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Association Between Orthonasal Olfaction and Chemosensory Perception in Patients With Smell Loss

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Objectives: Self-ratings seem to be the most effortless strategy for assessment of patients' chemical senses. Notably, although flavor perception strongly relies on olfaction, the relationship between self-reported flavor perception and orthonasal olfactory tests have hitherto not been considered. The aim of this study was to investigate the relationship between self-perceived olfactory function (SO), taste (ST), and flavor perception (SF) and smell test results in patients with olfactory dysfunction (OD).

Methods: We included 203 patients with quantitative OD. Group comparison, bivariate correlation, and ordinal logistic regression were employed to quantify the relationships between predictor variables (age, gender, reason for OD, and orthonasal olfaction—summed scores of threshold, discrimination, and identification [TDI]) and outcomes of SO and SF ("impaired," "average," or "good").

Results: Group comparison revealed significant differences between SO and SF ($P < .001$). Stronger correlations were found between SO and TDI (r = 0.64), compared to SF and TDI (r = 0.27). No relevant correlation was found between ST and TDI (r = 0.10). Higher TDI was associated with odds of higher SO in univariate (odds ratio = 1.25) and multivariable analyses (adjusted odds ratio = 1.23), and both models showed good fit of data. Conversely, regression models on the associations between TDI and changes in SF did not meet the assumption of goodness of fit.

Conclusion: We found that higher orthonasal olfactory performance was associated with odds of higher SO in patients with OD, even after controlling for olfactory-relevant factors. To the contrary, similar models based on flavor perception failed to describe these relationships. This indicates for SF and ST to be less represented by the TDI compared to SO.

Key Words: chemical senses, smell, taste, flavor, olfaction, anosmia, hyposmia.

Level of Evidence: 4

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INTRODUCTION

Reduced olfactory performance is a major complaint in patients with olfactory dysfunction (OD) and can significantly impact quality of life, especially in areas related to food intake.[1] This is not surprising considering that our sense of smell identifies odorants via the nostrils (orthonasal olfaction) and through the pharynx (retronasal olfaction). The latter odor pathway is believed to contribute a major share to our multisensory flavor system.[2,3] Major advancements in the knowledge of olfactory rehabilitation and new treatment options have been made in the last decades, hence counseling gained significant importance for patients with OD.[4–6] During recording of medical history, it seems obvious that asking for the sense of smell would be the easiest and most effortless way of evaluation; however, studies have demonstrated differences between measured and self-perceived olfactory function and thus olfactory testing has become an almost indispensable means of determining olfactory performance.[7,8] Conversely, when it comes to impaired flavor perception in these patients, literature remains sparse on possible associations with measured orthonasal olfactory performance or demographical factors.[9] Elucidating these, however, is urgently anticipated by physicians in order to acquire a better understanding of the patient's perspective and consequently improve patient counseling.

Medical history taking usually represents the first step in a physician–patient interaction. For patients with OD, obtaining a detailed history, especially one that includes relevant information about gustatory and flavor perception, is crucial for diagnosis and further treatment.[10] Furthermore, because demographic variables such as age and gender have also been associated with olfaction, these factors must also be considered.[11,12] Due to the mostly unknown role of the sense of smell in the general population as the prominent determinant of flavor perception, physicians are often faced with the smell and taste confusion.[13] Patients with OD regularly complain about their sense of taste during eating and drinking ("I have lost my sense of taste, my food tastes dull") when in fact they mean their sense of smell.[14,15] Consequently, specifying questions about self-assessment of the chemical senses (e.g., "basic sense of taste, such as sweet and sour") also represents an integral part during history taking.[13]

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In clinical routine, it is recommended to measure olfactory function based on validated test methods.[10,16] One of these tests is represented by Sniffin' Sticks (Burghart Medical Technology, Wedel, Germany), which measure orthonasal olfactory function based on three subdimensions: threshold (T), discrimination (D), and identification (I).[17,18] Large normative datasets allow to distinguish between normal olfactory function (normosmia), reduced olfactory function (hyposmia), and loss of olfactory function (anosmia) based on overall subdimension scores (TDI).[19,20]

The aim of this study was to depict the associations between self-reported chemosensory function (smell, taste, and flavor perception) and orthonasal olfactory test results in a cohort of patients with OD. Both self-perceived and objective test results were used as predictor and criterion variables, and computed models were subsequently adjusted for olfactory-related factors.

