


Examination of Olfactory Training Effectiveness in Relation to Its Complexity and the Cause of Olfactory Loss

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Objective: Although the effectiveness of olfactory training (OT) had already been documented, the optimal regimen for such training remains unexplored. We examined whether the complexity of OT, namely alteration of odor quantity and quality, increases its effectiveness.

Design: One-hundred eight patients ($M_{\text{age}} = 60.1 \pm 1$) with postinfectious ($n = 57$) or idiopathic ($n = 51$) olfactory dysfunction underwent OT preceded and followed by examination of olfactory function.

Methods: Subjects were randomly assigned to one of the three experimental conditions: 1) simple training comprising four basic, single-molecule substances; 2) complex training involving four odor mixtures; and 3) odor-altering training in which patients changed sets of mixtures every 2 months.

Results: The analysis of variance revealed that the benefit seen in this sample was not affected by the complexity of OT with regard to odor mixtures or alteration of odor type. The highest increase of the Sniffin' Sticks (Burghardt GmbH; Wedel, Germany) threshold, discrimination, and identification (and overall TDI) score was observed in postinfectious patients.

Conclusion: We conclude that the outcomes of OT are not strongly influenced by the training regimen. However, further investigation of OT regimens is required, particularly with regard to training duration.

Key Words: olfactory training, Sniffin' Sticks, threshold, discrimination, identification.

Level of Evidence: 2b.

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INTRODUCTION

Previous studies have demonstrated reduced quality of life in patients with olfactory dysfunction.^{1,2} Furthermore, such dysfunction has been suggested to affect approximately 15% of the general population.^{3–5} Although treatment options for smell loss are limited, regular, structured exposure to odors through olfactory training (OT) has been shown to be effective.^{6–9} It is thought that repeated exposure to odors may stimulate regeneration of the olfactory system, although the exact mechanisms by which this occurs are unknown.¹⁰

Olfactory training is particularly attractive as a therapeutic approach due to its simplicity, low cost, and

lack of potential side effects. The efficacy of OT has been demonstrated in studies involving patients with various underlying etiologies, including viral infection, head trauma, or advanced age.^{11–13} Classically, OT involves structured smelling of four odors (one from each of the four odor categories: flowery, fruity, spicy, and resinous).¹⁴ Subjects are asked to sniff each odor twice a day for a period of at least 4 months. To date, surprisingly few studies have addressed the potential to improve OT outcomes through modification of the training regimen. There are some reports addressing the issue of treatment prolongation, but currently these findings are inconclusive, with some studies showing significant improvement in OT outcomes^{7,15} and other showing no effect.¹⁰ However, it seems that alteration of the odors used during training does have a positive effect.¹⁰ In the current study, we aimed to determine the ideal protocol for OT in patients with olfactory impairment, with particular focus on number and quality of odors used.

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MATERIALS AND METHODS

Ethics Statement

The study was performed in accordance to the Declaration of Helsinki on Biomedical Studies Involving Human Subjects. Informed written consent was obtained from all participants. The study design and consent approach was approved by the ethics review board at the Technische Universität (TU) Dresden (EK312082014).

TABLE I.
Demographic Characteristics of Sample With Regard to Cause of Olfactory Loss.

	Mean Age	Mean Olfactory Loss Duration (Months)	Proportion of Females
Simple (n = 40)	59.5 ± 1.6	23.1 ± 5.9	45%
Complex (n = 36)	62.5 ± 1.8	17.8 ± 5.2	66.7%
Altering (n = 32)	60.3 ± 1.7	20.2 ± 5.5	40.6%
Postinfectious (n = 57)	58.4 ± 1.1	22 ± 5.3	54.4%
Idiopathic (n = 51)	63.5 ± 1.6	18.8 ± 3.5	47.1%

