

Use of Olfactory Training in Post-Traumatic and Postinfectious Olfactory Dysfunction

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Objectives/Hypothesis: There is evidence that the olfactory system can be modulated by repeated exposure to odors, a procedure called *olfactory training*. The aim of this study was to assess the effectiveness of olfactory training in patients with postinfectious and post-traumatic olfactory dysfunction.

Study Design: Prospective study of 119 patients with postinfectious and post-traumatic olfactory dysfunction.

Methods: Two groups of patients (postinfectious and post-traumatic) performed the olfactory training (n = 49 and n = 23, respectively) over a period of 16 weeks and were compared with two control groups of the same etiology (n = 32 and n = 15). Patients with sinusitis, neurologic, or idiopathic disease were excluded. Training was performed twice daily with the use of four odors (phenyl ethyl alcohol [rose], eucalyptol [eucalyptus], citronellal [lemon], and eugenol [cloves]). Olfactory testing was performed by means of the Sniffin' Sticks test battery (threshold, discrimination, identification) at the time of diagnosis, and 8 and 16 weeks later. All patients evaluated their olfactory function by means of a visual analogue scale (0–100).

Results: Compared to controls, training patients in both groups presented significantly higher scores of olfactory function as measured by the Sniffin' Sticks test. This increase was measured in 67.8% of postinfectious and 33.2% of post-traumatic patients. Subjective ratings were in accordance with the olfactory test results. Subset analysis showed that olfactory function mainly increased olfactory identification followed by discrimination in both training groups.

Conclusions: The present study suggests that a 16-week short-term exposure to specific odors may increase olfactory sensitivity in patients with postinfectious and post-traumatic olfactory dysfunction.

Key Words: Anosmia, post-traumatic, postinfectious, olfactory training.

Level of Evidence: 3b.

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INTRODUCTION

Olfactory dysfunction affects a significant percentage of the general population, estimated at around 15%.¹ Although it remains undiagnosed in some patients, olfactory loss has a severe impact on their quality of life.² Numerous studies report that upper respiratory tract infections (URTIs) and craniofacial trauma are among the most frequent causes of olfactory disorders.^{3–6} However, there is no proven and universally accepted effective therapy yet for post-URTI and post-traumatic olfactory dysfunction. An alternative treatment based on modulation of the regeneration process of the olfactory system via repeated exposure to an odor has been described by Hummel et al.⁷ The idea was based on Hen-

ning's work on primary odors and basic odor categories.⁸ There is an increasing body of clinical evidence regarding the beneficial effect of repeated odor exposure in olfactory function in normal subjects and patients with olfactory dysfunction.^{7,9–12} A characteristic example in normal subjects is the higher sensitivity of wine traders in detecting wine odors.¹³ In another study, repeated exposure to androstene for 6 weeks significantly increased the sensitivity of 121 young normal subjects.¹² Hummel et al. used four odors as representatives of significant odor categories (flowery, fruity, aromatic, and resinous); 40 patients of various etiologies were exposed to them twice per day for 12 weeks. The procedure, called olfactory training, had very promising preliminary results.⁷ This study presents the results of olfactory training focusing on two major causes of olfactory dysfunction (post-URTI and post-traumatic) in a single tertiary institution with a Smell and Taste Clinic.

MATERIALS AND METHODS

Patients

All patients included in the study were either self-referrals or referred from another institution to the Smell and Taste Clinic, Second Academic Otorhinolaryngology Department, Aristotle University of Thessaloniki Medical School over a period of 3 years.

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The patients had a detailed clinical evaluation, including nasal endoscopy. Depending on the clinical findings and the detailed, structured history, olfactory dysfunction was classified as either post-URTI or post-traumatic, following an infection of the upper respiratory tract or a closed head injury, respectively.

Age, gender, and duration of the disease were recorded in all patients. In post-traumatic patients we obtained information related to the severity of trauma, namely: 1) hospital stay and 2) brain imaging findings. In the case of hospital stay, patients were divided into three categories: no hospitalization, hospitalization, and hospitalization with intensive care unit (ICU) stay. Imaging data divided patients into two groups: those with brain damage and those with no findings.

