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Parosmia is Associated with Relevant Olfactory Recovery After Olfactory Training

David T. Liu, MD; Maha Sabha; Michael Damm, MD; Carl Philpott, MD; Anna Oleszkiewicz, PhD; Antje Hähner, MD; Thomas Hummel, MD

Objective/Hypothesis: This study aims to determine the association between parosmia and clinically relevant recovery of olfactory function in patients with post-infectious olfactory dysfunction (PIOD) receiving olfactory training.

Study Design: Retrospective cohort study.

Methods: This was a retrospective cohort study of patients with PIOD that received olfactory training. Adult patients with the major complaint of quantitative smell loss were recruited and treated at several ENT clinics in German between 2008 and 2018. The outcome was based on the association between smell-loss related factors (including parosmia and phantosmia) and clinically relevant changes in overall and subdimension olfactory function of threshold, discrimination, and identification using binary logistic regression analysis.

Results: A total of 153 participants with PIOD were included. Clinically relevant improvements in overall olfactory function were more likely in those that had lower baseline olfactory function. Relevant improvements in discrimination function were more likely in those that had lower baseline olfactory function and those that had parosmia at the initial visit. Similarly, relevant improvements in odor identification were more likely in those that had a lower baseline olfactory function and in those who had parosmia at the first visit. Clinically significant improvements in odor threshold were more likely in those who were older in age.

Conclusions: This study demonstrated that the presence of parosmia is associated with clinically relevant recovery in olfactory discrimination and identification function in patients with PIOD receiving olfactory training.

Key Words: Smell, olfaction, olfactory training, smell loss, anosmia, hyposmia, parosmia.

Level of Evidence: 4

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INTRODUCTION

The olfactory system is important for our response to the environment and olfactory dysfunction (OD) represents a critical loss of information. The causes are diverse, including upper airway respiratory tract infections post-infectious olfactory dysfunction (PIOD), head traumas, idiopathic reasons, and impairments secondary to sinonasal or neurodegenerative diseases.[1] OD can be categorized into qualitative and quantitative impairments. Qualitative OD can be further subdivided into parosmia, defined as distorted odor perception in the presence of an odor and phantosmia, defined as odor perception in the absence of an apparent odor source.[2] Both parosmia and phantosmia can occur alone but are most commonly present along with quantitative OD.[1] Parosmia has been associated with better clinical outcome in terms of spontaneous olfactory recovery.[3–5] However, literature on the significance of parosmia as a predictor of olfactory rehabilitation in patients with OD receiving therapy remains sparse. Therefore, further elucidating its role as prognostic factor in olfactory recovery is needed for clinical counseling, especially when considering its prevalence of up to 60% among patients with certain etiologies of OD.[6]

Although quantitative impairments of the sense of smell are common and may affect up to one quarter of the general population, the prevalence of qualitative impairments appears significantly lower.[7,8] Notably, presence of parosmia varies among patients with quantitative OD, depending on the underlying cause of smell loss. Although parosmia is most commonly found in patients with PIOD, distorted odor perceptions are also reported in posttraumatic, idiopathic, and sinonasal causes.[9] Previous studies on parosmia as prognostic factor in olfactory

From the Smell and Taste Clinic, Department of Otorhinolaryngology, Medical Faculty Carl-Gustav Carus (D.T.L., M.S., A.O., A.H., T.H.), Technical University of Dresden, Dresden, Germany; Department of Otorhinolaryngology, Head and Neck Surgery (D.T.L.), Medical University of Vienna, Vienna, Austria; Department of Otorhinolaryngology (M.D.), ENT-Medicine Cologne (HNO-Heilkunde Köln) and University Hospitals of Cologne, Cologne, Germany; Norwich Medical School (C.P.), Chancellor's Drive, University of East Anglia, Norwich, UK; The Norfolk Smell and Taste Clinic (C.P.), Norfolk and Waveney ENT Service, Waveney, UK; and the Institute of Psychology (A.O.), University of Wroclaw, Wroclaw, Poland.

