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MISCELLANEOUS

Olfactory training ball improves adherence and olfactory outcomes in post-infectious olfactory dysfunction

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Abstract

Purpose In an effort to make olfactory training (OT) simpler, we designed an 'olfactory training ball' (OTB)—a baseball-size ball with four odor-containing tubes to use in OT. The study aimed to investigate the effects of OT with the OTB in comparison to classical OT with special attention to the effects of adherence to OT on olfactory outcome measures.

Methods Sixty patients with olfactory dysfunction following infections of the upper respiratory tract received OT either with classical methods—sniffing odors from jars (COT)—or the OTB for 12 weeks. Patients exposed themselves to the odors for 5 min twice daily. Adherence was measured with a modified version of the Morisky scale. Before and after OT, all patients underwent extensive olfactory testing using the Sniffin' Sticks test.

Results At the end of the 12 weeks of OT, TDI composite score (22.1 ± 2.8 vs. 19.9 ± 4.7, $P = 0.044$) and odor discrimination subtest scores (9.1 ± 1.8 vs.7.6 ± 2.5, $P = 0.013$) of the OTB group were significantly higher than that of the COT group. Adequate adherence to OT was significantly higher in patients receiving OTB when compared to those receiving COT (63% vs. 30%, $P = 0.019$).

Conclusion The present study shows that a novel OT device, the OTB, provides better adherence to the training process compared to COT. Moreover, findings of the current study show that better adherence to the OT process is associated with better olfactory outcomes.

Keywords Olfaction · Smell · Olfactory training · Olfactory training ball

Introduction

Repetitive, regular exposure to odors, the so-called olfactory training (OT), is a treatment option especially in patients with olfactory loss following infections of the upper respiratory tract [1, 2]. Improvement in olfactory function in association with OT has been shown in patients with post-traumatic, post upper respiratory tract infection (URTI), and idiopathic olfactory dysfunction (OD) [3]. However, the benefits of OT are more prominent in subjects with post-URTI compared to those with post-traumatic or idiopathic OD [4]. The improvement in OD with OT in subjects with post-traumatic OD and idiopathic OD is limited and insignificant [5, 6]. In fact, OT is the first successful therapy regime in patients with post-infectious olfactory dysfunction [7]. Patients receiving OT are typically exposed to four intense odors (phenyl ethyl alcohol: rose, eucalyptol: eucalyptus, citronellal: lemon, and eugenol: cloves) twice a day for at least 12 weeks. However, different versions of olfactory training have been used. Langdon et al. recently showed the effect of olfactory training in patients with post-traumatic olfactory loss using the BASTAT-6 olfactory test kit [5]. To allow for activation of more olfactory receptor neurons, modified olfactory training (MOT) has been described by Altundag and colleagues [3]. It is based on the utilization of a wide variety of odors including menthol, thyme, tangerine, jasmine, green tea, bergamot, rosemary, and gardenia in addition to the odors used in classical OT. Moreover,

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unlike classical OT, these odors were not only based on single molecules but mixtures of odorants. However, the study conducted by Oleszkiewicz et al. has reported that the outcomes of OT are not strongly influenced by the training regimen [6].

In previous studies, the period of OT varied between 12 and 56 weeks [8, 9]. Active integration of the subject into this process during this period, and thus, patient's adherence to the training material, appears to be a critical factor in achieving the expected success from OT. Although current information regarding the adherence of patients to OT is limited and largely based on the author's anecdotal clinical experience, we suggest that an elaborated structure of the current OT sets and the complexity of the training process might complicate the patients' adherence to OT.

We hypothesized that a new approach to OT using new instruments might facilitate the patients' adherence to OT, and thus, improve the outcome expected from OT. For this purpose, we designed an 'olfactory training ball' (OTB) which is very simple and easy to use for patients. The present study aimed to compare COT and the OTB with respect to patients' adherence to OT and the resultant improvement in olfactory function.