Patients with evidence of chronic rhinosinusitis with or without polyps in nasal endoscopy were excluded. Idiopathic olfactory dysfunction and diagnosis of a neurologic disorder such as Alzheimer or Parkinson disease were also exclusion criteria.

The olfactory training procedure was explained in detail to all patients, and they were asked to decide between following this scheme or waiting for spontaneous recovery. All training patients provided written informed consent according to a protocol in accordance with the Helsinki Declaration for human subjects.¹⁴ The study design was approved by the ethics committee of the Medical Faculty of Aristotle University of Thessaloniki.

Olfactory Testing

Olfactory function was evaluated by means of the Sniffin' Sticks battery test,¹⁵ with a verbal adaptation to the Greek population.¹⁶ Odor identification, discrimination, and threshold were assessed, and a total threshold/discrimination/identification (TDI) score was obtained for each patient. A TDI score of <16.5 corresponds to functional anosmia, a score between 16.5 and 30.5 defines hyposmic values, and a score of >30.5 corresponds to normosmic values.¹⁵ All patients were tested at the initial assessment and 2 and 4 months later at follow-up appointments. Improvement of olfactory function was considered a change in TDI score of ≥ 6 .¹⁷

The subjective estimation of olfactory function was also recorded at baseline and each follow-up by means of a visual analogue scale scored from 0 to 100, where 0 represents absence of olfactory ability and 100 perfect olfactory function. In addition, patients were asked about the presence or absence of qualitative olfactory dysfunction (parosmia/phantosmia).

Olfactory Training

Olfactory training was performed over a period of 16 weeks. The odorants were chosen to be representative of four basic odor categories as established by Henning.⁸ These categories are flowery, fruity, aromatic, and resinous. Specifically, patients exposed themselves twice daily to four odors: phenyl ethyl alcohol (rose), eucalyptol (eucalyptus), citronellal (lemon), and eugenol (cloves), in a similar way as described by Hummel et al.⁷ Olfactory training included exposure to odorants twice per day for 5 minutes. Every session included rotated exposure to each odorant for 10 seconds, with time intervals of 10 seconds between odors. Patients were advised to sniff the odors twice daily, in the morning and in the evening. Patients of the training groups who reported missing ≥ 7 training days were not included in the study. Patients in the nontraining group did not follow any other medical or alternative form of treatment. Training patients and controls were evaluated at 8 and 16 weeks from the baseline assessment.

Statistical Analysis

For statistical analysis, Statistical Packages for Social Sciences (version 17.0; SPSS, Chicago, IL) was used. Demographics and clinical data are presented as means \pm standard deviation or numbers (%). Comparisons between the training patients and controls were performed using the *t* test for unpaired samples. The significance level was set at $P = .05$. Correlation analyses were performed according to Pearson. Bonferroni tests were used for post hoc analyses.

RESULTS

Participants

In total, 119 patients of 124 were included in the statistical analysis of this study (48 male/71 female, mean age = 48.9 ± 9.2 years, range = 20–73 years). Specifically, the two study groups were as follows: the post-URTI group consisted of 49 training patients and 32 controls, and the post-traumatic group of 23 training patients and 15 controls. Five patients discontinued the training scheme (two post-URTI, three post-traumatic) and were excluded from the study (discontinuation rate = 4%). Three of them reported no experienced benefit as the cause of their decision, and two patients reported irritation of the nose and headache after odorant exposure.

At baseline assessment in both study groups, the training and nontraining patients had similar age and sex distribution. In addition, at the time of diagnosis the above subgroups did not differ significantly in the olfactory test results.

Demographics of both groups are presented in detail in Table I.

Comparison of Psychophysics, Training Patients Versus Controls

Comparison of TDI score differences between baseline assessment and after 16 weeks between controls and the training patients with both pathologies together showed a positive effect of training, with significantly better olfactory test results ($F_{1,117} = 12.14$, $P = .008$).

