Factors associated with relevant olfactory recovery after olfactory training: a retrospective study including 601 participants*

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Abstract

Background: Olfactory training (OT) represents a therapeutic option for multiple etiologies of olfactory dysfunction (OD) that also benefits normosmic subjects. In this retrospective study, we report the effectiveness of OT and factors associated with relevant changes in olfactory function (OF) in large groups of normosmic participants and patients with OD, including a control group that performed no training.

Methods: This was a retrospective pooled analysis including 2 treatment cohorts of 8 previously published studies. Adult participants that either presented with the major complaint of quantitative OD or normosmic volunteers were recruited at various ENT clinics and received OT or no training. The outcome was based on changes in objective olfactory test scores after OT.

Results: A total of 601 patients with OD or normosmic subjects were included. OT was more effective compared to no training. No interaction was found between OT and OF. In multivariate analysis, higher baseline OF (adjusted odds ratio, aOR, 0.93) and posttraumatic (aOR, 0.29) or idiopathic OD (aOR, 0.18) compared to postinfectious causes were significantly associated with lower odds of relevant improvements in patients with OD receiving OT. Subgroup analysis of normosmic participants receiving OT further revealed a significant association of age and baseline olfactory function with improvements of overall OF.

Conclusions: This study demonstrated that OT was more effective than no training in patients with various causes of OD. Additionally, baseline olfactory performance and etiology of OD were identified as important factors associated with relevant improvements after OT.

Key words: rhinology, olfaction, olfactory training, hyposmia, anosmia, clinical important difference, neuronal plasticity, smell, chemical senses

Introduction

Impairments of the human olfactory system can significantly decrease quality of life and be potentially dangerous on an individual level[(1)]. It is well known that olfactory function decreases during the course of life and estimates are that impairments of the sense of smell affect up to one quarter of the general population[(2–5)]. The causes of such conditions are diverse, including aging, sinonasal disease, head trauma, upper respiratory infection, and neurodegenerative disease. Apart from established treatment strategies for OD secondary to sinonasal causes, which aim to treat the underlying conditions such as chronic rhinosinusitis[(6)], therapeutic options are still limited for

other subgroups. A promising approach to improve olfactory function is represented by olfactory training (OT)[7]. Previous meta-analysis have suggested its usefulness in treatment for olfactory dysfunction (OD) of multiple causes. However, lack of quantifiable data and control groups were factors that limited power[8–10]. Hence there appears to be a need to clarify these issues in order to provide further evidence for the effectiveness of OT and to elucidate potential factors associated with relevant recovery in normosmic participants and patients with OD.

The neuronal plasticity in the human olfactory system represents a treatment target to improve olfactory function. A simple, cost-effective, and side-effect free strategy is represented by OT, which is defined as conscious sniffing of different odors on a regular daily base. This stimulation has shown beneficial effects not only in patients with multiple causes of OD[7,11–19], but also in normosmic participants of different age groups[20–22]. Previous meta-analysis on the effect of OT have provided first evidence, that patients receiving OT showed higher recovery rates (in terms of overall olfactory function) compared to a no-training group[9]. Additionally, it was suggested that patients with postinfectious olfactory loss benefit more from OT compared to posttraumatic smell loss[10]. However, the effect of demographic variables or the mechanisms in idiopathic smell loss as prognostic factors in patients with OD still remain unclear. Understanding what factors modulate olfactory recovery in these individuals would be of great clinical significance, as it might improve patients' counselling in a way that calibrates expectations more appropriately. Moreover, modulating factors might also serve as scientific base from which to generate new hypothesis on olfactory recovery, since its exact mechanism can only be speculated upon based on current literature.

Therefore, the aim of this study was (i) to explore the effectiveness of OT in a large cohort of over 600 participants with various degrees of olfactory function, also including control groups that received no training and (ii) to identify factors that are associated with clinically relevant recovery of olfactory function in participants receiving OT.

Materials and methods

Ethical statement

This retrospective study was conducted in accordance with the Declaration of Helsinki on biomedical research involving human subjects and was approved by the Ethics Committee of the Faculty of Medicine at the TU Dresden (EK251112006).

Subjects

This pooled data analysis included patients with quantitative olfactory loss that presented at the Smell and Taste clinic, Department of Otorhinolaryngology, Technical University of Dresden and adult participants from eight previously published studies that either presented at various ENT clinics with the major complaint of quantitative OD or were recruited as normosmic volunteers between 2008 and 2018[7,12,19,23–26]. Diagnosis was made based on medical history and clinical assessment of the ear, nose and throat.