Materials and methods

Patient selection

All consecutive patients diagnosed with olfactory dysfunction following infections of the upper respiratory tract in the Ear, Nose, and Throat Department of a tertiary center, between March and August of 2019 were enrolled in this randomized, prospective study. Exclusion criteria were pregnancy, prior OT, age < 18 years, concomitant sinonasal disease, and post-traumatic olfactory dysfunction. Power calculations based on our pilot study with 12 patients (Pre-OTB composite olfactory score: 15.3 ± 4.1 vs. post-OTB composite olfactory score: 19.8 ± 4.8, effect size 0.80, alpha error 0.5, actual power 0.95) revealed that at least 23 patients were required to study the impact of OTB on olfactory function.

Post-URTI olfactory dysfunction was diagnosed by an experienced otolaryngologist on the basis of a detailed history and nasal endoscopy. Patients were randomly attributed to one of the two OT regimens in a 1:1 ratio. Group 1 received OT described by Altundag et al. [3]. Patients allocated to group 2 received OT with the OTB (Fig. 1).

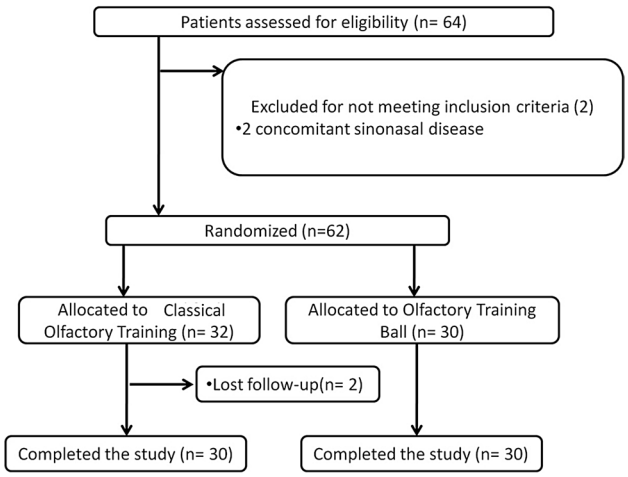

Fig. 1 Flowchart demonstrating patients' allocation

Classical olfactory training

In the first 4 weeks, patients allocated to the COT group received phenyl ethyl alcohol (PEA) (rose), eucalyptol (eucalyptus), citronellal (lemon), and eugenol (cloves) twice daily. In the following 4 weeks, participants in the COT group were exposed to the odors of menthol, thyme, tangerine, and jasmine. During the last 4 weeks, green tea, bergamot, rosemary, and gardenia were used for patients in the COT group. For this purpose, 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) were given to the patients every four weeks.

Olfactory training balls

Patients in OTB group received OT from sphere-shaped, polystyrene balls that were specifically designed by the investigators for this study to provide a light-weight, ergonomic, and safe OT set (Fig. 2). Each OTB had 4 holes to hold the 4 odor-containing shatterproof tubes (Eppendorf Tubes®) which were easy to open and close. Eppendorfs, which were placed in the holes (~ 4 cm in depth) on the polystyrene balls, were glued to fix them into the ball. 1 ml of odorants was added into each tube. Three OBs were used with yellow (1st 4 weeks), orange (2nd 4 weeks), and red (3rd 4 weeks) colors representing different periods of OT. Each OTB was containing the same odor sets as COT for the respective time period. Patients exposed themselves to the odors in each tube for 5 min twice a day for the recommended period. Patients were advised to sniff the odors twice a day; in the morning before breakfast and in the evening before bedtime.