Specifically, at the end of 16 weeks the post-URTI training group exhibited the highest percentage of improved patients (67.8%) followed by the post-traumatic training group (33.2%) and the control post-URTI group (33%). The lowest improvement was observed in the post-traumatic control group (13.3%; Fig. 1). Comparison of TDI means showed that the training patients in the post-URTI group had significantly higher results than controls in both follow-up appointments. This was not the case in the post-traumatic group, where the results of training patients were significantly better only at the second follow-up appointment (Fig. 2). Subtest analysis showed significant differences in odor identification and a trend for significance in odor discrimination between training and nontraining groups for both disorders. However, this was not the case for odor threshold (Table I).

Comparison of Subjective Ratings, Training Patients Versus Controls

Analysis of subjective rating means in the post-URTI group showed that the training patients at both

TABLE I.
Demographics of the Study Groups.

Characteristic	URTI Group, n = 81			Post-Traumatic Group, n = 38		
	Training, n = 49	Control, n = 32	P	Training, n = 23	Control, n = 15	P
Age, yr	51.5 ± 5.2	53.1 ± 4.4	.21	42.2 ± 4.9	40.1 ± 3.7	.1
Gender, No.	15 M/34 F	11 M/21 F	.1/.03	13 M/10 F	9 M/6 F	.2/.06
Duration of disease, mo	9.2 ± 3	8.7 ± 2.5	.87	11.5 ± 3.2	12.1 ± 3.8	.9
Patients with imaging findings, No.	—	—	—	7 M/6 F	5 M/3 F	.05/.006
TDI, baseline	18.95 ± 2	19 ± 2.3	.9	14.9 ± 2.1	13.8 ± 2.4	.09
TDI, 16 weeks	25.2 ± 1.8	20.5 ± 2	>.001	20 ± 2.1	15 ± 1.9	>.001
Identification baseline	8.6 ± 1.4	8.8 ± 1.7	.77	6.5 ± 1.5	6.2 ± 1.7	.68
Identification, 16 weeks	12.2 ± 1.3	9.6 ± 1.2	.04	9.5 ± 1.2	7.1 ± 1.1	.05
Threshold, baseline	2.4 ± 1.4	2.3 ± 1.6	.91	2.1 ± 1.2	1.8 ± 0.9	.82
Threshold, 16 weeks	2.5 ± 1.3	2.6 ± 1.8	.9	2 ± 1.2	2.1 ± 1.3	.9
Discrimination, baseline	7.8 ± 1.8	7.9 ± 1.6	.95	6.4 ± 1.4	5.7 ± 1.3	.61
Discrimination, 16 weeks	10.4 ± 1.1	8.3 ± 1.3	.065	8.3 ± 1.2	5.9 ± 1.4	.075

F = female; M = male; TDI = threshold/discrimination/identification score; URTI = upper respiratory tract infection.

follow-up appointments rated their olfactory function significantly higher than controls. Training patients presented a significant increase at every appointment compared with the previous one ($P < .05$); however, this was not the case in the control group, in which significance was seen only between the second and third assessments ($P = .004$). Similar analysis in the post-traumatic group showed a significant difference between groups only at the last assessment ($P < .001$; Fig. 3). Training patients had a significant increase of their ratings at both follow-up assessments ($P < .05$), and controls presented a significant increase only between baseline and the first assessment ($P = .008$).

Gender and Age

The factor gender had no significant effect on olfactory recovery in both groups. Comparing the presence of olfactory improvement between male and female subjects, no statistical significance was detected (post-URTI: training $P = .41$ nontraining $P = .38$; post-trauma: training $P = .31$, nontraining $P = .34$). Similarly, the factor age did not present any effect on olfactory function improvement. No correlation was found between a TDI change of ≥ 6 and the age of the patients, with only a trend toward significant negative correlation in the post-URTI nontraining subgroup ($r = -0.13$, $P = .078$).

