Individual importance of olfaction decreases with duration of smell loss*

David T. Liu[1], Gerold Besser[1], Bernhard Prem[1], Marlene M. Speth[2], Ahmad R. Sedaghat[3], and Christian A. Mueller[1]

[1] Department of Otorhinolaryngology, Head and Neck Surgery, Medical University of Vienna, Vienna, Austria

[2] Department of Otorhinolaryngology, Kantonsspital Aarau, Aarau, Switzerland

[3] Department of Otolaryngology - Head and Neck Surgery, University of Cincinnati College of Medicine, CI, United States of America

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Abstract

Background: The personal importance of a lost neurologic - motor or sensory - function in several conditions has been shown to decrease as the afflicted patient becomes accustomed to not having that function. It is unknown how the importance of olfaction changes with duration of olfactory dysfunction (OD). The aim of this study was to evaluate the association between duration of smell loss and individual significance of olfaction, and whether this relationship would be modulated by other factors, such as etiology of smell loss.

Methods: This is a retrospective study including a total 163 subjects with different degrees of olfactory function. Individual significance of olfaction was measured using the Importance of Olfaction Questionnaire (IOQ). Demographics, olfactory function, duration and etiology of OD were evaluated. Group comparisons, bivariate correlations, analyses of variance and multivariate linear regression were applied to detect differences and associations with the outcome measure of IOQ.

Results: A significant negative correlation was found between duration of OD and the IOQ. Other important findings include a significantly higher IOQ in patients with posttraumatic- compared to idiopathic OD and in patients with higher aggravation scores compared to the lower aggravation group. Multivariate regression analysis further confirmed that duration of smell loss was independently associated with IOQ.

Conclusions: The duration of smell loss is negatively correlated with the individual importance of olfaction, suggesting that patients develop coping mechanisms for adjusting to OD.

Key words: anosmia, hyposmia, smell loss, olfactory dysfunction, duration, importance of smell, patient reported outcome measure, prom, response shift, coping

Introduction

Olfaction plays a critical role in various aspects of daily life so olfactory dysfunction (OD) results in a significant loss of information, such as sensory stimulation and environmental cues [1–5]. The reasons for OD are diverse, including head injuries, viral infections, idiopathic reasons, and sinonasal or neurodegenerative disorders [1]. OD onset and course are diverse and can manifest in various forms that range from partial (hyposmia) to a complete loss of smell (anosmia) [1,6,7]. OD has a significant impact on quality of life (QoL) [8–12]. It is therefore not surprising that patients would even consider skull base surgery to restore their missing sense [13].

In comparison to olfactory-related QoL, which mainly focuses on the burden of patients suffering from OD, individual significance of olfaction represents the importance of olfaction in patients' daily lives [14–16]. The "The "Importance of Olfaction Questionnaire" (IOQ) questionnaire is a tool that has been developed to quantify the significance of olfaction for an individual [14]. Previous descriptive studies have demonstrated that olfaction is important in both normosmic and OD patients [14–16]. However, it has been shown that patients with OD report lower importance for olfaction compared to their normosmic counterparts [15,16].

Age and geographical location have also been found to be associated with variability in an individual's determined significance of olfaction [14–17]. However, the mechanisms for lower individual importance of olfaction in OD patients compared to normosmics remain unclear.

It is well described that after neurological injury leading to motor deficit (e.g., paralysis), affected patients' recalibrate their frame of reference for self-appraisal over time - i.e. the patient eventually redefines a new "normal" for him/herself to incorporate the functional impairment [18–21]. This phenomenon is referred to as response shift [18]. It is very possible that after an insult to olfaction, over time patients may adapt their outlook to become accepting and tolerant of OD - that it loses importance in day-to-day life. Understanding that such an adaptive/coping phenomenon could occur - and what factors may modulate it - in patients with OD would be of great clinical significance in counseling patients who may otherwise be distraught by an acute sensorineural olfactory loss. Thus, in this study, we sought to determine whether the individual significance of olfaction decreases with duration of OD and whether factors such as degree of olfactory function or etiology of the OD may modulate this relationship.