Participants

We determined sample size by utilizing G*Power software version 3.1.9.2.¹⁶ Within the repeated measures design with between-within group interactions (described in detail in the Statistical Approach section) to obtain power of .95 with alpha level set to .05 to detect moderate effects of $f = .25$,⁹ the projected sample size was at least 90 subjects. Based on previous experience in running longitudinal studies involving OT, we initially recruited approximately 50% more participants due to the possible dropouts. All patients were referred from general practitioners; ear, nose, and throat specialists; or neurologists to the Interdisciplinary Centre for Smell and Taste of the TU Dresden with postinfectious or idiopathic olfactory dysfunction. Apart from OT, the patients did not receive any other specific treatment protocol at the clinic. Of all participants, those who did not complete both sessions (n = 35; $M_{\text{age}} = 58.3 \pm 2.7$; 20 females) were excluded from the sample. Exclusion from the study was independent from the cause of olfactory loss, $\text{Chi}^2(1) = 1$, $P = .75$, and was not related to any treatment protocol, except for the current study protocol that required participants to provide researchers with olfactory performance measurements twice, pre- and post-OT. Interestingly, we found a significantly higher mean baseline TDI score (threshold + discrimination + identification) in subjects who did not complete OT ($M = 20 \pm 1$) than in those who completed OT ($M = 17.6 \pm .6$), suggesting that severity of olfactory impairment might positively affect compliance in OT. Further, we excluded those who initially obtained a TDI score above 30.5 points (n = 2) in the first session because their result indicated normosmia. The final sample consisted of 108 anosmic or hyposmic patients (55 females). Descriptive statistics for experimental groups can be found in Table I.

Procedure

All participants took part in two sessions: before and after OT. During the first session, a standardized medical interview was conducted. During both sessions, olfactory function was assessed using the Sniffin' Sticks (Burghardt GmbH; Wedel, Germany).¹⁷ The duration of OT ranged from 4 to 12.5 months ($M = 6.4 \pm 1.1$ months). Participants were randomly assigned to one of the three experimental groups: 1) simple training comprising the four basic single-molecule substances (Sigma-Aldrich, Steinheim, Germany): anethole, eucalyptol, citronellal, and eugenol; 2) complex training involving four odor mixtures (multi-molecule substances provided by Frey + Lau, Henstedt-Ulzburg, Germany) with a dominant scent of rose (order #P0604034), eucalyptus (#S0100741), lemon (#P0119551), or cloves (#S0100148); and 3) odor-altering training in which patients changed sets of odorants every 2 months. In the first phase, they performed training with the following odorants a) rose (#P0604034), eucalyptus (#S0100741), lemon (#P0119551), and cloves (#S0100148). In the second phase, the odorants used were b) cinnamon (#S0100148), thyme (#P0123774), chocolate

(#P0603444), and peach (#P0606040). In the last phase, they used odorants of c) coffee (#P0604646), lavender (#P0123527), honey (#P0610351), and strawberry (#P0603875). Odors were delivered to all participants in brown glass bottles (volume: 60 mL, height: 65 mm, diameter of opening: 35 mm) containing a cotton ball soaked with 4 mL of an odorous substance. Participants were asked to sniff them twice a day—in the morning and in the evening—before or at least 30 minutes after a meal.

Statistical Approach

Statistical analysis was performed using IBM SPSS Statistics 24.0 software (SPSS Inc., IBM Corp., Armonk, NY, U.S.A.) with the level of significance set to alpha = .05. We first examined potential differences between experimental groups with relation to duration of olfactory loss, initial olfactory performance, and duration of OT by the means of multivariate analysis of variance, with training regimen and the cause of olfactory loss included as independent variables. In order to examine the increase in olfactory function across the experimental groups, we performed a repeated measures analysis of variance with session (first vs. second) included as a within-subject factor. The training setting (simple vs. complex vs. altering) and cause of olfactory loss (postinfectious vs. idiopathic) were included as between-subject factors. The duration of training was treated as a covariate. Overall, Sniffin' Sticks result (TDI) as well as results obtained in each of the subtests, namely olfactory T, D, and I, were treated as dependent variables. Further, utilizing χ^2 statistic, we examined between-groups difference in the distribution of subjects who exhibited improvement of clinical significance.

RESULTS

There was no significant difference in duration of olfactory loss or initial olfactory performance (all $F_s < 2.7$, $P_s > .10$) between the different OT training regimen groups. There was also no significant between-groups difference in the duration of OT (all $F_s < 1.25$, $P_s > .29$).

Results of the analysis of variance indicated a significant main effect of session on the overall TDI score: $F(1,101) = 23.4$, $P < .001$, and $\eta^2 = .19$. Pairwise comparisons showed that, across all groups, results significantly improved between the first ($M = 17.5 \pm .6$) and the second ($M = 20.1 \pm .7$) session. Inspection of the Sniffin' Sticks subtests revealed that this effect was present in T score: $F(1,101) = 22.8$, $P < .001$, and $\eta^2 = .18$, showing a significant improvement of olfactory sensitivity between the first ($M = 2.4 \pm .2$) and the second ($M = 3.9 \pm .3$) session. This effect was also present in I score: $F(1,101) = 8.8$, $P = .004$, and $\eta^2 = .08$, indicating a significant improvement of identification abilities