Olfactory testing

Orthonasal olfactory function was evaluated birhinally using the "Sniffin' Sticks" test (Burghart Medical Technology, Wedel, Germany[27,28]. The "Sniffin' Sticks test is based on felt-tip pens presented approximately 2 cm in front of both nostrils and evaluates three olfactory dimensions: Threshold, Discrimination, and Identification. Odor Threshold (T) is tested based on a multiple staircase using a three-alternative, forced-choice procedure (3-AFC) utilizing 16 pen-triplets containing phenyl ethyl alcohol prepared in a dilution series (1:2 in propylene glycol) starting from 4%. Each triplet consists of one pen containing the diluted odor and two pens containing solvent, which are presented in a randomized order. Subjects are blindfolded and the task is to identify the odorized pen, starting from the lowest dilution concentration. The Threshold score is then calculated as the mean value of the last four reversal points on the staircase ladder. Odor discrimination (D) is also tested using a 3-AFC method utilizing 16 felt-tip pen triplets. Participants are blindfolded and three pens are presented in a randomized order with two pens containing identical odors and the third containing a distinctive odor. The task is to identify the distinctive one. The Discrimination score is then calculated as the sum of correctly identified pens. Odor Identification (I) is tested using a four-alternative, forced-choice paradigm based on 16 felt-tip pens containing distinctive odors. The task is to identify the correct odor out of four descriptors. The Identification score (I) is calculated as the sum of correctly identified odors. Summed TDI score allows classification of subjects into different levels of olfactory performance. The 10th percentile within each age group (which is defined for intervals of ten years) is defined as cut-off score to distinguish between normal olfactory function (normosmia, normosmics) and OD. The latter can be further divided into hyposmia (reduced olfactory function) or functional anosmia (loss of olfactory function)[29,30].

Olfactory training

Participants from the OT group were instructed to expose themselves at least twice a day (morning and evening) to four different odors (phenylethyl alcohol: rose odor, eucalyptol: eucalyptus odor, citronella: lemon odor, and eugenol: cloves odor) for approximately 10 seconds. The control group consisted of participants that performed no training. Olfactory performance was evaluated twice at the beginning (TDI1) and at follow up visit after training (TDI2).

Table 1. Demographics and olfactory test results. Continuous data are presented as mean (standard deviation). Categorical data are presented as number (%). Responders represent subjects that reached the minimally clinical important difference of 5.5 points in TDI score at follow-up visit.

	Control, N = 58		Olfactory training, N = 540					
	Normosmics, N = 43	OD, N = 15		Normosmics, N = 60		OD, N = 480		
			Overall	Responders, N = 20 (33%)	Non responders, N = 40 (67%)	Overall	Responders, N = 167 (35%)	Non responders, N = 313 (65%)
Demographics								
Age in years	56.3 (2.2)	45.6 (2.2)	60.1 (7.6)	58.0 (6.4)	61.9 (7.9)	57 (11.1)	55.2 (12.0)	57.8 (10.5)
Gender	30F, 13M	8F, 7M	45F, 15M	28F, 12M	17F, 3M	264F, 216M	85F 82M	179F, 134M
Olfactory characteristics								
Overall Baseline TDI	33.0 (3.3)	18.0 (2.1)	33.7 (3.2)	31.4 (2.9)	34.9 (2.7)	17.4 (6.2)	16.5 (5.9)	18.0 (6.2)
Follow up TDI	34.6 (2.8)	19.7 (2.1)	37.4 (3.6)	39.4 (2.1)	36.3 (3.7)	21.4 (7.4)	25.6 (6.1)	19.1 (7.0)
Reason for OD								
Postinfectious	-	15	-			N = 294	131 (45 %)	163 (55%)
Baseline TDI		18.0 (2.1)				18.6 (5.7)	17.1 (5.5)	19.7 (5.6)
Follow up TDI		19.7 (2.1)				23.6 (6.7)	26.5 (5.6)	21.3 (6.6)
Posttraumatic	-	-	-			N = 98	24 (24%)	74 (76%)
Baseline TDI						14.7 (6.6)	13.2 (6.3)	15.1 (6.6)
Follow up TDI						17.3 (7.4)	22.0 (7.3)	15.8 (6.8)
Idiopathic	-	-	-			N = 88	12 (14%)	76 (86%)
Baseline TDI						17.0 (6.1)	15.8 (7.3)	17.2 (5.8)
Follow up TDI						18.4 (6.6)	23.4 (5.7)	17.8 (6.4)

Statistical analyses

To assess the effect of OT on olfactory recovery (defined as TDI2-TDI1) in normosmic volunteers and patients with OD, a two-way ANOVA (2 ×2 factorial design) including two between-subject variables: (i) training: OT and control group, and (ii) OF: normal and OD was computed.