Materials and methods

Subjects

This retrospective study was carried out at the Department of Otorhinolaryngology, Head and Neck Surgery, Medical University of Vienna and approved by the ethics committee of the Medical University of Vienna (1479/2019). Subjects included in this study either presented at the Department of Otorhinolaryngology, Medical University of Vienna with the main complaint of quantitative OD or were recruited as healthy volunteers for a recent research project [22]. We evaluated all subjects that underwent thorough olfactory testing between 1/2017 and 11/2019 and included those that filled out the importance of smell questionnaire (IOQ) prior to testing as part of a routine pre-testing procedure. Questionnaires were collected in paper pencil style and managed by the corresponding author. Subjects were excluded if they did not report the IOQ. All subjects received standardized history, clinical examination including nasal endoscopy and olfactory testing [23]. Suspected underlying etiologies associated with OD were classified according to the recent "Position paper on olfactory dysfunction"[1] and noted together with the time since onset of OD (in months) in Table 1.

Table 1. Demographics and clinical characteristics.

	Demographics		
	Normosmics (n = 50)	OD (n = 113)	
Age, mean in years (SD)	31.1 (10)	45.6 (18.2)	
Gender (N)	26F, 24M	66F, 47M	
	Olfactory characteristics		
TDI, mean (SD)	34.5 (2.8)	19 (7)	
Dimensions, mean (SD)			
Threshold	7.1 (2.6)	2.9 (2.2)	
Discrimination	13.6 (1.8)	7.9 (2.8)	
Identification	13.9 (1.2)	8.3 (3.5)	
Olfactory function, N (%)			
Hyposmics	—	71 (63%)	
Anosmics	—	42 (37%)	
		Reason, N (%)	**Duration of OD in months, mean (SD)**
Posttraumatic		12 (10.6%)	12 (10)
Postinfectious		34 (30.1%)	20 (33)
Sinonasal		34 (30.1%)	48 (68)
Idiopathic		32 (28.3%)	65 (123)
Congenital		1 (0.9%)	—
	Importance of olfaction		
IOQ18, mean (SD)	35 (6.1)	33 (9.5)	
IOQ subscales, mean (SD)			
Association	13.4 (2.6)	11.4 (3.9)	
Consequence	10.4 (2.5)	10.4 (3.4)	
Application	11.2 (3)	11.2 (3.9)	
Aggravation score	—	2.1 (1.4)	

Olfactory testing

Olfactory performance was assessed by means of the Sniffin' Sticks test (Burghart Messtechnik, Wedel, Germany), which measures overall olfactory performance based on three subdimensions: Threshold (T), Discrimination (D), and Identification (I). Sniffin' Sticks are based on felt tip pens, impregnated with different odors of various concentrations [6,24]. The exact procedure (including detailed descriptions) is explained elsewhere [6,24].

In short, T was measured based on 16 pen triplets in a reverse staircase procedure using n-butanol as odorant. D was measured based on a three-alternative, forced-choice procedure also utilizing 16 pen triplets. I was measured using 16 pens impregnated with various odors (familiar to the German-speaking population; German version) based on a four-alternative, forced-choice procedure. Summed scores of TDI can be compared to large, normative datasets and olfactory performance can be classified into: (i) Normosmia (TDI ≥ 30.75), (ii) hyposmia (TDI < 30.75 and > 16), and (iii) functional anosmia (TDI ≤ 16) [25,26].