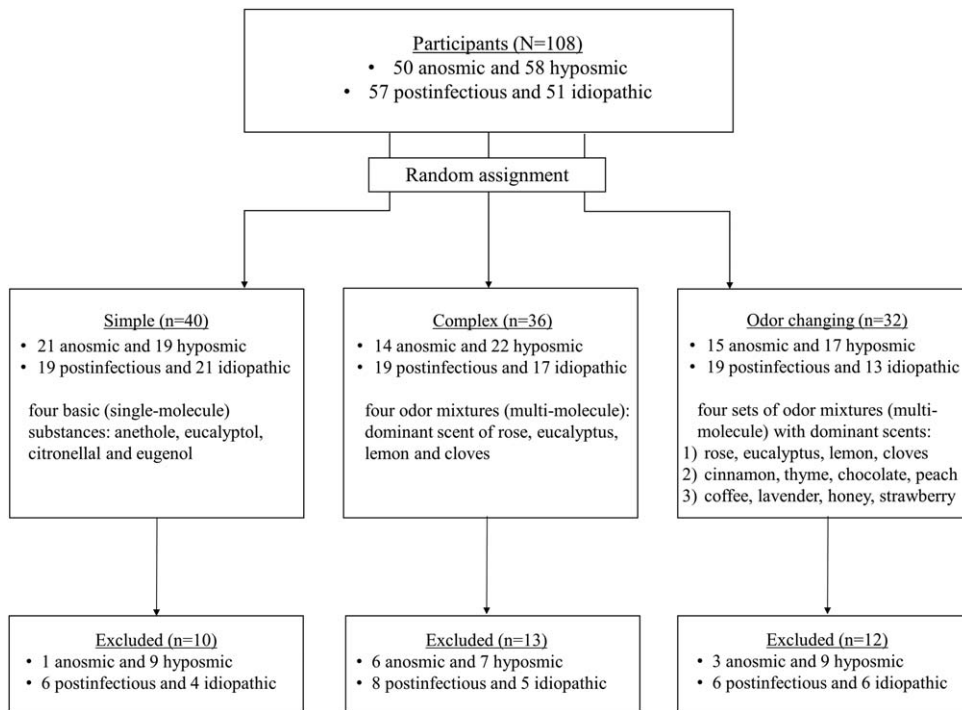


Fig. 1. Descriptive information regarding the entire study sample and subsamples across the experimental conditions.

between the first ($M = 7 \pm .3$) and the second ($M = 7.8 \pm .3$) session. The main effect of session on D score was not significant: $F(1,101) = 1.2, P = .27$. We noted a significant main effect of the cause of olfactory loss on TDI score: $F(1,101) = 9.3, P = .003$, and $\eta^2 = .08$, wherein postinfectious patients ($M = 20.5 \pm .8$) obtained overall higher scores as compared to idiopathic patients ($M = 17 \pm .8$). This effect was noted for D score: $F(1,101) = 9.6, P = .002$, and $\eta^2 = .09$, with higher scores observed in postinfectious patients ($M = 9 \pm .3$) than idiopathic ($M = 7.5 \pm .4$); and I score: $F(1,101) = 6.4, P = .013$, and $\eta^2 = .06$, again suggesting that postinfectious patients ($M = 8.1 \pm .4$) outperformed those with idiopathic olfactory loss ($M = 6.7 \pm .4$); but not on T score: $F(1,101) = 1.9, P = .17$. Most importantly, we observed an interaction between the cause of olfactory loss and session on the overall TDI score: $F(1,101) = 11.9, P = .001$, and $\eta^2 = .11$, indicating that the biggest advance in the olfactory performance (expressed in the TDI score) was seen in postinfectious group as compared to idiopathic. This was true for T score: $F(1,101) = 4.7, P = .03$, and $\eta^2 = .05$; and I score: $F(1,101) = 4.8, P = .03$, and $\eta^2 = .05$; but not D score: $F(1,101) = 3.6, P = .06$. There was no significant main effect of training regimen. Neither the interaction between session and training regimen nor the interaction between session, training regimen, and cause of olfactory loss was significant, indicating that there was no difference in OT efficacy between the different training regimens (all P s > .05).