The next step included a subgroup analysis of normosmic volunteers and patients with OD of the OT group to identify factors associated with clinically relevant changes in olfactory function, which were defined as TDI changes greater or equal 5.5[31].

Binary logistic regression models were fitted and included following variables: age (years), gender (male and female), baseline olfactory function (TDI), duration of OT (weeks), and reason of OD in the patient group (postinfectious, posttraumatic, and idiopathic). All independent variables were entered in the models, and statistical estimates were generated to calculate adjusted odds ratios (aOR) with 95% confidence interval.

Data were analyzed using SPSS (SPSS version 23.0 for Windows; IBM Corp., Armonk, NY, USA) and GraphPad Prism 8.4.2 (GraphPad Software, Inc., La Jolla, CA, USA). Normality of data distributions was analyzed based on histograms and Q-Q plots. A p-value of < 0.05 was considered statistically significant.

Results

Participants

The effect of OT was analyzed in 601 subjects (254 men, 347 women, age = 57 ± 11 years (mean ± SD)). Participants were first stratified into two main groups: (i) the control group (N = 58) consisted of 20 men, 38 women, age = 54 ± 14 years (mean ± SD) that performed no training and (ii) the OT group (N = 543) that included 234 men, 309 women, age = 57.3 ± 10.9 years (mean ± SD) performing OT. The OT group performed training7 for a mean duration of 30.6 weeks (SD = 8.4 weeks). Participants from the control group were followed up for a mean period of 23 weeks (SD = 8 weeks)[7,11,24]. Normosmic volunteers and subjects with OD (defined as TDI scores below the 10th percentile within each age group) were included in both groups. The subgroup of patients with OD included in the OT group (N = 483) represented various causes of OD including: 294 postinfectious-, 98 posttraumatic-, 88 idiopathic-, and 3 sinonasal- related OD. Our 3 cases of sinonasal-related OD were excluded from regression analysis due to insufficient group size. We performed our analysis using listwise exclusion which resulted in 51 subjects being excluded from the final analysis sample of 601 subjects (Table 1).

Table 2. Factor associated with clinically relevant changes of olfactory function in normosmic participants receiving OT (N = 60). Multivariate analysis was performed using a binary logistic regression model, adjusted for age, baseline olfactory function, and gender.

Variables	Clinically relevant changes of olfactory function	
Age	0.89 (0.80-0.98)	0.02*
TDI baseline	0.55 (0.39-0.77)	<0.001*
Gender		
Female	Reference	Reference
Male	0.18 (0.03-1.4)	0.10

Adjusted odds ratios, aOR (95%CI) and p values. *Statistical significance is set at $p < 0.05$.

The effectiveness of olfactory training is higher compared to no training and is independent from baseline olfactory function

A mixed model ANOVA (2x2) was computed to depict the effect of training (OT and control group), olfactory function (normosmic or OD), and their combined interaction on improvements of olfactory function (TDI2 – TDI1).

The analysis revealed no interaction between OT and olfactory function ($F(1,597) = 0.52$, $p = 0.57$, $\eta p2 = 0.01$). There was a main effect of OT ($F(1,597) = 11.2$, $p < 0.001$, $\eta p2 = 0.02$) with higher recovery in the OT group ($M = 3.35$, $SE = 0.21$) compared to the control group ($M = 1.5$, $SE = 0.5$). To the contrary, no significant effect was found for olfactory function groups ($F(1,597) = 0.90$, $p = 0.34$, $\eta p2 = 0.02$).

Age and baseline olfactory function are associated with clinical improvement of olfactory function in normosmic participanty receiving olfactory training

The next step included a subgroup analysis of normosmic participants receiving OT to identify factors that were associated with clinically relevant changes in olfactory function. These included: age, gender, and baseline olfactory function. Clinically relevant improvement of olfactory function was defined as TDI improvements greater or equal 5.5 points at follow up visit.

Binary logistic regression analysis revealed that relevant recovery of overall olfactory performance was less likely in those that had that had higher baseline olfactory olfactory function (adjusted odds ratio; aOR, 0.55; 95% CI, 0.39-0.77; Table 2) and those that were older in age (aOR, 0.89; 95% CI, 0.80-0.98). No relevant association was found with gender ($p = 0.10$).

Baseline olfactory function and etiology of smell loss are associated with clinical improvement of olfactory function in patients receiving olfactory training

We were next interested in determining which factors (age, gender, duration of OT, baseline olfactory function, reason for OD) were associated with relevant improvements in olfactory performance in patients with OD receiving OT.