Importance of olfaction questionnaire (IOQ)

The primary outcome of interest was the individual significance of olfactory function that was assessed using the Importance of Olfaction Questionnaire (IOQ) developed by Croy et al. [14]. The

IOQ is a olfaction specific survey that consists of 20 items based on 4-point Likert-scale responses (ranging from 0="I totally disagree" to 3= "I totally agree"). Items of the IOQ are divided into four subscales: (i) Association (six questions reflecting unconscious processes that are triggered by the sense of smell), (ii) Application (six questions reflecting intentional use of olfaction in daily life activities), (iii) Consequence (six questions reflecting conclusions that are drawn based on olfactory perception), and (iv) Aggravation (two questions reflecting the tendency to overestimate the importance of smell loss). The 20-item IOQ (IOQ20) including all subscales was recommended for use in patients with OD (range 0-60; higher scores indicating higher importance of olfaction), whereas the 18-item IOQ (IOQ18) including only the Association, Application, and Consequence subscales was proposed for use in normosmic subjects (range 0-54) [14,27].
All included OD patients completed the IOQ20, while all included normosmic patients completed the IOQ18. Consistent with Croy et al. [14,15], we used summed scores of individual IOQ items to calculate IOQ total and subscale scores. Additionally, an Aggravation cut-off score of 2 was used to distinguish between high (≥2) and low aggravation (< 2) in our cohort of OD patients, as previously described [16].

Statistical analysis

Statistical analysis and data visualization were performed using SPSS 25.0 (Chicago, IL, USA) and GraphPad Prism 8.4.1 (GraphPad Software, Inc., La Jolla, CA, USA). Normality of data distributions was analyzed based on histograms and Q-Q plots. Unpaired Student's t-test were used to compare differences between the low and high aggravation groups. Multiple group comparisons were performed using one-way analysis of variance (ANOVA) followed by Tukey's post hoc tests. Bivariate correlations were performed based on Pearson's correlation coefficient, r. Univariate and multivariable linear regression was used to associate IOQ18 (as dependent variable) in OD patients with age, gender, duration of smell loss in months, etiology of OD, aggravation level and olfactory function as TDI in our cohort of patients with OD. P value < 0.05 was considered statistically significant.

Results

Demographics

The association between olfactory-related factors and the IOQ was analyzed in 163 adult subjects (age range: 18-83 years, mean age/standard deviation: 46/18, 92 women, 71 men). Etiology of smell loss in patients with OD (n=113) included 12 posttraumatic-, 34 postinfectious-, 34 sinonasal-, 32- idiopathic, and one congenital- related OD (Table 1). Out of the 34 patients with sinonasal OD, 9 had prior endoscopic sinus surgery and 4 had septorhinoplasty surgery. Although 203 patients with OD were initially evaluated, patients that did not fill out the IOQ were excluded from this study, resulting in a total of 90 patients being excluded from the analysis sample of 113 patients with smell loss.

Importance of olfaction in normosmics, hyposmics, and anosmics

We first sought to compare the importance of smell in patients with OD compared to normosmic patients. We began by stratifying OD patients as hyposmics (n = 71) and anosmics (n = 42), according to their objective olfactory test result, and comparing them to normosmics (n = 50). This analysis used the IOQ18 score since it included normosmics. One-way ANOVA revealed no significant difference in total IOQ18 score across normosmics, hyposmics, and anosmics [$F(2, 159) = 3.12$, $p = 0.42$]. However, we observed a large variation in IOQ18 scores in OD patients, which suggested some additional factors could serve to differentiate these patients from normosmics with respect to the importance of smell. We therefore hypothesized that the duration of OD could be a factor that impacts the importance of olfaction in patients with OD.

