Parosmia is associated with relevant olfactory recovery after olfactory training

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Abstract

Objectives This study aims to determine the association between parosmia and clinically relevant recovery in olfactory function in patients with smell loss receiving olfactory training. Design and setting This was a retrospective cohort study of patients 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. Participants A total of 243 participants were included. Main outcome measures Changes in olfactory function after olfactory training. Age, gender, baseline olfactory function, etiology and duration of smell loss, duration of training, and presence of parosmia and phantosmia were assessed for their impact on clinically relevant changes in overall and subdimension olfactory function using binary logistic regression analysis. Results Relevant improvements in discrimination function were more likely in those that had lower baseline olfactory function, postinfectious reasons compared to posttraumatic or idiopathic causes and those that had parosmia at initial visit. Relevant improvements in odour identification were more likely in those that had a lower baseline olfactory function, female gender, and in those who had parosmia at the first visit. Clinically significant improvements in odour threshold were more likely in postinfectious causes compared to posttraumatic reasons and those who were older in age. Conclusions This study demonstrated that the presence of parosmia is associated with clinically relevant recovery in olfactory function in patients with smell loss receiving olfactory training.

Key points

1. Parosmia is associated with clinically relevant improvements in discrimination and identification function in patients with smell loss receiving olfactory training.
2. Clinically relevant recovery of overall olfactory performance was more likely in those that had lower baseline olfactory function at initial visit and in postinfectious smell loss compared to posttraumatic or idiopathic causes.
3. Recovery of suprathreshold olfactory function discrimination and identification was distinct from threshold improvements.

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, 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 odour perception in the presence of an odour and phantosmia, defined as odour perception in the absence of an apparent odour 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 counselling, especially when considering its prevalence of up to 60 percent among patients with certain etiologies of OD.[6]

While 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. While parosmia is most commonly found in patients with postinfectious OD, distorted odour perceptions are also reported in posttraumatic, idiopathic, and sinonasal causes.[9]Previous studies on parosmia as prognostic factor in olfactory 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. While 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 odours 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 aetiology of smell loss (i.e. postinfectious) 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 counselling patients who may otherwise be confused by distorted odour 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 various causes of OD receiving OT.

Material and Methods

Study population

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, postinfectious, 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 or phantosmia (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 1**).

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: (i) Threshold (T), (ii) Discrimination (D), and (iii) Identification (I). Summed scores 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 odours twice a day for at least 15 seconds each.[13] Participants either received: (i) four multi-molecule substances with a dominant scent of the odours stated hereafter for the entire study period (rose odour, phenyl ethyl alcohol; eucalyptus odour, eucalyptol; lemon

odour, citronella; cloves odour, eugenol), (ii) four single molecule substances for the entire study period (anise odour, anethol; eucalyptus odour, eucalyptol; lemon odour, citronella; cloves odour, eugenol), or (iii) twelve multi-molecule substances, which were alternated twice every eight weeks as a group of four (first phase: phenyl ethyl alcohol, eucalyptol, citronella, 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 to assess the associations 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: (i) for overall olfactory function: TDI improvement greater or equal 5.5 points at follow up visit, (ii) for threshold function: T improvement greater or equal 2.5 points at follow up visit, and (iii) for discrimination and identification function: improvement 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), reason for OD (postinfectious, posttraumatic, and idiopathic), 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. Hierarchical cluster analysis and the associated dendrogram were computed based on the Ward clustering method and the Squared Euclidian distance to identify possible groupings between changes after OT in T, D and I in terms of similarity. Data were analyzed using SPSS (SPSS version 23.0 for Windows; IBM Corp., Armonk, NY, USA). This study employed a level of significance of 0.05. According to the previously reported and widely used sample size calculation-criterion of ten events per variable in logistic regression analysis, we needed at least 80 patients with parosmia. Because we included 81 patients with parosmia, this study is sufficiently powered to conduct the described analysis for parosmia as predictive value.[17]

Results

Participants

The association between presence of distorted olfactory perception and improvement of olfactory performance after OT was analysed in 246 subjects (106 men, 140 women, mean (±SD) age 58.7 ± 7.3 years). Diagnosis included 153 postinfectious-, 31 posttraumatic-, and 62 idiopathic- related OD (**Table 1**). Olfactory training was performed for a mean (±SD) period of 25.8±8 weeks. Although 292 participants were initially included in the study, the 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 aetiology

We first sought to determine the presence of parosmia and phantosmia for each aetiology group separately. Parosmia was most frequently present in postinfectious OD (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 postinfectious smell loss (13.7%).

Association between OD and aetiology with relevant improvement in overall olfactory function

The next step included an analysis of associations between smell-loss related factors: (i) age, (ii) gender, (iii) aetiology of smell loss (infections, trauma, and idiopathic), (iv) duration of smell loss (months), (v) duration of training (weeks), (vi) baseline olfactory function, and (vii) 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) 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, 0.93; 95%CI, 0.88-0.97;**Table 2**), and

postinfectious OD compared to posttraumatic (aOR, 0.28; 95%CI, 0.10-0.81) or idiopathic OD (aOR, 0.16; 95%CI, 0.06-0.41).