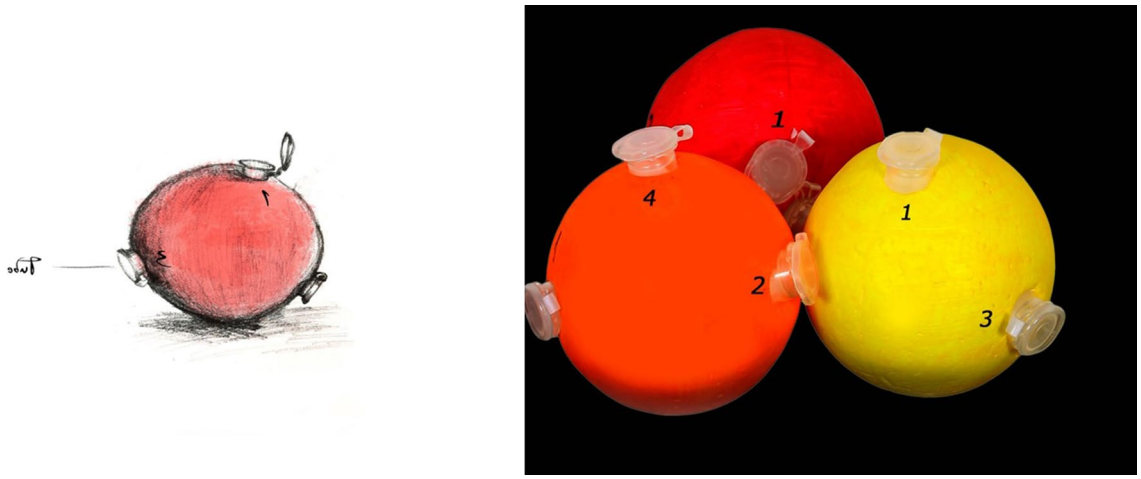

Fig. 2 A drawing and photo demonstrating the olfactory training ball

The OTB method was identical to COT with respect to the volume of odor in each tube. The duration of every session and the duration of sniffing the odors were the same for both groups.

Olfactory testing

The "Sniffin' Sticks" test (Burghart, Wedel, Germany) consists of three subtests that measure odor threshold (T), odor discrimination (D), and odor identification (I). It was used to evaluate olfactory function before and after the training period of 12 weeks [10]. Each subtest had a maximum score of 16, and the sum of the scores from the three subtests provided the global olfactory score (TDI score; Threshold, Discrimination, Identification) with a maximum of 48 points. Patients with a TDI composite score ≥ 30.5 were defined as normosmic whereas those with a TDI composite score between 16.5 and 30.5 were defined as hyposmic, and patients with a TDI composite score < 16.5 were defined as functionally anosmic [11].

Adherence to olfactory training

At the end of the OT period, each subject underwent a self-reported assessment of their adherence to the OT method they received. Written answers to a questionnaire consisting of 4 items (modified from the 4-item Morisky scale) were obtained by a research fellow blinded to patients' groups and kept in individual charts throughout the study period [12]. Answers to the questions were analyzed on an individual basis for each question. In this study, adequate adherence was defined as a response of 'no' to all of the questions, and a response of 'yes' to any of the questions was defined as inadequate adherence.

Outcome measures

We looked at the following two outcome measures: (1) the difference in adherence to OT among participants receiving COT or OTB, (2) the change in olfactory testing scores from baseline to the completion of the study in COT and OTB groups.

Statistical analyses

Statistical analyses were carried out using SPSS for Windows, version 19 (SPSS, Chicago, IL, USA). Distribution of the variables was studied with the Kolmogorov–Smirnov test. Continuous variables were given as the mean ± standard deviation and categorical variables as a percentage. Continuous variables of the two study groups were compared using Student *t* test and Mann Whitney *U* test. The Chi-square test was used for comparison of the categorical variables. Paired samples *t* test was used to compare the olfactory test scores obtained at baseline and at the end of 12 weeks. Correlation analyses were carried out to identify the association between the change in olfactory test scores throughout the study and selected variables. A two-sided P value < 0.05 was interpreted as statistically significant.