Duration of smell loss is negatively correlated with IOQ20 and subscales in patients with olfactory dysfunction

We next checked for correlation between individual significance of olfaction and time since onset of OD using Pearson's correlation. For this analysis, we used the IOQ20, as well as its subscales, since only OD patients were included. We excluded our one case of congenital anosmia from further analysis since this patient never had a sense of smell and therefore would never be able to assign "importance" to olfaction. Notably and as expected, importance of the sense of smell was non-existent, since this patient scored 0 on the IOQ20.
Bivariate correlation revealed a negative correlation between time since onset of impairment and overall IOQ20 ($r = -0.48$, $p < 0.001$, Figure 1). We next checked for correlations between time since onset of OD and the four subscales of the IOQ20: Association (which reflects unconscious processes that are triggered by the sense of smell), Consequence (which reflects conclusions that are drawn based on olfactory perception), Application (which reflects the intentional use of olfaction in daily life activities), and Aggravation (which reflects the tendency to overestimate the impact of olfactory loss). In subscale analysis Application showed the highest negative correlation ($r = -0.42$, $p < 0.001$), followed by Consequence ($r = -0.39$, $p < 0.001$), Association ($r = -0.36$, $p < 0.001$), and Aggravation ($r = -0.27$, $p = 0.004$). Hence, IOQ20 and its subscale scores decrease with longer duration of OD.

IOQ20 and subscales differ significantly between various etiologies of olfactory dysfunction

We were next interested in determining whether differences in

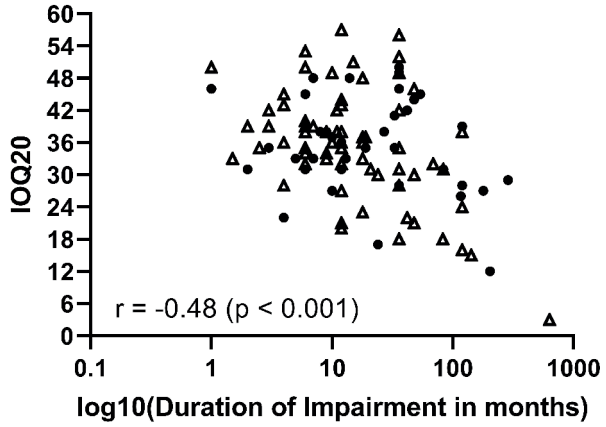

Figure 1. Scattergram depicting the correlation between duration of smell loss and the overall IOQ20 scores. The y-axis represents the score range. The x-axis represents the log10-transformed duration of smell loss in month. *Triangles represent hyposmic patients. Black points represent anosmic patients.

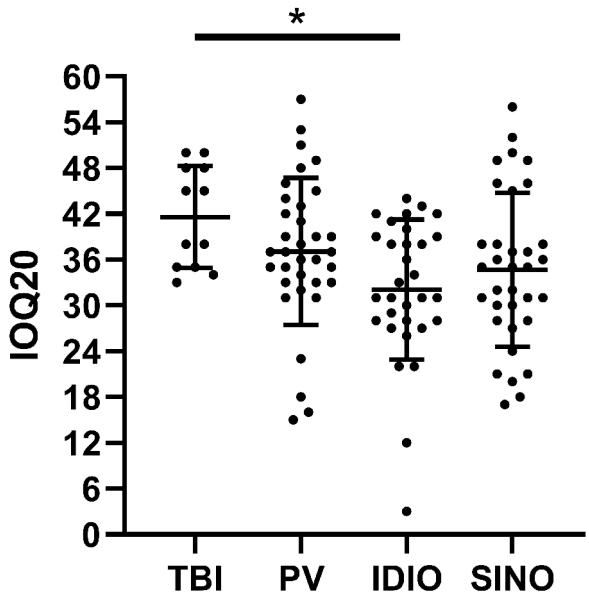

Figure 2. Scattergram (mean ± SD) of overall IOQ20 scores by different etiologies of smell loss groups between. *P < 0.05. Abbreviations: TBI = Traumatic brain injury, PV = Postinfectious, IDIO = Idiopathic, SINO = OD secondary to sinonasal diseases.

