patients received only an olfactory training and the other 18 patients a combination of training and topical steroids. When using only the olfactory training, the patients showed a significant effect after 8 months, and in accordance with the present data, mainly because of an increase in odor discrimination [14]. In summary, we could conclude that a longer training period than of 12 weeks, i.e., of 32 weeks or even longer might produce better results.

The optimal time period of such an olfactory training is a question for future study, Furthermore, future studies need to answer a lot of questions: The most important question is if the improvement of the sense of smell only has a temporary effect after the training is stopped or if the training has a permanent effect? Second, the physiological mechanisms behind the increase of the olfactory function after training has to be explored in more detail in the future. This may be possible through use of recordings of odor-evoked response potentials at the human olfactory epithelium by the use of an electro-olfactogram to document the increases of responsiveness to odors through olfactory training at the level of the olfactory epithelium [15]. Alternatively, structural magnetic resonance imaging (MRI) or functional MRI could be applied during the training to measure the volume growth of the olfactory bulb and higher brain regions after olfactory training [16, 17]. Finally, it should be examined where the limit of the training is concerning the duration of the olfactory loss, i.e., if also patients with a long history of olfactory dysfunction might profit from such training.

Conflict of interest The authors indicate that they have no conflict of interest.

References

1. Neuland C, Bitter T, Marschner H, Gudziol H, Guntinas-Lichius O (2011) Health-related and specific olfaction-related quality of life in patients with chronic functional anosmia or severe hyposmia. Laryngoscope 121(4):867–872. doi:10.1002/lary.21387
2. Holbrook EH, Leopold DA (2006) An updated review of clinical olfaction. Curr Opin Otolaryngol Head Neck Surg 14(1):23–28. doi:10.1097/01.moo.0000193174.77321.39
3. Blomqvist EH, Lundblad L, Bergstedt H, Stjarne P (2003) Placebo-controlled, randomized, double-blind study evaluating the efficacy of fluticasone propionate nasal spray for the treatment of patients with hyposmia/anosmia. Acta Oto-laryngol 123(7):862–868
4. Reden J, El-Hifnawi D, Zahnert T, Hummel T (2011) The effect of a herbal combination of primrose, gentian root, vervain, elder flowers, and sorrel on olfactory function in patients with a sino-nasal olfactory dysfunction. Rhinology 49(3):342–346. doi:10.4193/Rhin
5. Reden J, Herting B, Lill K, Kern R, Hummel T (2011) Treatment of postinfectious olfactory disorders with minocycline: a double-blind, placebo-controlled study. Laryngoscope 121(3):679–682. doi:10.1002/lary.21401
6. Reden J, Lill K, Zahnert T, Haehner A, Hummel T (2012) Olfactory function in patients with postinfectious and posttraumatic smell disorders before and after treatment with vitamin A: a double-blind, placebo-controlled, randomized clinical trial. Laryngoscope 122(9):1906–1909. doi:10.1002/lary.23405
7. Youngentob SL, Kent PF (1995) Enhancement of odorant-induced mucosal activity patterns in rats trained on an odorant identification task. Brain Res 670(1):82–88
8. Livermore A, Laing DG (1996) Influence of training and experience on the perception of multicomponent odor mixtures. J Exp Psychol Hum Percept Perform 22(2):267–277
9. Hummel T, Rissom K, Reden J, Hahner A, Weidenbecher M, Huttenbrink KB (2009) Effects of olfactory training in patients

with olfactory loss. Laryngoscope 119(3):496–499. doi:10.1002/lary.20101
10. Czarnecki LA, Moberly AH, Turkel DJ, Rubinstein T, Pottackal J, Rosenthal MC, McCandlish EF, Buckley B, McGann JP (2012) Functional rehabilitation of cadmium-induced neurotoxicity despite persistent peripheral pathophysiology in the olfactory system. Toxicol Sci 126(2):534–544. doi:10.1093/toxsci/kfs030
11. Haehner A, Tosch C, Wolz M, Klingelhoefer L, Fauser M, Storch A, Reichmann H, Hummel T (2013) Olfactory training in patients with Parkinson's disease. PLoS One 8(4):e61680. doi:10.1371/journal.pone.0061680
12. Hummel T, Sekinger B, Wolf SR, Pauli E, Kobal G (1997) 'Sniffin' sticks': olfactory performance assessed by the combined testing of odor identification, odor discrimination and olfactory threshold. Chem Sens 22(1):39–52
13. Kobal G, Klimek L, Wolfensberger M, Gudziol H, Temmel A, Owen CM, Seeber H, Pauli E, Hummel T (2000) Multicenter investigation of 1,036 subjects using a standardized method for the assessment of olfactory function combining tests of odor identification, odor discrimination, and olfactory thresholds. Eur Arch Otorhinolaryngol 257(4):205–211
14. Fleiner F, Lau L, Goktas O (2012) Active olfactory training for the treatment of smelling disorders. Ear Nose Throat J 91(5):198–203, 215
15. Lapid H, Hummel T (2013) Recording odor-evoked response potentials at the human olfactory epithelium. Chem Sens 38(1):3–17. doi:10.1093/chemse/bjs073
16. Bitter T, Gudziol H, Burmeister HP, Mentzel HJ, Guntinas-Lichius O, Gaser C (2010) Anosmia leads to a loss of gray matter in cortical brain areas. Chem Sens 35(5):407–415. doi:10.1093/chemse/bjq028
17. Bitter T, Josiger M, Mentzel HJ, Burmeister HP, Gudziol H, Guntinas-Lichius O (2011) Detection of olfactory areas in functional MRI—how many repetitions are necessary? Laryngorhinootologie 90(3):145–150. doi:10.1055/s-0030-1267216