Table 3. Factor associated with clinically relevant changes of olfactory function in patients with OD receiving OT (N = 480). Multivariate analysis was performed using a binary logistic regression model, adjusted for age, baseline olfactory function, gender, duration of OT, and reason for OD.

Variables	Clinically relevant changes of olfactory function	
Age	0.99 (0.97-1.01)	0.13
TDI baseline	0.93 (0.90-0.97)	<0.001*
Gender		
Female	Reference	Reference
Male	1.40 (0.93-2.10)	0.10
Duration of OT	1.02 (0.99-1.05)	0.15
Etiology		
Postinfectious	Reference	
Posttraumatic	0.29 (0.17-0.51)	<0.001*
Idiopathic	0.18 (0.09-0.36)	<0.001*

Adjusted odds ratios, aOR (95%CI) and p values. *Statistical significance is set at $p < 0.05$.

Binary logistic regression analysis revealed that clinically relevant improvements in OF were less likely in those that had higher baseline olfactory function (aOR, 0.93; 95% CI, 0.90-0.97). Similarly, improvements were also less likely in posttraumatic (aOR, 0.29; 95% CI, 0.17-0.51) and idiopathic OD (aOR, 0.18; 95% CI, 0.09-0.36) compared to postinfectious causes. No relevant associations were found with gender ($p = 0.10$), age ($p = 0.13$) and duration of OT ($p = 0.15$; Table 3).

Discussion

OT has become a first-line treatment option for multiple etiologies of OD[7,11–19] and has also shown beneficial effects in normosmic participants of different age groups[20–22]. To the best of our knowledge, this is the largest cohort study including over 600 participants with various degrees of olfactory (dys)function to explore the effectiveness of OT, also including control groups that underwent no training. Our analysis demonstrated that OT was more effective in terms of olfactory recovery compared to no training in both patients with OD and normosmic participants. Moreover, we identified baseline olfactory function and etiology of smell loss as potential factors associated with relevant recovery of olfactory function after OT. Additional important results also include the identification of modulators that are associated with clinically relevant recovery of olfactory function in normosmic participants receiving OT.

In reference to the therapeutic effect of OT, this was commensurate with previous meta-analyses indicating that OT significantly improves overall olfactory performance[8–10]. Furthermore, we add to the growing literature showing that short-term olfactory recovery after OT shows no relevant interaction with olfactory performance groups, suggesting that OT is similarly effective in both OD patients and normosmic subjects. This is noteworthy, considering that no other treatment option has yet demonstrated this main effect on olfactory recovery in otherwise normosmic subjects. Moreover, since more than three quarters of people over the age of 80 show relevant impairments to the sense of smell- which leads to well-known impairments to daily life activities of affected individuals - OT might also emerge as valuable option for the general population to improve and maintain olfactory performance[1,30]. Although the exact mechanism behind olfactory recovery in health and disease is not entirely clear, previous electrophysiological imaging-based studies suggested that OT not only improves responsiveness of the olfactory epithelium[32] and the central processing of olfactory sensory information, but also increases olfactory related brain areas (such as the olfactory bulb or the grey matter volume) on a structural level[33]. Interestingly, longitudinal investigations on structural and functional changes in patients with posttraumatic OD receiving OT provided further evidence that recovery of olfactory function may be more pertained to top-down rather than bottom-up (peripheral-central) mechanisms[25].

The results from our analyses furthermore provided evidence, that higher baseline olfactory performance, and posttraumatic or idiopathic OD (compared to postinfectious smell loss) were also significantly associated with lower odds of clinically relevant improvement of olfactory function. One explanation for differences in olfactory recovery rates between postinfectious, posttraumatic, and idiopathic smell loss relates to their pathophysiological frameworks. While there is at least preliminary evidence that postinfectious smell loss leads to a reduced number of olfactory receptors[32,34], posttraumatic smell loss is usually believed to damage the olfactory system more severely as a result of olfactory fiber shearing or brain damage following head injury[35,36]. Moreover, these differences are also believed to be the reason for poorer prognosis in spontaneous recovery rates of posttraumatic OD compared to postinfectious smell loss[37,38].