IOQ20 may arise based on different causes of OD. We therefore analyzed differences in IOQ20 total and subscale scores based on the etiology of smell loss using ANOVA with post-hoc Tukey's multiple comparisons test. One-way ANOVA revealed significant differences in total IOQ20 score [(F(3, 108) = 3.99, p = 0.009] for different OD-etiology groups (Figure 2). Tukey's post-hoc comparison tests revealed that patients with posttraumatic OD experienced significantly higher IOQ20 (p = 0.010) compared to the idiopathic group.

We next looked at differences in the four subscale scores across different etiologies of smell loss using one-way ANOVA. We found significant differences in the Association subscale score for different etiologies [F(3, 108) = 3.706, p = 0.014]. Tukey's post hoc testing revealed significantly higher Association scores in the posttraumatic group compared to the postinfectious (p = 0.048), idiopathic (p = 0.001), and OD secondary to sinonasal disease groups (p = 0.035). In comparison, while one-way ANOVA tests revealed differences in Application [F(3, 108) = 2.95, p = 0.036] and Consequence scores [F(3,108) = 2.88, p = 0.040] between different etiologies of smell loss, post-hoc tests did not reach statistical significance. Contrariwise, one-way ANOVA revealed no differences in Aggravation scores between different etiology groups [F(3, 108) = 0.99, p = 0.397].

Significant differences in IOQ18 and subscales between high and low aggravation patient groups

The Aggravation subscale score may serve as an internal, patient-specific barometer for the tendency to overestimate the significance of smell loss in OD patients. We therefore sought to determine whether the IOQ18 (consisting of the Association, Application, and Consequence subscales) would be related to the Aggravation subscale. For that reason, we assessed differences in total IOQ18 and its subscales in patients stratified as having high (≥2) vs. low (< 2) Aggravation subscale scores (Figure 3) [16].

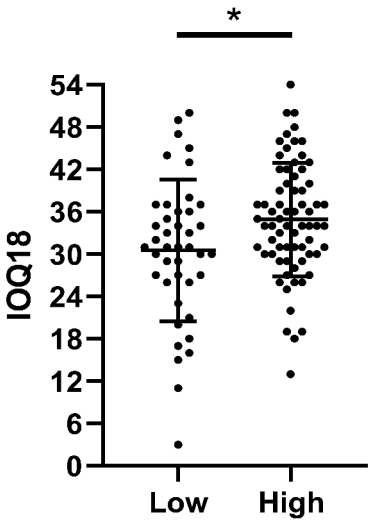

Figure 3. Scattergram (mean ± SD) of overall IOQ18 by high and low aggravation groups of patients with smell loss. * P < 0.05. Abbreviations: Low = Low aggravation group, High = high aggravation group.

We found a significantly higher total IOQ18 (p = 0.010) in the high aggravation group (mean = 34.9, SD = 8.1) compared to the low aggravation group (mean = 30.6, SD = 10). Similarly, there were significantly higher Association subscale scores (p =

Table 2. Associations with IOQ18 score.

	Univariate analysis		Multivariable analysis	
	β (95% CI)	P value	β (95% CI)	P value
Duration of smell loss (months)	-0.47 (-0.63 - 0.30)	<0.001	-0.38 (-0.56 - -0.20)	<0.001
Etiology of smell loss				
Postinfectious	Reference	—	Reference	—
Posttraumatic	0.23 (0.05 - 0.42)	0.013	0.14 (-0.05 - 0.33)	0.136
Sinonasal disease	-0.08 (-0.27- 0.11)	0.415	-0.13 (-0.36 - -0.09)	0.238
Idiopathic	-0.22 (-0.41 - -0.04)	0.018	-0.14 (-0.35 - -0.06)	0.176
TDI	0.02 (-0.17 - 0.21)	0.815	0.03 (-0.17 - 0.23)	0.775
Age	0.02 (-0.17 - 0.21)	0.843	0.007 (-0.18 – 0.19)	0.938
Gender				
Female	Reference	—	Reference	—
Male	-0.05 (-0.24 - 0.13)	0.591	-0.06 (-0.23 – 0.11)	0.496
Aggravation				
Low	Reference	—	Reference	—
High	0.23 (0.05-0.42)	0.013	0.14 (-0.03 – 0.32)	0.112

β = Linear regression coefficient (standardized).