Results

A total of 60 patients (mean age 49 ± 10 years, 30 male) were enrolled in this study. The two groups were similar with respect to age, sex, duration of olfactory dysfunction, and baseline olfactory test scores (Table 1). However, at the end of the 12 weeks of OT, TDI composite score (22.1 ± 2.8 vs. 19.9 ± 4.7, $P = 0.044$) and odor discrimination subtest scores (9.1 ± 1.8 vs.7.6 ± 2.5, $P = 0.013$) of the OTB group

Table 1 Baseline characteristics and olfactory test scores of the study groups

	COT group ($n=30$)	OTB group ($n=30$)	P value
Age, years	50.2 ± 10.7	47.8 ± 11.0	0.405
Disease duration, years	9.5 ± 7.2	10.3 ± 7.8	0.697
Sex, male	15 (50%)	15 (50%)	1.000
T baseline	2.8 ± 1.2	2.7 ± 1.1	0.892
D baseline	6.5 ± 1.8	6.6 ± 1.7	0.770
I baseline	7.0 ± 1.9	6.7 ± 1.8	0.538
TDI baseline	16.2 ± 4.4	16.1 ± 4.3	0.901

Data are presented as mean ± standard deviation for continuous variables and frequency (percentage) for categorical variables

COT classical olfactory training, *D* odor discrimination, *I* odor identification, *T* odor threshold, *OTB* odor training ball, *TDI* composite olfactory score

Table 2 The change in olfactory test scores from baseline to 3 months

	Before OT ($n=30$)	After OT ($n=30$)	P value
T score			
COT group ($n=30$)	2.8 ± 1.2	2.9 ± 0.9	0.116
OTB group ($n=30$)	2.7 ± 1.1	3.1 ± 0.8	0.015
D score			
COT group ($n=30$)	6.5 ± 1.8	7.6 ± 2.5	< 0.001
OTB group ($n=30$)	6.6 ± 1.7	9.1 ± 1.8	< 0.001
I score			
COT group ($n=30$)	7.0 ± 1.9	9.3 ± 1.7	< 0.001
OTB group ($n=30$)	6.7 ± 1.8	9.8 ± 1.2	< 0.001
TDI score			
COT group ($n=30$)	16.2 ± 4.4	19.9 ± 4.7	< 0.001
OTB group ($n=30$)	16.1 ± 4.3	22.1 ± 2.8	< 0.001

COT classical olfactory training, *D* odor discrimination, *I* odor identification, *T* odor threshold, *OTB* odor training ball

were significantly higher than that of the COT group. Paired samples t test results demonstrated a significant improvement in olfactory test scores compared to baseline values at the end of the 3 months in both the COT and the OTB groups. Odor threshold subtest score in COT group did not show the same improvement (Table 2, Fig. 3). An improvement of > 5.5 points in TDI was observed in 21 (70%) patients of the OTB group and in 9 patients (30%) of the COT group ($P=0.02$).

Responses of the participants to the 4-item Morisky scale are presented in Table 3. Subjects receiving the OTB were more careful about taking OT than the subjects receiving COT. The number of patients expressing their carelessness at times about taking the OT was significantly lower in the OTB group than those in the COT group (23% vs. 57%, $P=0.008$). In addition, the number of participants who forgot to take the OT at least once was significantly lower in the OTB group than that of the COT group (37% vs. 63%, $P=0.035$). Adequate adherence to OT was significantly higher in patients receiving OTB when compared to those receiving COT (63% vs. 30%, $P=0.019$).

Table 4 shows the association between the change in olfactory test scores throughout the study and age, sex, duration of olfactory loss, and adherence to OT. Adherence to OT was significantly correlated with the changes in odor threshold ($r=0.26$, $P=0.042$), odor discrimination ($r=0.29$, $P=0.022$), odor identification ($r=0.39$, $P=0.002$), and TDI composite score ($r=0.31$, $P=0.014$) from baseline to the end of the 12 weeks. The change in odor discrimination subtest score was negatively correlated with age ($r=-0.28$, $P=0.030$) and the change in odor identification subtest score was negatively correlated with the duration of olfactory dysfunction ($r=-0.33$, $P=0.009$).