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Send correspondence to Thomas Hummel, MD, Smell and Taste Clinic, Department of Otorhinolaryngology, Technical University of Dresden, Fetscherstrasse 74, 01307 Dresden, Germany. E-Mail: thummel@msx.tu-dresden.de

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recovery provided first evidence, that the presence of parosmia at the initial visit might be associated with a higher number of clinically relevant improvements compared to the parosmia-free group.[3–5]

Treatment for smell loss relates to its underlying cause and pathophysiology. Although treatment strategies for OD secondary to (chronic) sinonasal diseases aim to resolve the underlying conditions, olfactory training (OT) aims to enhance olfactory recovery based on the neuronal plasticity of the olfactory system.[10] OT is recommended as conscious sniffing of at least four different odors at least twice daily for several months and has emerged as a simple and side-effect free treatment option for various causes of smell loss. Previous studies and meta-analysis provided evidence that OT is effective in patients with OD, but also healthy subjects of different age groups to improve olfactory function.[10] It has been suggested, that etiology of smell loss (i.e., PIOD) and longer duration of OT might serve as prognostic factor for better outcomes in terms of olfactory recovery.[10] However, the literature on symptoms of qualitative OD as predictor of olfactory recovery after OT remains sparse. Understanding its impact would be of great clinical significance in counseling patients who may otherwise be confused by distorted odor perceptions in quantitative smell loss. Hence, the aim of this study was to elucidate the prognostic value of parosmia and phantosmia in terms of olfactory rehabilitation in a cohort of patients with PIOD receiving OT.

MATERIAL AND METHODS

Study Population

This retrospective study followed with the Declaration of Helsinki. Its design was approved by the Ethics Committee of the Faculty of Medicine at the TU Dresden (EK251112006). This pooled data analysis included adult participants from three previously published studies on OT.[11–13] Adult patients were either self-referrals or referred from outside institutions to tertiary-care otorhinolaryngology departments between 2008 and 2018. Inclusion criteria were posttraumatic OD, PIOD, and idiopathic smell loss. Exclusion criteria were TDI above 30.5 (indicating normal olfactory function), pregnancy, and acute or chronic sinonasal diseases. At the initial visit, patients were asked for presence of parosmia ("Do you smell odors differently compared to previous experiences?") or phantosmia ("Do you smell odors in absence of an apparent source?") based on a binary outcome of yes and no, time since onset of OD (in month), and possible causes for their smell loss. Diagnosis was made based on the recent "Position paper of olfactory dysfunction[1]" (Table I).

TABLE I.
Demographics, Olfactory Test Results, and Smell-loss Related Variables.

Demographics	
Mean age (years)	58.7 (7.3)
Gender	140 Female, 106 Male
Smell-loss related factors	
Aetiology	
Post-infectious	153 (62.2%)
Posttraumatic	31 (12.6%)
Idiopathic	62 (25.2%)
Duration of OT (weeks)	25.8 (8.0)
Presence of (at first visit)	
Parosmia	81 (32.9%)
Phantosmia	43 (17.5%)
Duration of OD (months)	22.0 (41.8)
Olfactory function	
Baseline olfactory function (TDI)	17.6 (7.0)
Follow up olfactory function (TDI)	20.8 (7.9)

Continuous data are presented as mean (standard deviation). Categorical data are presented as number (%).

Olfactory Testing

Olfactory testing was performed twice birhinally (before and after training) by means of the validated Sniffin' Sticks test (Burghart Medical Technology, Wedel, Germany).[14] The Sniffin' Sticks test is divided into subtests, covering three olfactory dimensions: 1) threshold (T), 2) discrimination (D), and 3) identification (I). Summed scores of subdimensions threshold, discrimination, and identification (TDI) allow the categorization of olfactory performance into normosmia, hyposmia, and functional anosmia based on normative data of over 9000 healthy subjects.[15] The test procedure is described in detail elsewhere.[14] Furthermore, Sniffin' Sticks can also be used for follow-up testing with minimally clinically important differences defined for summed scores and each of the subtests separately.[16]

Olfactory Training

All patients included during this study received OT as a therapy for their smell loss.[11–13] Olfactory training is defined as conscious sniffing of (usually four) different odors twice a day for at least 15 seconds each.[13] Participants either received: 1) four single molecule substances for the entire study period (anise odor, anethol; eucalyptus odor, eucalyptol; lemon odor, citronella; cloves odor, eugenol), 2) four multi-molecule substances (mixtures of single molecule substances) with a dominant scent of the odors stated hereafter for the entire study period (rose odor, phenyl ethyl alcohol; eucalyptus odor, eucalyptol; lemon odor, citronellal; cloves odor, eugenol), or 3) twelve multi-molecule substances, which were alternated twice every eight weeks as a group of four (first phase: phenyl ethyl alcohol, eucalyptol, citronellal, eugenol; second phase: cinnamon, thyme, chocolate, peach; third phase: coffee, lavender, honey, strawberry). Previous studies have shown that the effect of OT in olfactory rehabilitation is consistent within studies that applied different training protocols.[11–13]

Statistical Analyses

Binary logistic regression models were computed in patients with PIOD to assess the associations

TABLE II.
Factor Associated with Clinically Relevant Changes of Overall and Olfactory Subdimension Function in Patients with PIOD.