In order to verify if variance in the results across the two sessions can be explained by length of the OT, we tested an analogous model of repeated measures; however, this time we also included the OT duration as a covariate. Within the new model, we found a

significant main effect of the cause of olfactory loss on TDI score: $F(1,101) = 9.2, P = .003$, and $\eta^2 = .09$, in which postinfectious patients ($M = 20.5 \pm .8$) obtained overall higher scores as compared to idiopathic patients ($M = 17 \pm .8$); D score: $F(1,101) = 9.5, P = .003$, and $\eta^2 = .09$, with higher scores observed in postinfectious patients ($M = 9 \pm .3$) than idiopathic ($M = 7.5 \pm .4$); and I score: $F(1,101) = 6.4, P = .013$, and $\eta^2 = .06$, again suggesting that postinfectious patients ($M = 8.1 \pm .4$) outperformed those with idiopathic olfactory loss ($M = 6.7 \pm .4$). The cause of olfactory loss had no effect on T score: $F(1,101) = 1.9$, and $P = .17$. An interaction between the cause of olfactory loss and session was found to be significant, and this effect was observed for TDI score: $F(1,101) = 11.9, P = .001$, and $\eta^2 = .11$, confirming that the OT was more effective in postinfectious group as compared to idiopathic, even when variation in the duration of training was taken into account statistically. This was pronounced for T score: $F(1,101) = 4.8, P = .03$, and $\eta^2 = .05$; and I score: $F(1,101) = 4.6, P = .03$, and $\eta^2 = .04$ (see Fig. 1); but not D score: $F(1,101) = 3.6$, and $P = .06$. Main and interaction effects have been depicted in Figure 2.

Finally, we evaluated the changes in measured olfactory function according to its clinical significance^{13,18} by comparing the numbers of participants who improved their TDI results by 5.5 points or more between the sessions. The difference between the training regimen groups for the number of subjects who presented a significant improvement was not significant: $\chi^2(2) = 1.86, P = .39$. However, the test performed for the groups differing in olfactory loss cause was significant (and survived Bonferroni correction): $\chi^2(1) = 17.5, P < .001$, indicating that more postinfectious patients

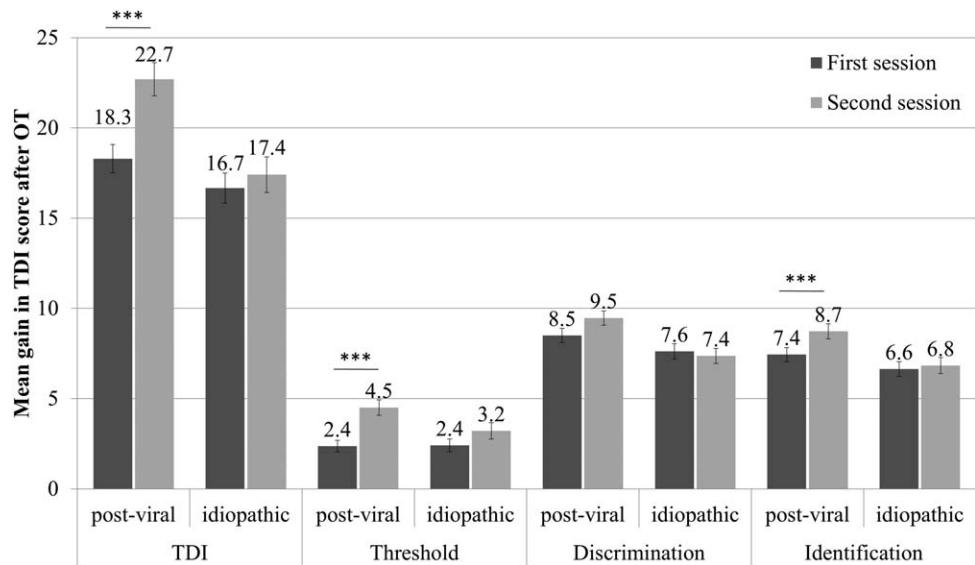


Fig. 2. Olfactory function in postinfectious and idiopathic patients before and after OT. *** $P < .001$. OT = olfactory training; TDI = threshold, discrimination, and identification.

presented improvement of clinical significance as compared to idiopathic patients. The number of observed statistical improvements and proportions can be found in Table II.

DISCUSSION

Olfactory training outcome was not significantly affected by the complexity of the training regimen. Neither the use of odor mixtures nor the alteration of odorants significantly increased effectiveness. We observed highest improvement in patients with postinfectious smell loss. However, with respect to clinical criteria, we did observe the highest absolute number of improvements within the changing odors regimen, but this effect was not statistically significant.