Discussion

The present study demonstrates that in patients with olfactory dysfunction, implementation of OTB compared to COT is associated with better adherence to the olfactory training process. Our findings also show that despite the similarity in olfactory test results at baseline, OTB provides more favorable results than the COT in terms of odor discrimination subtest score and TDI composite score at the end of the 12 weeks OT period. This study, for the first time, shows that adequate adherence to the training process is significantly correlated with the improvement in olfactory test score derived from OT, similar to a previous work on the association between adherence to an odor exposure protocol and favorable outcome [13].

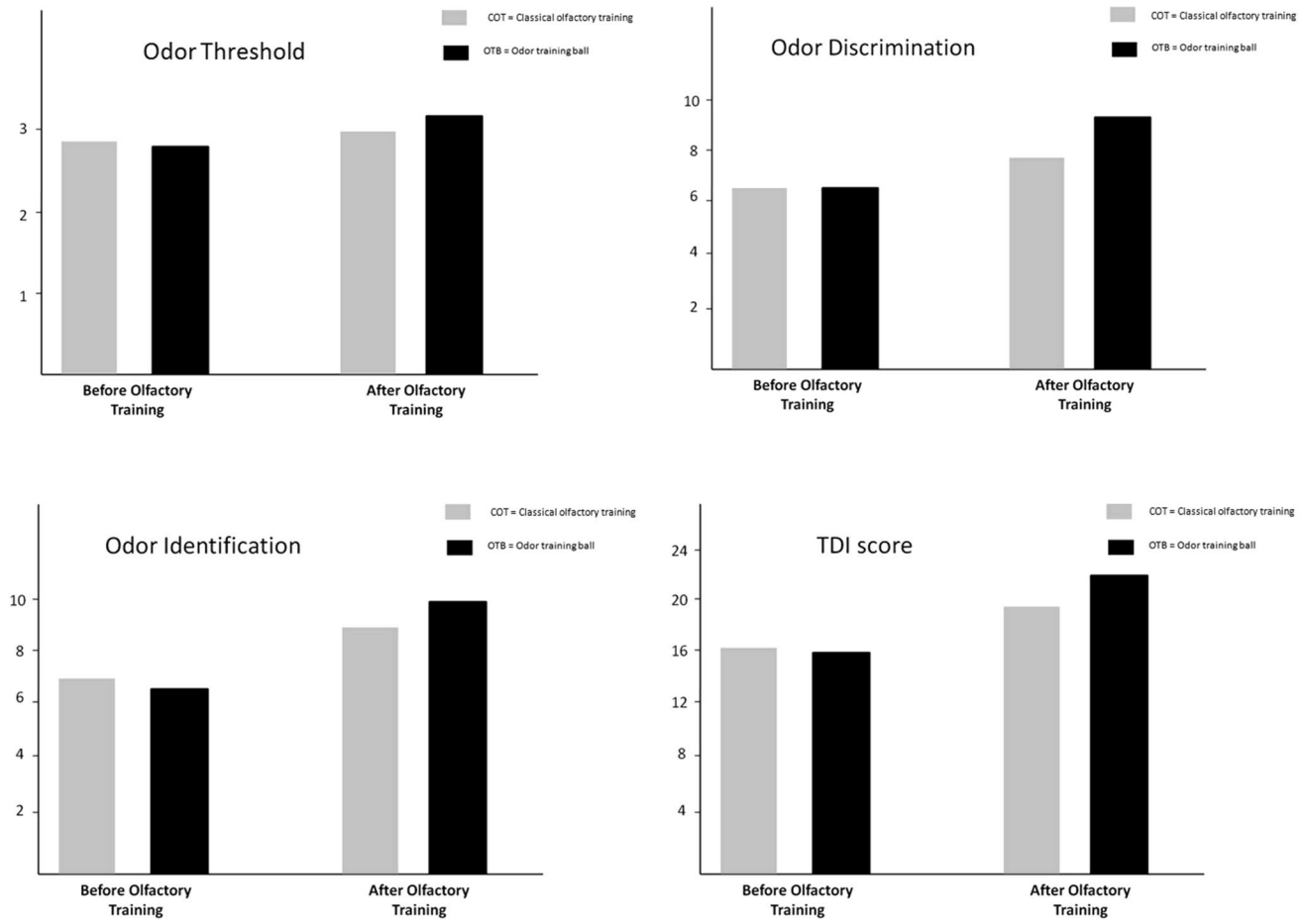

Fig. 3 The change in olfactory tests in the two groups from baseline to the end of the olfactory training

Table 3 Modified Morisky scale evaluating the OT adherence of the study groups

	COT group ($n=30$)	OTB group ($n=30$)	P value
Do you ever forget to take the OT? (yes)	19 (63%)	11 (37%)	**0.035**
Are you careless at times about taking the OT? (yes)	17 (57%)	7 (23%)	**0.008**
When you feel your smelling is getting better, do you sometimes stop the OT? (yes)	0 (0%)	0 (0%)	1.000
Sometimes if you feel your smelling is getting worse, do you stop the OT? (yes)	0 (0%)	0 (0%)	1.000
Adequate adherence	9 (30%)	19 (63%)	**0.019**

P values highlighted in bold indicate statistical significance

COT classical olfactory training, *OT* olfactory training, *OTB* odor training ball