Variables	TDI		Threshold		Discrimination		Identification	
Age (years)	1.01 (0.96–1.07)	0.81	1.07 (1.00–1.13)	**0.03**	1.00 (0.95–1.05)	0.87	0.99 (0.95–1.05)	0.75
Gender								
Female	Reference							
Male	0.87 (0.42–1.80)	0.70	0.59 (0.28–1.26)	0.17	1.88 (0.90–3.92)	0.09	0.63 (0.28–1.45)	0.28
Baseline olfactory function (TDI)	0.92 (0.87–0.97)	**0.002**	1.02 (0.96–1.08)	0.52	0.91 (0.86–0.96)	**0.001**	0.91 (0.86–0.97)	**0.004**
Duration of smell loss (month)	0.97 (0.94–1.00)	0.11	0.99 (1.00–1.01)	0.66	1.00 (0.99–1.01)	0.96	0.97 (0.93–1.01)	0.17
Presence of								
Parosmia	1.12 (0.59–2.46)	0.62	1.11 (0.53–2.33)	0.78	2.88 (1.25–6.11)	**0.006**	3.38 (1.50–7.60)	**0.003**
Phantosmia	1.11 (0.41–3.00)	0.94	0.42 (0.13–1.33)	0.14	0.80 (0.27–2.32)	0.68	1.76 (0.61–5.10)	0.30
Duration of OT (weeks)	1.02 (0.97–1.07)	0.11	1.00 (0.91–1.00)	0.05	1.03 (0.98–1.08)	0.22	1.00 (0.95–1.05)	0.96

Adjusted odds ratios, aOR (95%CI) and *P* values. **Statistical significance** is set at $P < .05$. Multivariate analysis was performed using binary logistic regression models, adjusted for age, baseline olfactory function, gender, duration of training, duration of smell loss, and presence of parosmia or phantosmia.

between demographics, olfactory-related factors, and clinically relevant changes in overall olfactory function (TDI) and the sub-dimensions threshold (T), discrimination (D), and identification (I). Clinically relevant changes were defined based on the following cut-off scores: 1) for overall olfactory function: TDI improvement greater or equal 5.5 points at follow up visit, 2) for threshold function: T improvement greater or equal 2.5 points at follow up visit, and 3) for discrimination and identification function: improvements greater or equal 3 points at follow up visit.[16] Olfactory-related variables included: age (years), gender (male and female), olfactory function at first visit (baseline olfactory function, TDI), duration of olfactory training (weeks), duration of smell loss (month), and presence of parosmia or phantosmia at first visit. All demographics and olfactory-related variables were entered in the models, and statistical estimates were generated to calculate adjusted odds ratios (aOR) with 95% confidence interval to control for the impact of potential confounders mentioned above. Data were analyzed using SPSS (SPSS version 25.0 for Windows; IBM Corp., Armonk, NY, USA). This study used a level of significance of 0.05.

RESULTS

Participants

The presence of distorted olfactory perception and improvement of olfactory performance after OT was analyzed in 246 subjects (106 men, 140 women, mean (±SD) age 58.7 ± 7.3 years). Diagnosis included 153 post-infectious-, 31 posttraumatic-, and 62 idiopathic- related OD (Table I). Olfactory training was performed for a mean (±SD) period of 25.8 ± 8 weeks. Although 292 participants were initially included in the study, further analysis was performed on the basis of 'listwise' exclusion in case of missing values, resulting in a total of 46 subjects being excluded from the final analysis sample (n = 246).

Frequency of Qualitative OD by Etiology

We first sought to determine the presence of parosmia and phantosmia for each etiology group separately. Parosmia was most frequently present in PIOD (40.5%), followed by posttraumatic OD (25.8%), and idiopathic OD (17.7%). In contrast, phantosmia was most commonly present in idiopathic OD (25.8%), followed by posttraumatic OD (19.3%) and PIOD (13.7%).