We observed a significant effect of OT on olfactory sensitivity (T score), suggesting that such training could have an influence on postinfectious patients' olfactory system, for example, by increasing the number of odor receptors¹⁹ or increasing the volume of the olfactory bulb.^{20,21} This supports previous findings in which patients with postinfectious dysfunction benefit most from OT.^{11,22} Furthermore, because the pathophysiology of postinfectious dysfunction is assumed to involve the peripheral olfactory system, it would follow that T score improves following OT in this group. We also found that odor identification (I score) significantly improved after OT in postinfectious

patients. This is in line with previous reports suggesting that OT may induce changes in subjects' higher cognitive processes, leading to improved perception of suprathreshold odors.^{10,23} Therefore, our results support the two lines of research showing that OT might positively influence both cognitive processes involved in odor perception^{10,23} and neural processes responsible for odor detection.^{11,22}

The specific regimen used did not significantly affect OT efficacy. Neither alteration of the odorants nor complexity of the stimuli significantly affected change in olfactory function, although all three versions of OT were associated with significant improvement in test scores. Furthermore, the OT regimen did not affect the proportion of patients who achieved a clinically significant improvement (change in TDI score after training of 5.5 points or more). This seems to contradict former studies showing that modifications of OT can significantly improve its effectiveness.¹⁰ Such discrepancies may be due to differences in patient demographics. In the study reported by Altundag et al., the sample included only postinfectious patients, who are known to be more responsive to OT than other etiologies of smell loss.^{10,11,22} Our cohort included patients with idiopathic olfactory impairment, a group that demonstrates only modest improvements in olfactory function after OT. The inclusion of such patients may have confounded our results. Alternatively, the rotation of odors every 8 weeks (as performed in our

TABLE II.
The Number and Proportion of Patients With Clinically Significant Improvement of Overall TDI Score Following OT.

Experimental Group	Number of Patients With Significant Improvement	Proportion	Significance
Simple (n = 40)	7	17.5%	$P = .000017$
Complex (n = 36)	9	25.0%	
Altering (n = 32)	10	31.3%	
Postinfectious (n = 57)	23	40.4%	
Idiopathic (n = 51)	3	5.9%	

OT = olfactory training; TDI = threshold, discrimination, and identification.

study) as opposed to every 12 weeks (as used in Altundag's study) might have contributed to the disparity in results obtained.¹⁰ One must further consider the stability of olfactory function improvement after OT.¹³ Despite the lack of significant effect on outcome in our study, one may speculate that more complex OT, namely involvement of a wider variety of odorants, could potentially produce more stable improvement by causing more diverse olfactory stimulation and a more enriching olfactory experience.⁶ This question should be addressed in future studies.

There were two limitations to this study: First, we did not include a control group and therefore cannot compare olfactory improvement in patients across different OT regimens to a matching sample performing placebo OT. However, the effectiveness of OT has been well established in previous work.^{7,9,10} Our primary aim was to compare the relative effectiveness of the three alternative OT regimens but not necessarily to reinvestigate the effectiveness of OT per se. Furthermore, we were reluctant to relegate patients to placebo treatment because OT is a standard of care in our center. Nevertheless, for future studies aiming to further investigate OT regimens, we would recommend using a crossover study design. Due to our lack of a control group, we cannot exclude the confounding effect of spontaneous recovery from our results. Former studies suggest that spontaneous recovery can be observed in approximately one-third of postinfectious patients.^{24–26} Although we are unable to exclude the possible effects of spontaneous recovery, the improvement in our training cohort occurred approximately within 6 months, as opposed to at least the 12-month period typical of untreated patients.^{24,26} Further studies with placebo control should be performed. Another limitation of the current study was our lack of information regarding OT compliance. We did not instruct patients to keep training diaries in order to reduce participant burden. However, in future studies, this should be done in order to control compliance ratio.

CONCLUSION

The current study supports the use of OT in olfactory dysfunction treatment, particularly in postinfectious patients. Over the period of 6 months, we observed an increase in overall olfactory performance of clinical significance in 20% to 30% of patients, with alteration of odorants apparently being the most effective regimen in clinical terms. However, further work is needed to propose most effective training regimen and to determine the optimal OT duration, particularly with regard to OT duration.