The World Health Organization defines adherence as "the degree to which the person's behavior corresponds with the agreed recommendations from a health care provider" [14]. Previous data have shown that up to 50% of the patients scheduled for a medication do not receive it correctly [15, 16]. Adherence to the medications has been found limited even if these medications were prescribed against life-threatening diseases such as coronary artery disease, diabetes mellitus, congestive heart failure, and chronic viral infectious diseases including AIDS [17–20].

Olfactory training is distinct from oral and parenteral medications as it is based on smelling several odors for a certain period that ranges between 12 and 56 weeks. It has been shown that regular exposure to odors improves smell perception through the stimulation of olfactory receptor neurons [21, 22]. Still, there is no study addressing the role

Table 4 Correlation analysis demonstrating the association between the change in olfactory test scores throughout the study and selected variables

$n=60$	ΔT		ΔD		ΔI		ΔTDI	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Age	0.153	0.244	**−0.281**	**0.030**	0.127	0.333	0.068	0.605
Sex	0.008	0.950	0.094	0.473	0.142	0.280	0.001	0.994
Duration	0.011	0.932	0.168	0.199	**−0.334**	**0.009**	0.208	0.110
Adequate adherence	**0.264**	**0.042**	**0.296**	**0.022**	**0.391**	**0.002**	**0.316**	**0.014**

P values highlighted in bold indicate statistical significance

ΔT change in odor threshold subtest score from baseline to the end of the 3 months, *ΔD* change in odor discrimination subtest score from baseline to the end of the 3 months, *ΔI* change in odor identification subtest score from baseline to the end of the 3 months, *ΔTDI* change in global olfactory score from baseline to the end of the 3 months

of adherence to OT on olfactory outcomes. Therefore, our findings are critical to show the strong impact of adherence to OT on the improvement in olfactory test scores.