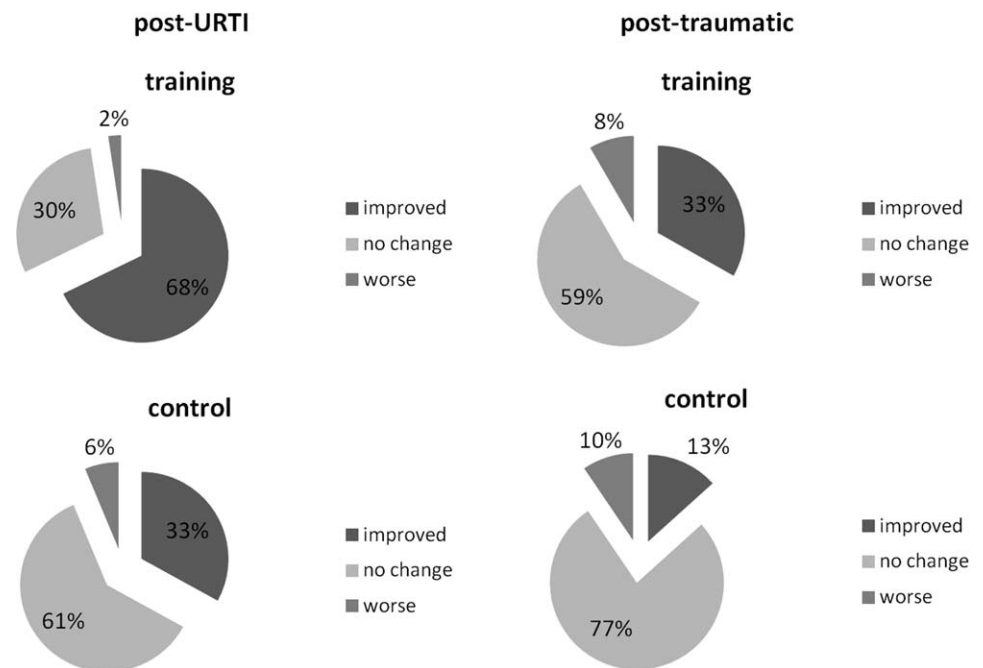


Fig. 1. Percentages of individual improvement, no change, or worsening within the study groups (change in the threshold/discrimination/identification score of olfactory function of ≥ 6). URTI = upper respiratory tract infection.

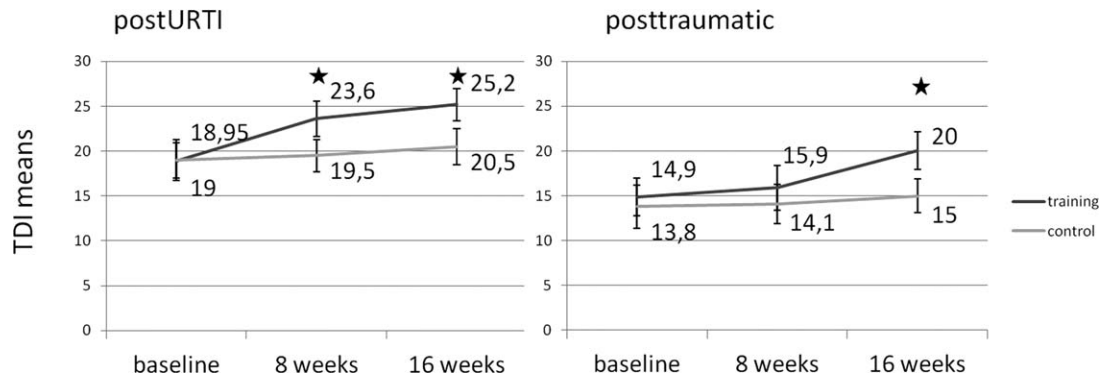


Fig. 2. Comparison of threshold/discrimination/identification (TDI) score means between training and nontraining patients in both groups at baseline, and 8 and 16 weeks later. URTI = upper respiratory tract infection, * $P < 0.05$.

Severity and Duration of Olfactory Dysfunction

Severity of olfactory dysfunction (anosmia/hyposmia) at baseline assessment did not correlate with the improvement of olfactory function in all groups (all $r < 0.11$).