0.010) in the high aggravation (mean = 12.2, SD = 3.5) compared to the low aggravation group (mean = 10.4, SD = 4). Likewise, there were significantly higher Application subscale scores (p = 0.040) in the high (mean = 11.8, SD = 3.4) compared to the low aggravation group (mean = 10.3, SD = 4.2). Contrariwise, there was no significant difference (p = 0.090) in the Consequence subscale score between the high (mean = 10.9, SD = 3.2) and low aggravation groups (mean = 9.9, SD = 3.4).

Duration of olfactory dysfunction is independently associated with the individual significance of olfaction

Because we identified duration of OD, etiology of OD and "aggravation" as factors that could impact individual significance of olfaction, we checked for formal association between IOQ18 score (as dependent variable), and duration of OD, etiology of OD, and aggravation level as independent variables, while also controlling for objective olfactory function as TDI score, gender, and age using linear regression.

On univariate regression we first found that IOQ18 was associated with duration of OD (β = -0.47, p < 0.001), etiology of OD as posttraumatic (β = 0.23, p = 0.013) and idiopathic (β = -0.22, p = 0.002) compared to postinfectious OD, and high aggravation (β = 0.23, p = 0.013) compared to the low aggravation group.

On multivariable linear regression we found that duration of OD (β = -0.38, p < 0.001) was independently associated with lower IOQ18 scores (Table 2).

Discussion

Although studies dedicated to assessing the individual significance of olfaction have demonstrated differences between health and disease, there is a gap of knowledge with respect to the mechanisms for these differences [14–16]. This is not surprising, considering that the olfactory system still remains a "neglected sense" [1,28,29], which is also reflected in the number of studies conducted compared to other sensory organs [30]. Moreover, the improvable management and counselling of patients with OD prior to their presentation at Smell and Taste clinics also demonstrates the need to raise awareness and literacy among the medical profession for the sense of smell [28,31]. While smell loss is a common condition [1,32–36], the importance of OD to patients - and therefore its functional impact on the affected individual - may vary. Previous studies of other neurological deficits have found that factors such as passing time since the incidence of the deficit may be associated with less importance of the neurological deficit to the patient [18–21]. In this study, we showed that longer duration since development of OD was associated with less importance of the sense of smell to the affected patients, while controlling for demographics and OD-related variables such as reason for smell loss.

The role of olfactory performance on the individual significance of olfaction has been described previously in detail [15,16]. In those studies, the authors reported significant lower overall IOQ and subscale scores for anosmics, compared to hyposmics, and normosmics. In our analyses, we did not identify such a relationship and instead found a wide variation in the IOQ scores of hypos-

mics and anosmics. Indeed, we also did not find any significant association between objective olfactory function measured with Sniffin' Sticks and IOQ18. These results suggest that the influence of olfactory performance on the individual significance might have been overestimated, at least in general applicability. Instead, we hypothesized that the variation of IOQ scores in hyspomics and anosmics may be the result of other factors such as duration and etiology of the OD, which we did indeed find to be the case.