MATERIAL AND METHODS

The study was conducted according to the Declaration of Helsinki on biomedical research involving human subjects and was approved by the ethics committee of the Medical University of Vienna (EK-Nr.: 1479/2019). Olfactory test results were analyzed from 203 patients (111 female, 92 male, range 14.2–86.6 years, mean ± standard deviation [SD]: 54.2 ± 16.6) presenting at the Department of Otorhinolaryngology, Head and Neck Surgery of the Medical University of Vienna (Vienna, Austria) between January 2017 and November 2019 with the symptom of smell loss and Sniffin' Sticks (Burghart Medical Technology) (TDI) score below 31.[19,20] All patients were referred from general practitioners, otolaryngologists, or neurologists and underwent structured anamnesis, nasal endoscopy, and imaging (magnetic resonance or computed tomography) whenever applicable.[10] Additionally, patients were asked for potential causes for their OD and assigned to six different groups according to the etiology of smell loss.[16] Part of these patients were included in previously published studies by our working group.[21,22]

Questionnaires

Self-reported of chemosensory function smell (SO), taste (ST), and flavor perception (SF) was assessed prior to olfactory tests using three numeric scales ranging from 1 to 10 (left-hand end, 1 = no perception; right- hand end, 10 = perfect perception). These scales were further explained as follows: Self-assessment of olfactory function ("How would you rate your sense of smell?"), self-assessment of taste ("How would you rate your basic taste, e.g. sweet, sour, salty, and bitter?"), and self-assessment of flavor perception ("How would you rate your flavor perception, e.g., herbs and wine?").

Sniffin' Sticks Test

Olfactory function was evaluated using the Sniffin' Sticks test (Burghart Medical Technology), which combines T, D, and I in a multi-dimensional approach to olfactory testing. The Sniffin' Sticks (Burghart Medical Technology) test consists of marker-like pens containing various odors that are placed 2 cm beneath both nostrils. The testing procedure is described in detail elsewhere.[17,18] Large reference datasets are available, allowing olfactory diagnosis based on points achieved: Normosmia was defined as TDI ≥ 31, hyposmia as TDI > 16 and < 31, and functional anosmia as TDI ≤ 16 points.[18,20,23]

Statistical Analysis

Patient characteristics, objective test scores, and self-assessment of chemosensory function were described as mean ± SD. Normality of data was first assessed using graphical visualization followed by Kolmogorov–Smirnov normality test with P value set at .05. To determine correlation coefficients between self-assessment of chemosensory perception smell, taste, and flavor with objective olfactory tests, scatter plots were first visualized, followed by the calculation of Spearman correlation coefficient. We interpreted coefficients (r_s) < 0.4 as weak, 0.4–0.7 as moderate, and > 0.7 as strong.[24]

Because self-reported sense of smell and flavor perception are ordered categories, we used ordered logistic regression to model the relationship between olfactory performance and self-perceived chemosensory perception. We estimated separate models for SO and SF and transformed answers into three discrete and hierarchical categories: 1–3 = "impaired," 4–6 = "average," and 7–10 = "good." The primary explanatory variable was orthonasal olfactory function, measured as TDI. We also included age, gender, and reason for olfactory loss

Table I.
Descriptive Characteristics of All Patients Included.

Patients With Olfactory Dysfunction (n = 203)		
Age	54.2 ± 16.6	
Gender	111 f (54.7%)	92 m (45.3%)
Sniffin' Sticks test (TDI)		
TDI	18.3 ± 6.8	
Threshold	2.8 ± 2.3	
Discrimination	8.0 ± 2.8	
Identification	7.6 ± 3.5	
Anosmic	87 (42.9%)	
Hyposmic	116 (57.1%)	
Self-assessment of chemosensory function		
Smell	2.6 ± 1.8	
Taste	4.8 ± 3.0	
Flavor	4.1 ± 2.8	
Reason for olfactory dysfunction		
Posttraumatic	32 (15.7%)	
Postinfectious	68 (33.5%)	
Sinonasal	37 (18.2%)	
Idiopathic	59 (29.1%)	
Neurodegenerative	4 (2.0%)	
Congenital	3 (1.5%)	

Variables are presented as mean ± standard deviation or n (%).
f = female; m = male; TDI = Sniffin' Sticks test score (sum of T, D, and I: threshold, discrimination, identification).