Since the sample sizes of patients with posttraumatic smell loss (n = 31) and idiopathic OD (n = 62) were insufficient for further regression analysis, we only included patients with PIOD (n = 153) in our binary logistic regression models.

Association Between OD with Relevant Improvement in Overall Olfactory Function

The next step included an analysis of associations between smell-loss related factors: 1) age, 2) gender, 3) duration of smell loss (months), 4) duration of training (weeks), 5) baseline olfactory function, and 6) presence of parosmia or phantosmia at initial visit with clinically relevant recovery of overall olfactory function (defined as TDI improvement greater or equal 5.5 points) in patients with PIOD at follow-up visit. Therefore, a binary logistic regression model was computed.

Analysis revealed that relevant recovery of overall olfactory performance was more likely in those that had lower baseline olfactory function (adjusted odds ratio; aOR, 0.92; 95%CI, 0.87–0.97; Table II).

Association Between Parosmia and OD with Relevant Improvement in Discrimination

The next step sought to determine associations between smell-loss related variables (see above) and relevant changes in discrimination function (defined as D improvement greater or equal 3.0 points) at follow-up visit.

Logistic regression analysis revealed that relevant improvements in discrimination function were more

likely in those that had lower baseline olfactory function (aOR, 0.91; 95%CI, 0.86–0.96) and those that had parosmia at first visit (aOR, 2.88; 95%CI, 1.25–6.11).

Association Between Parosmia and Gender with Relevant Improvement in Identification

We were then interested in identifying smell-loss related factors that are associated with clinically relevant improvements in odor identification function (defined as improvement greater or equal 3.0 points) at follow-up visit.

Binary logistic regression analysis revealed that relevant improvements in identification were more likely in those that had lower baseline olfactory function (aOR, 0.91; 95%CI, 0.86–0.97) and those that had parosmia at first visit (aOR, 3.38; 95%CI, 1.50–7.60).

Association Between Age with Relevant Improvement in Threshold

We were next interested in determining which of above-mentioned smell loss-related variables were associated with clinically relevant improvements in olfactory threshold performance (defined as T improvement greater or equal 2.5 points) at follow up visit (Fig. 1).

Binary logistic regression analysis revealed that clinically relevant improvements in threshold function were more likely in those who were older in age (aOR, 1.07, 95%CI 1.00–1.13).

DISCUSSION

Although studies dedicated to assessing the prognostic value of qualitative OD in smell loss provided first evidence that parosmia might serve as a prognostic factor for spontaneous recovery of olfactory function,[3–5] there remains a gap of knowledge relating to its predictive value in patients receiving OT, which is currently the first-line treatment option for different etiologies of smell loss.[1] In this study, we showed that the presence of parosmia at initial visit was associated with clinically significant recovery in suprathreshold olfactory function discrimination and identification in patients with PIOD receiving OT. We also found that changes in suprathreshold olfactory functions after OT were distinct from threshold improvements, possibly indicating that the improvement of function of olfactory subdimensions may be based on changes at different stages of olfactory processing. Specifically, it has been hypothesized that odor thresholds reflect peripheral function to a higher degree than odor discrimination and odor identification.[17,18] According to this avenue of thought it may be that the presence of parosmia at the first visit appears to represent a positive sign in terms of the improvement of the central nervous extraction of olfactory information.

The most important results emerged from our subgroup analysis of factors associated with significant recovery of suprathreshold olfactory function discrimination and identification. Our analyses revealed that both lower baseline olfactory function and presence of parosmia at initial visit were prognostic predictors for clinically relevant recoveries in patients with PIOD. The reason for parosmia as positive predictor in suprathreshold recovery after OT can only be speculated upon. However, it has been suggested that OT mainly improves cognitive processing of olfaction-related sensory information.[19] Recent work based on magnetic resonance imaging (MRI) further provided evidence, that OT is not only associated with increase of olfactory bulb and grey matter volume on a structural level, but also re-established the intensity of functional connectivity within the olfactory system.[20] Moreover, MRI scanning in posttraumatic olfactory loss has suggested that recovery of olfactory function after OT may be largely due to top-down rather than bottom-up mechanisms.[21] In line with the previously proposed mechanism of incomplete afferent sensory information in distorted odor perceptions, it might be speculated that symptoms of parosmia can be interpreted as early signs of recovery. Following on from this, OT might effectively improve cognitive processing of (incomplete) sensory information, hence resulting in improved outcome of patients that report parosmia.