Regarding the associations between demographics and relevant recovery after OT in our cohort of normosmic subjects, analysis revealed age-related differences in improvement rates but no relevant influence of gender. Although the exact mechanism by which age affects olfactory recovery has yet to be elucidated, studies in mammals provided evidence on the idea of an age-related increase in olfactory neuron apoptosis. Specifically, it has been hypothesized that the increased apoptosis rate might be linked to decreased olfactory function in older people[39,40]. The influence of gender on olfactory function has been previously outlined in detail[2,29,41–43]. More specifically, it has been shown that gender differences in odor identification largely occur in younger adults, but to a lesser degree in older people over the age of 50 years[43]. The authors hypothesized that differences in gonadal steroid levels - i.e estrogen levels in women of reproductive age – might be one reason for women to outperform men between the age of 18-50 years. Since our cohort of normosmic subjects mainly consisted of older people (>50 years), the decline in estrogen levels in women might also serve as an explanatory variable for our non-significant findings on gender-related differences of improvement rates. Regarding the association between baseline olfactory function and clinical improvement of olfaction, this was also commensurate with previous findings on prognostic factors associated with spontaneous recovery of olfactory function[44]. It seems to be associated with the idea that improvement on an olfactory test score is easily possible if the starting point is at a low level. In contrast, an improvement on an olfactory test score may be more difficult if the function is already relatively good.

The role of residual olfactory function and demographical factors on spontaneous, clinically relevant recovery of olfactory function has been described previously based on a retrospective analysis[44]. The authors reported recovery rates of 29% in patients with OD, who had been tested twice within 1.3 years. Interestingly, no patient showed relevant spontaneous recovery in our control group, but this discrepancy might be explained by the small group size and the length of the re-visit interval, since our cohort was tested no later than 36 weeks after the initial visit. Moreover, although the mean duration of OT was only 31 weeks in our cohort of patients receiving OT, relevant changes of overall OF were observed in 35% of patients. Interestingly, 14% of normosmic subjects included in the control group also showed relevant improvements of olfactory function. Although these findings were rather unexpected, one plausible explanation might relate to the individual importance of olfaction after enrollment, which may have resulted in an increased use of the sense of smell throughout the day[45].

Another important result emerged from subgroup analysis of patients with OD receiving OT. Analyses revealed that higher residual olfactory function was negatively associated relevant improvement of olfactory function. This finding was not unexpected, since a previous report on prognostic factors also identified lower olfactory function as the most important factor associated with relevant spontaneous recovery of olfactory function in patients with smell loss[44].

This present study is unique as it uses a large dataset to study the effect of OT and different olfactory specific factors on clinically relevant changes in olfactory function However, this was a retrospective analysis and therefore comes with all limitations associated with this study design. First, information on como-

rbidities such as diabetes or cardiac diseases was not available in the current data set. This information may be useful in future studies to gain more insight into olfactory rehabilitation. Secondly, since the control group receiving OT mainly consisted of older, normosmic subjects, results from logistic regression analysis may not be generalizable beyond the study population. Thirdly, although we were able to depict the exact type of OT used in all of those studies, subtle differences between the various studies in terms of the training regimens applied might have also influenced the results. However, because the effect of OT was consistent in all studies, heterogeneity in training protocols might not have affected OT results to a large extend. Since OT is usually performed twice daily for several months, assessment of therapy adherence might have also further elucidated compliance-related differences in recovery outcomes. Fourthly, since the diagnosis of idiopathic OD usually requires comprehensive assessment including history taking, clinical examination, and structural imaging, differences between diagnostic pathways might exist between study centers. However, this bias is mitigated since all patients with idiopathic OD were included from one study center. Finally, improvements in olfactory function after OT (especially in normosmic subjects) might also relate to the test itself – i.e. the learning effect of repeated olfactory testing – which is most evident in odor identification testing[46,47]. However, considering that the identification subtest only represents one third of the TDI test and testing was performed at a mean interval of 31 weeks, this effect might not have biased the results.

This study adds to the current literature on clinical olfactory research in two important ways. First, it provides further evidence that OT represents an effective therapeutic option for multiple etiologies of smell loss that also benefits normosmic subjects. Second, it adds valuable insights to factors associated with changes in olfactory function in participants receiving OT, therefore allowing clinicians to improve patients' counselling in a way that calibrates expectations appropriately.

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Conclusion

This study demonstrated that OT was more effective than no training in normosmic participants and patients with OD. Additionally, baseline olfactory performance and etiology of smell loss were identified as relevant factors associated with improvement of OD after OT. Subgroup analysis of normosmic participants receiving OT also revealed a significant association of age with improvement of overall olfactory function, which is consistent with previously published factors associated with spontaneous recovery in patients with OD.

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Authorship contribution

DTL: concept of study, collection of data, analysis of results, write up of manuscript, critical review of all contents; GB, BP, and MMS: concept of study, critical review of all contents; ARS and CAM: concept of study, analysis of results, critical review of all contents.

Conflict of interest

The authors declare that there are no conflicts of interests regarding the publication of this paper.

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