Currently, there are various methods of olfactory training [3, 10]. The number and the variety of odors used for training are higher in modified olfactory training. Changing the types of odors periodically as indicated in the modified olfactory training has been shown to enhance the likelihood of success of OT therapy [3]. Nevertheless, the increasing complexity of OT might also be impractical for patients' use, and thus, may impair the expected improvement in olfactory dysfunction. Our findings reveal that OT with OTB provides better 12-week-olfactory-test scores compared to COT even when the same odors were used for the same time period. We suppose that the superiority of OTB over COT is a consequence of the enhanced adherence to the OT process achieved with OTB. A systematical review of 54 studies by Pantuzza and colleagues revealed that increased regimen complexity is associated with a reduction in medication adherence [23]. The odor sets used in COT consist of separate glass bottles for each odor. The lack of favorable ergonomic features, the low risk for breaking the bottles, and the need for light protection of the odors may complicate the adequate adherence and maintenance of the OT.

In this study, we used a novel, unique OT set which is practical and easy to carry due to its spherical shape and light-weight. The ability of the OTB to hold the four odor tubes allowed patients to receive the daily training sessions quickly. Also, the pleasant touch and easy handling provided by the OTB might have improved the re-establishment of olfactory function. In addition, the training protocol was somewhat different in our study from the previous trials. Each odor was smelled for 5 min in each session. This technique is different from those described in previous studies and therefore might have influenced the response to the OTB used in our study. Francis et al. have shown that processing of touch and smell stimuli are represented in the orbitofrontal cortex and are coordinated to provide the neural basis of emotions such as reward or punishment [24]. The sensation of a pleasant touch, therefore, might be perceived as a reward and improve the subjects' adherence to the OT process. In addition, there is close interaction between the olfactory and the trigeminal systems which takes place in brain areas like the piriform cortex, insula, anterior cingulate cortex, or the primary somatosensory cortex. OT has been shown to induce an increase in the functional connectivity of the olfactory network with the anterior entorhinal cortex, the inferior prefrontal cortex, and the primary somatosensory cortex [25]. Therefore, even in functionally anosmic patients who are not able to perceive odors consciously, exposure to CO2 as an odorless but painful stimulant causes the activation of the olfactory, integrative, and somatosensory network [26].

Besides touch, we speculate that color also might have an impact on odor perception. Osterbauer et al. showed a neurophysiological correlate of the cross-modal visual influences on olfactory perception using functional magnetic resonance imaging [27]. Perceived congruency of the odor-color pairs leads to a progressive increase in the activity in caudal regions of the orbitofrontal cortex and in the insular cortex. With that in mind, we speculate that multimodal sensory integration and olfactory training-induced plasticity in the neural circuitry achieved with the use of different colors in addition to the pleasant touch that OTBs serve might have contributed to the re-establishment of olfactory network and the resulting improvement in the olfactory function observed in our study.

There are several limitations concerning the present study. First, a placebo control group was not included in this study. However, employment of an OT process with liquids that do not contain any odor would be easily recognized by the subjects' social surroundings and thus hamper the active participation of the subject in the training process. Second, we used a modified version of the Morisky scale for evaluation of the patients' adherence to the OT. Although this scale has not been validated for such treatment modality, it appeared suitable because of its ease of use and quick administration [28–33].

Conclusion

This study is the first to address the adherence concept in OT and to identify the impact of patients' adherence to the OT on olfactory outcomes. The present study shows that a novel OT instrument, the OTB, provides better adherence to the training process compared to the COT. Moreover, findings of the current study show that adherence to the OT process significantly correlates with the olfactory outcomes indicated by the increase in OD, OI, and TDI composite scores observed in our study population. Our results suggest that implementation of a simple, ergonomic, and easy-to-carry OT set improves the expected outcomes of OT through the increase in patients' adherence.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by OS, OAD AA, and TH. The first draft of the manuscript was written by OS and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Compliance with ethical standards

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

Ethical standards Written informed consent was obtained from all participants and the study protocol was approved by the Institutional Ethics Committee (10840098-604.01.01-E.12637). The study was carried out in accordance with the ethical standards laid down in the 1964 declaration of Helsinki and its later amendments.

Informed consent Informed consent was obtained from all individual participants included in the study.

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