In reference to the importance of smell and duration of OD, subscale analysis revealed that the Application and Consequence subscales demonstrated stronger negative correlations with duration of OD compared to the Association and Aggravation subscales. Our results suggest that adjustments regarding daily use and decision making in affected individuals might be more related to time since OD - and likely, coping/adjustment by the patient - compared to adjustments to olfactory-triggered emotions or frustration that one may feel due to OD. It is yet unclear the time frame over which such coping processes may take although our data suggest a duration on the scale of several years. One theoretical framework for changes in patient reported outcomes measurements over time, such as the IOQ, is represented by the "response shift" theory, which has gained popularity in recent years. Response shift refers to changes in patient-reported outcome measures (PROMs) over time, which are due to changes in internal frameworks and reconceptualization, in order to cope better with new circumstances (such as smell loss) rather than external factors such as treatment [19,37,38]. One explanation for higher importance of olfaction in posttraumatic OD compared to idiopathic reasons might be related to the disease onset of these causes. Posttraumatic OD is usually categorized as a "sudden" cause for OD, with patients noticing the loss of smell and seeking professional medical help immediately. Similarly, postinfectious OD is also categorized as "sudden" reason, since patients also notice their loss of smell after experiencing an acute infection to the upper respiratory tract. Noteworthy, a recent analysis of seasonal variations in patients visiting a specialized Smell and Taste clinic revealed peaks in March. However, these were not attributable to postinfectious causes [39]. In comparison, smell loss associated with neurodegenerative or inflammatory sinonasal diseases and OD attributed to idiopathic causes are categorized as "gradual" or "progressive" smell loss. Impairments to the sense of smell usually go unnoticed in these patients, since they usually "miss" the onset of impairment. Therefore, differences in time to seek medical help and resulting shifts in internal frameworks regarding to the importance of olfaction might also serve as an explanatory variable for higher individual significance in "sudden" etiologies [1].

Another important result emerged from our subgroup analysis of patients with OD grouped into those with high and low OD-associated aggravation. Our analyses revealed higher overall IOQ score, and Association and Application subscale scores in patients from the high aggravation group. Consistent with our results, two previous studies on patients with OD also demonstrated significantly higher overall IOQ and subscale scores in high aggravation patients [15,16]. Interestingly, higher aggravation scores have also been linked to higher scores on depression-related PROMs [15]. The authors reasonably suggested that the Aggravation score might also be useful in clinical routine to identify patients that might need further professional help to cope with their smell loss [15]. Since the Aggravation subscale only consists of 2-items, it can be analyzed quickly (for example, in context of routine clinical practice) and allow for grouping of patients into low and high aggravation groups, which may also improve patient-centered care strategies.

Considering the clinical relevance of this study, our results might be implemented easily into daily practice. More awareness needs to be raised for the question regarding onset of smell loss. The consideration of a low individual significance of olfaction in cases of long-term olfactory loss is crucial, since olfactory training has become the first-line treatment option for various aetiologies of smell loss [1,40,41]. This training protocol is usually recommended for at least four to six months (twice on a daily base), which makes patients therapy adherence and compliance crucial [41,42]. Therefore, motivating patients to take part in the treatment and taking a more active interest in their own health might lead to better treatment outcomes, which suggests that capturing OD patients early after onset of OD may be quite important.

The present study uses a large and comprehensive dataset of patients with OD to study the effect of OD-related variables on the individual significance of olfaction. However, this study also has limitations. First, this was a retrospective study which has all of limitations inherent to that study design. To minimize selection bias, we aimed to include all subjects that filled out the IOQ prior to olfactory testing, independent from the disease status. Additionally, and more specifically, this was a cross-sectional study while a longitudinal study would more directly capture the shift in the importance of olfaction over time in OD patients. Notably, patients with posttraumatic OD may also be unaware of their olfactory impairment, possibly due to cognitive dysfunction, hence generalizations for different etiologies based on the acuity of OD must be made very cautiously [43,44]. Our results are nevertheless necessary to serve as motivation for pursuing such longitudinal study in the future.

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Conclusion

This study adds to the current literature on patients with smell loss showing that duration of OD is negatively correlated with individual importance of olfaction. This finding suggests that patients develop coping mechanisms for adjusting to 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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Christian Albert Mueller MD
Department of Otorhinolaryngology
Head and Neck Surgery
Medical University of Vienna
Vienna General Hospital (AKH)
A-1090 Vienna
Austria

Tel: +43 1 40400 33340
Fax: +43 1 40400 33320
E-mail:
christian.a.mueller@meduniwien.ac.at