BIBLIOGRAPHY

- Hummel T, Nordin S. Olfactory disorders and their consequences for quality of life. *Acta Otolaryngol* 2005;125:116–121.
- Croy I, Nordin S, Hummel T. Olfactory disorders and quality of life—an updated review. *Chem Senses* 2014;39:185–194.
- Wysocki C, Gilbert A. National Geographic Smell Survey: effects of age are heterogeneous. *Ann N Y Acad Sci* 1989;561:12–28.
- Frasnelli J, Hummel T. Olfactory dysfunction and daily life. *Eur Arch Otorhinolaryngol* 2005;262:231–235.
- Landis BN, Hummel T. New evidence for high occurrence of olfactory dysfunctions within the population. *Am J Med* 2006;119:91–92.
- Livermore A, Laing DG. Influence of Training and experience on the perception of multicomponent odor mixtures. *J Exp Psychol* 1996;22:267–277.
- Damm M, Pikart LK, Reimann H, et al. Olfactory training is helpful in postinfectious olfactory loss: a randomized, controlled, multicenter study. *Laryngoscope* 2014;124:826–831.
- Pekala K, Chandra RK, Turner JH. Efficacy of olfactory training in patients with olfactory loss: a systematic review and meta-analysis. *Int Forum Allergy Rhinol* 2016;6:299–307.
- Sorokowska A, Drechsler E, Karwowski M, Hummel T. Effects of olfactory training: a meta-analysis. *Rhinology* 2017;55:17–26.
- Altundag A, Cayonu M, Kayabasoglu G, et al. Modified olfactory training in patients with postinfectious olfactory loss. *Laryngoscope* 2015;125:1763–1766.
- Hummel T, Rissom K, Reden J, Hahner A, Weidenbecher M, Huttenbrink K-B. Effects of olfactory training in patients with olfactory loss. *Laryngoscope* 2009;119:496–499.
- Schriever VA, Lehmann S, Prange J, Hummel T. Preventing olfactory deterioration: olfactory training may be of help in older people. *J Am Geriatr Soc* 2014;62:384–386.
- Konstantinidis I, Tsakiropoulou E, Bekiaridou P, Kazantzidou C, Konstantinidis J. Use of olfactory training in post-traumatic and postinfectious olfactory dysfunction. *Laryngoscope* 2013;123:E85–E90.
- Henning H. *Der Geruch*. Leipzig, Germany: JA Barth; 1916.
- Konstantinidis I, Tsakiropoulou E, Konstantinidis J. Long term effects of olfactory training in patients with post-infectious olfactory loss. *Rhinology* 2016;54:170–175.
- Faul F, Erdfelder E, Lang A-G, Buchner A. G*power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods* 2007;39:175–191.
- Hummel T, Sekinger B, Wolf SR, Pauli E, Kobal G. 'Sniffin' Sticks': olfactory performance assessed by the combined testing of odour identification, odor discrimination and olfactory threshold. *Chem Senses* 1997;22:39–52.
- Gudziol V, Lotsch J, Hahner A, Zahnert T, Hummel T. Clinical significance of results from olfactory testing. *Laryngoscope* 2006;116:1858–1863.
- Youngentob SL, Kent PF. Enhancement of odorant-induced mucosal activity patterns in rats trained on an odorant identification task. *Brain Res* 1995;670:82–88.
- Gudziol V, Buschhuter D, Abolmaali N, Gerber J, Rombaux P, Hummel T. Increasing olfactory bulb volume due to treatment of chronic rhinosinusitis: a longitudinal study. *Brain* 2009;132:3096–3101.
- Huart C, Rombaux P, Hummel T. Plasticity of the human olfactory system: the olfactory bulb. *Molecules* 2013;18:11586–11600.
- Reden J, Herting B, Lill K, Kern R, Hummel T. Treatment of postinfectious olfactory disorders with minocycline: a double-blind, placebo-controlled study. *Laryngoscope* 2011;121:679–682.
- Fleiner F, Lau L, Goktas O. Active olfactory training for the treatment of smell disorders. *Ear Nose Throat J* 2012;91:198–203.
- Reden J, Mueller A, Mueller C, et al. Recovery of olfactory function following closed head injury or infections of the upper respiratory tract. *Arch Otolaryngol Head Neck Surg* 2006;132:265–269.
- Rombaux P, Huart C, Collet S, Eloy P, Negoias S, Hummel T. Presence of olfactory event-related potentials predicts recovery in patients with olfactory loss following upper respiratory tract infection. *Laryngoscope* 2010;120:2115–2118.
- Cavazzana A, Larsson M, Munch M, Hahner A, Hummel T. Postinfectious olfactory loss: a retrospective study on 791 patients. *Laryngoscope* 2018;128:10–15.