In the post-URTI group, patients with a shorter duration of olfactory loss had a higher chance of exhibiting improvement of overall olfactory function in both subgroups (training: $r = -0.27$, $P = .006$; nontraining: $r = -0.25$, $P = .009$). In contrast, no significant correlation could be found between the duration of olfactory loss and olfactory improvement in post-traumatic subgroups (training: $r = 0.11$, $P = .08$; nontraining: $r = 0.09$, $P = .1$).

Severity of Head Trauma

In the post-traumatic group, significant negative correlations were found within the training group between olfactory function improvement and factors indicating the severity of the trauma (history of ICU stay: $r = -0.28$, $P = .03$; brain damage in imaging: $r = -0.38$, $P = .007$). No history of hospitalization and hospital stay without ICU did not correlate with the TDI improvement ($r = 0.08$, $P = .25$ and $r = 0.10$, $P = .1$, respectively). This was not the case in the control group,

except that a negative trend was found between positive imaging findings and ≥ 6 TDI change ($r = -0.12$, $P = .08$).

Qualitative Disorders

The presence of parosmia and/or phantosmia at baseline assessment was not correlated with the improvement in TDI score in all subgroups (all $r < 0.1$).

DISCUSSION

To our knowledge, the present study is the largest showing that olfactory training is an effective method for olfactory rehabilitation in patients with post-URTI and post-traumatic olfactory dysfunction. Specifically, in the post-URTI group an improvement could be measured in almost two thirds of the patients in the training subgroup. In the post-traumatic group, improvement was found in one third of training patients. In both groups, controls presented significantly lower olfactory test results compared to the training patients. Two previous similar studies of olfactory training were small-cohort studies including various etiologies.^{7,11} Thus, clear conclusions regarding whether there is a beneficial effect of olfactory training on post-URTI and post-traumatic olfactory dysfunction could not be interpreted.

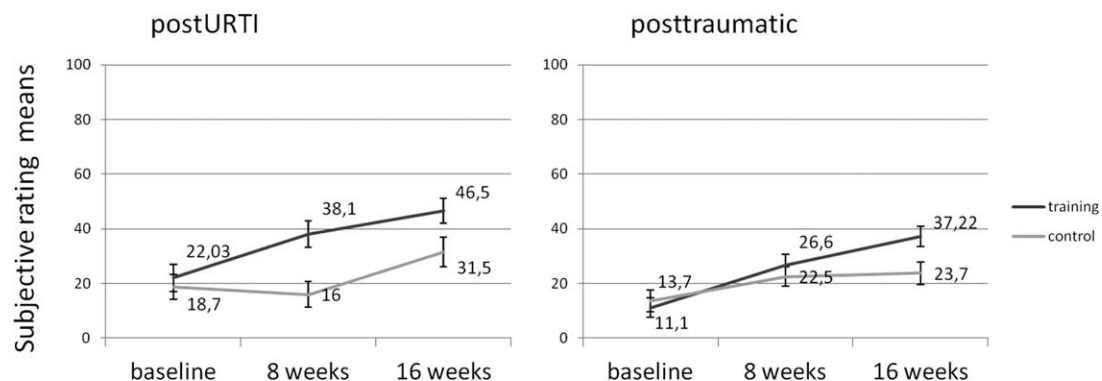


Fig. 3. Comparison of subjective ratings between training and nontraining patients in both groups at baseline, and 8 and 16 weeks later. URTI = upper respiratory tract infection.

The positive effect of olfactory training in our study was independent from age, sex, and severity of the disease, which allows a wide application of training procedure. The correlation found between duration of the disease and olfactory test results in post-URTI (controls and training) patients confirms its significance as a prognostic factor of olfactory outcome for this group, in agreement with previously reported studies.⁵ The negative correlation of olfactory outcome with the severity of trauma (ICU stay and brain imaging findings) is in agreement with previous studies reporting a clear association between the severity of trauma and the degree of olfactory dysfunction.^{18,19} This study adds to the present knowledge suggesting these factors as negative predictors of olfactory training outcome.

Interestingly, our data showed that olfactory test results are in agreement with what patients experienced as improvement in their olfactory function according to their subjective ratings at the second follow-up appointment. This is important during a long period of treatment, as patients are more likely to comply when the benefit can be experienced at a relatively early stage.