Association between parosmia, OD, and aetiology 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, 0.90; 95%CI, 0.86-0.95), postinfectious OD compared to posttraumatic (aOR, 0.33; 95%CI, 0.12-0.89) or idiopathic OD (aOR, 0.26; 95%CI, 0.11-0.62), and those that had parosmia at first visit (aOR, 2.35; 95%CI, 1.22-4.54).

Association between parosmia, gender, and OD with relevant improvement in identification

We were then interested in identifying smell-loss related factors that are associated with clinically relevant improvements in odour 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, 0.95; 95%CI, 0.90-0.99), female gender compared to male (aOR, 0.46, 95%CI, 0.24-0.85), and those that had parosmia at first visit (aOR, 2.23; 95%CI, 1.15-4.30).

Association between aetiology and 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.

Binary logistic regression analysis revealed that clinically relevant improvements in threshold function were more likely in postinfectious OD compared to posttraumatic OD (aOR, 0.22, 95%CI, 0.06-0.83) and those who were older in age (aOR, 1.08, 95%CI 1.03-1.14).

Because we identified recovery in sub-dimensions T, D, and I to be differently predicted by smell-loss related factors, we checked for similarities between these olfactory dimensions. Therefore, hierarchical cluster analysis was performed. Cluster analysis indicated that recovery of olfactory function discrimination and identification (both suprathreshold) was distinct from threshold improvements (**Fig 1**).

Discussion

Synopsis of key/new findings

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 aetiologies of smell loss.[1] In this study, we showed that presence of parosmia at initial visit was associated with clinically significant recovery in suprathreshold olfactory function discrimination and identification in patients 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 odour thresholds reflect peripheral function to a higher degree than odour discrimination and odour identification.[18,19]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. Furthermore, postinfectious OD (compared to posttraumatic and idiopathic OD) was associated with clinically relevant improvement in discrimination. Interestingly, regression analysis also revealed female gender as positive predictor for relevant changes in identification. 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.[20] 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.[21] 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.[22] In line with the previously proposed mechanism of incomplete afferent sensory information in distorted odour 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 hierarchical cluster 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.[18,19] Likewise, regeneration of olfactory subdimensions might also occur at different processing sites, hence resulting in more similarities between D and I compared to T. 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.

Comparisons with other studies

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[23], the heterogeneity of methods and questionnaires used has been suggested to be one major reason for this discrepancy.[24] In addition, qualitative olfactory dysfunction is – like in the present investigation – typically assessed in terms of the presence or absence. This lack of granularity may oversimplify a complex symptom. Nevertheless, our finding that parosmia was most commonly present in the postinfectious group was altogether not surprising. It has been previously reported that parosmia is most prevalent in postinfectious smell loss 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.[25] Considering the mechanism of olfactory coding[26], it is tempting to speculate that loss of OSN leads to incomplete patterns of afferent sensory information, resulting in distorted odour perceptions.

The role and clinical course of idiopathic phantosmia has been outlined in detail.[27] It has been suggested that idiopathic phantosmia can be seen as a harmless symptom rather than an early predictor of neurodegenerative diseases. Likewise, our results showed that phantosmia was not associated with clinically relevant recovery of olfactory function, hence was also not a relevant predictor for olfactory recovery after OT. Various theories have been postulated on the neurobiological causes of odour perceptions in the absence of an apparent source (olfactory hallucinations).[28] However, a previous study on the prevalence of phantosmia provided a first link between olfactory hallucinations and the presence of the *BDNF* met allele, which accounts for neuronal survival and synaptic plasticity.[29]

Clinical applicability of the study

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), the use of validated questionnaires, or the simple grading of parosmia, with questions on (i) frequency [daily, not daily], (ii) intensity [not intense, intense], (iii) social impact [present, absent].[9] Since OT has become the recommended first-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 smell loss that may otherwise be distraught by distorted odour perceptions.

Strengths and weaknesses of the study

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. However, this study also has limitations. Firstly, although we were able to depict the exact training type in all studies, subtle differences in odours 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, the missing values may have biased our results and compromised the statistical power. Nevertheless, our results are an important reference point on OD-related variables for clinicians during counselling of patients with smell loss.

Conclusions

This study adds to the current literature in three important ways. First, parosmia was associated with clinically relevant recovery of suprathreshold olfactory function after OT, 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. These variables can further be used in counselling 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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Figure legends

Figure 1. Dendrogram from hierarchical cluster analysis of changes in olfactory subdimensions threshold, discrimination, and identification after olfactory training indicating that threshold belongs to a separate cluster compared to suprathreshold functions. The horizontal axis represents the rescaled distance cluster combine.

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