Results from threshold, discrimination, and identification analysis provide further evidence for the "central-peripheral" hypothesis of olfactory subdimension processing. As mentioned above, it has been postulated that threshold represents peripheral olfactory function to a higher degree than discrimination and identification.[17,18] Although speculative, these findings stress the importance for future efforts in experimental and clinical research regarding olfactory neuron regeneration in different types of olfactory loss. More importantly, results provide further evidence that the assessment of both suprathreshold and threshold olfactory function represent the most meaningful approach to the human sense of smell.

Prior investigations on the prevalence rates of parosmia and phantosmia in patients with various causes of smell loss showed difference between study centers.[6–9] Since symptoms of isolated qualitative dysfunctions are hardly ever spontaneously reported by patients,[22] the heterogeneity of methods and questionnaires used has been suggested to be one major reason for this discrepancy.[23] In addition, qualitative olfactory dysfunction is – like in the present investigation – typically assessed in terms of the presence or absence. It has been previously reported that parosmia is most prevalent in PIOD and one possible explanation might relate to its pathophysiology. Although the exact mechanism is only partly delineated, there is at least preliminary evidence that the number of olfactory sensory neurons (OSN) is reduced in these patients.[24]

Considering the clinical relevance of the current investigation, results can be implemented effortless into clinical routine. The awareness for symptoms of qualitative OD must be raised among the medical profession. Parosmia and phantosmia can be easily assessed based on straightforward questions with binary outcomes (yes/no), psychophysical test methods, the use of validated questionnaires, or the simple grading of parosmia, with questions on 1) frequency (daily, not daily), 2) intensity (not intense, intense), 3) social impact (present, absent).[9,25] Since OT has become the recommended first-