In general, the results of the present study are in conjunction with previous experimental and clinical studies suggesting that the olfactory system has the plasticity to recover with training.^{7,10,11} Hummel et al. first described a structured method for olfactory training in patients with olfactory disorders, applying it for 12 weeks.⁷ In their series, 28% of the training group (including various etiologies) presented olfactory improvement in olfactory testing versus only 6% of the control group. Additional evidence comes from the same team in a recent paper assessing 70 Parkinson disease patients, showing benefit in 20% of training patients compared to 9% of controls after 12 weeks of olfactory training.¹⁰ In our study, the training protocol was based on the one proposed by Hummel; however, the training period was extended to 16 weeks. It is not known whether a prolonged exposure to odors has a continuous beneficial effect on olfactory function. Some authors have posed the question of whether this effect reaches a certain level and then this ability cannot be further increased.⁷ The present study extended the beneficial period of application from 12 weeks in previous studies^{7,10} to 16 weeks. In a recent study, olfactory training was applied for 8 months in 28 patients with various etiologies of olfactory dysfunction.¹¹ The results showed that olfactory function did not further increase between 4 and 8 months of training. However, larger studies are needed to clarify the time limits and the maintenance of beneficial effect in the long term.

Only five patients decided to drop out of the training scheme; two of them reported intolerance to odor exposure, suffering from headache and irritation of the nose. Considering the small number of patients who discontinued the training scheme, we assume that the suggested treatment is a well-tolerated procedure and that the vast majority of patients will follow it, as there is no long-term drug intake. Our anecdotal data show that patients who experience a beneficial effect tend to ask to continue the training scheme for a longer period; how-

ever, this is part of ongoing research in our department and not the purpose of the present study.

Electrophysiological studies have showed that repeated odor exposure in humans can produce increased recordings from the olfactory epithelium.⁹ However, the positive effect of olfactory training on olfactory function may not only be related to peripheral changes, but possibly also can be attributed to central changes.²⁰ There are studies suggesting that representations for odor categories exist in the olfactory bulb, and these are largely confined as spatial continuous zones.²¹ Thus, the use of different typical representatives of odor categories in a training scheme may induce a more extended activation than the use of, for example, four fruity odors.

According to our results, patients with training benefit increased mainly their identification and discrimination scores, indicating a more central effect of the training procedure. Olfactory threshold changes seem to be more related to peripheral changes, and odor discrimination and identification reflect generally higher cognitive functions.²² Previous studies had similar results, with Haehner et al.¹⁰ reporting mainly increased discrimination in training Parkinson disease patients and Fleiner et al.¹¹ reporting better identification and discrimination in training patients of various etiologies.

There is evidence that stability of odor category structures exists among different cultures.^{23,24} In general, we respond to odors as members of odor categories, in terms of representativeness in category membership. The typical representatives of odor categories in post-industrial countries are with small exceptions similar (e.g., rose for flowery odors). This is significant, as it allows a more standardized olfactory training application in these countries.

Another issue is the dominance of artificial odors in the olfactory environment of the industrialized world. Previous studies have showed that artificial odors matched similarly the odor representation for subjects from the Western world. However, the same odors for people in Eastern cultures who use more natural aromas in their products might not be typical representatives.^{23,24}

A limitation of our research is that it is not a placebo-controlled study. However, the use of odorless liquids for a placebo control group would be easily detected by the relatives of the patients, and thus we did not follow this procedure. In addition, a random allocation may be unethical and would decrease the number of motivated patients, as the intervention depends on patient's active participation. Another weakness is that the whole therapeutic process is based on patients' ability to follow a daily training program for a long period of time without medical supervision. In the future, the development of a device for this kind of treatment would be a helpful tool for the standardization of the procedure.

CONCLUSION

The present study suggests that olfactory training with specific odors for a period of 16 weeks may increase

olfactory sensitivity in patients with postinfectious and post-traumatic olfactory dysfunction, improving mainly their odor identification and discrimination.

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