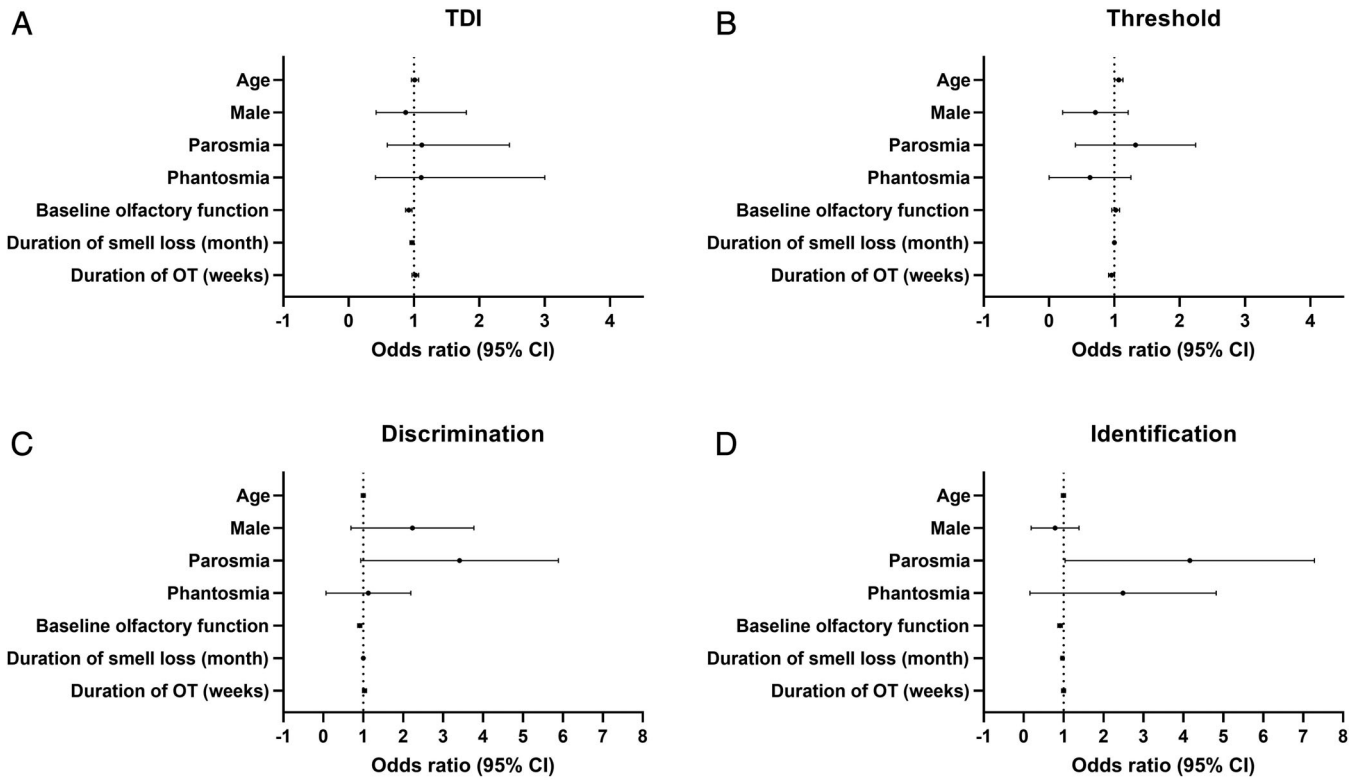

Fig. 1. Forest plots showing the associations between olfactory-related variables with relevant changes in overall olfactory function (TDI) and olfactory subdimensions threshold (T), discrimination (D), and identification (I) in patients with PIOD. Odds ratios (OR) were calculated using binary logistic regression models adjusted for age, gender (reference group female), presence of parosmia and phantosmia at first visit, baseline olfactory function, duration of smell loss (month), and duration of olfactory training (weeks). Points represent group-specific OR point estimates, and lines indicate the respective 95% confidence interval (CI).

line treatment protocol for certain causes of smell loss,[1] consideration of predictors for relevant recoveries after OT, such as parosmia might not only calibrate patients' expectations more appropriately but also comfort patients with PIOD that may otherwise be distraught by distorted odor perceptions. Previous studies also provided first evidence that longer duration of treatment (more than 8 months) might also increase the effectiveness of OT.[11,26,27] Patients that were included in this analysis received OT for up to 9 months, which is longer than the usually recommended duration of treatment. Since OT is usually recommended for at least six months (twice on a daily base), informing patients (and thus increasing the likelihood of treatment adherence[28,29]) remains a cornerstone during counseling.

The present study uses a comprehensive dataset including relevant olfactory demographics and smell-loss related variables to assess different factors associated with clinically relevant improvements after OT in patients with PIOD. However, this study also has limitations. Firstly, although we were able to depict the training regimen in all studies, small differences in odors used might have biased our results. Since previous studies have shown that the training effect was consistent among different training protocols, these differences might not have affected the outcome after OT to a large extent.[11,12] Secondly, although we tried to explore the presence of parosmia and phantosmia in different causes of smell loss, binary logistic regression analyses were performed only for patients with PIOD. Therefore, additional studies with larger sample sizes of various etiologies (such as posttraumatic or idiopathic smell loss) are needed to explore the associations between qualitative OD, reason for OD, and clinically relevant recovery of olfactory function after OT. However, our results do provide guidance regarding the magnitude of potential effects and the resultant sample sizes needed, as it is one of the few to examine the impact of parosmia on olfactory rehabilitation. Thirdly, we could not exclude the possibility that the observed association between lower baseline olfactory function and higher odds of relevant recovery after OT might be attributable to the regression to the mean (RTM) phenomenon, which is frequently described in longitudinal studies.[30] The RTM is a phenomenon wherein more unusual/extreme test scores are more likely to be followed by an average/mean score, regardless of any "real" change in olfactory function.

Finally, information on the presence of parosmia at follow-up visit was not available in the current dataset. Since parosmia is characterized by distorted odor perceptions, it might be hypothesized that lower identification and discrimination function at baseline visit reflected the interaction and negative effect of parosmia on odor identification and discrimination tasks, rather than a

quantitative dysfunction. Therefore, recovery from parosmia might also explain improved odor identification and discrimination function at follow-up visit.

CONCLUSION

This study adds to the current literature in three important ways. First, parosmia was associated with clinically relevant recovery of discrimination and identification (suprathreshold) function after OT in patients with PIOD, which highlights the need to further raise awareness for symptoms of qualitative OD in patients with smell loss. Secondly, it provides valuable insights into factors that modulate clinically relevant recovery of olfactory function after OT, which should be recommended for at least six months. These variables can further be used in counseling of patients to calibrate expectations and outcomes more appropriately. Thirdly, it adds evidence to the idea that the comprehensive analysis of different olfactory components, such as threshold and suprathreshold functions during psychophysical testing are indispensable when evaluating the human sense of smell.

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