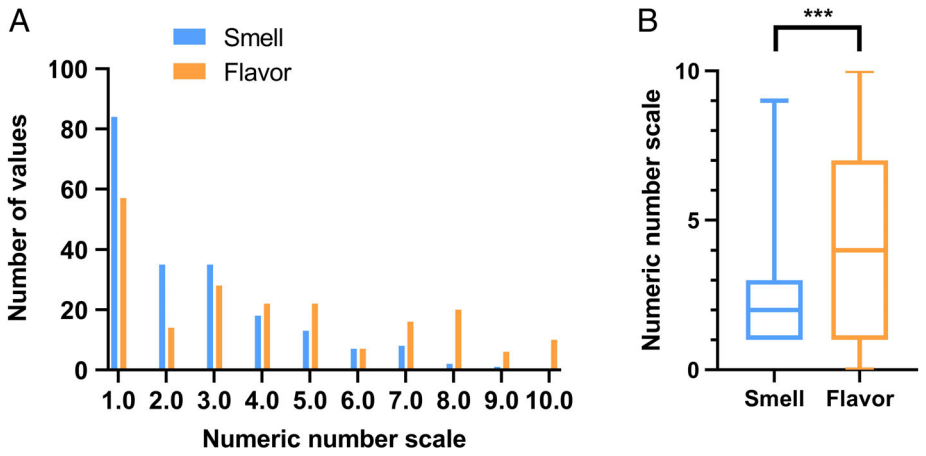

Fig. 1. Differences between self-assessment of olfactory performance and flavor perception in patients with OD. (A) Histogram of self-assessment scores in patients with OD. (B) Comparison between self-assessment of olfactory performance and flavor perception. Flavor: self-assessment of flavor perception; smell: self-assessment of olfactory performance. ***$P < .001$, Mann–Whitney U test. OD = olfactory dysfunction. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

(posttraumatic, postinfectious, sinonasal, idiopathic) as coviariates in order to reduce the uncertainty of potential confounders. Concerning reason for olfactory loss, we opted to exclude patients from the "congenital" (n = 3) and "idiopathic" (n = 4) groups from subsequent analysis due to insufficient group size. A test of proportional odds for all models was calculated to ensure assumptions to be met. The overall goodness of fit was assessed using Pulkstenis–Robinson modified chi-squared test (modified Pearson χ^2), with $P < .05$ indicating no goodness of fit.[25]

Finally, a receiver operating characteristic (ROC) curve was constructed. Diagnostic accuracy for the numeric self-assessment of olfactory function scale to discriminate between anosmia and hyposmia was calculated as area under the receiver operating characteristic curve (AUROC). Optimal cutoff score was then assessed using the Youden index, which maximizes diagnostic accuracy giving equivalent weight on sensitivity and specificity. Data were analyzed and visualized using the "foreign," "MASS," and "effects" package in R 3.5.1 (R Development Core Team, 2008; R Foundation for Statistical Computing, Vienna, Austria) and GraphPad Prism 8.4.1 (GraphPad Software, Inc., La Jolla, CA).

RESULTS

Significant Difference Between Self-Reported Olfactory Function and Flavor Perception in Patients With OD

Patient demographics and characteristics are detailed in Table I. To determine the differences between SO and SF in patients with OD, we performed group comparisons using the Mann–Whitney U test. Analysis revealed SO to be significantly lower compared to SF ($P < .001$) (Fig. 1A and B).

Hence, it seems that SO is substantially lower than SF in patients with OD. In a next step, we performed bivariate analysis to determine the correlation between SO, ST, and SF with TDI.

Table II.
Bivariate Correlation Between Self-Assessment of Chemosensory Function Smell, Taste, and Flavor Perception with the Sniffin' Sticks TDI and Its Subscores in Patients With OD.

		TDI	T	D	I
SO	r_s	0.64	0.54	0.47	0.56
	95% CI	0.55–0.72	0.43–0.63	0.35–0.57	0.45–0.64
	P	< .0001	< .0001	< .0001	< .0001
ST	r_s	0.10	0.07	0.02	0.12
	95% CI	–0.05 to 0.23	–0.08 to 0.21	–0.12 to 0.17	0.02–0.26
	P	0.17	0.34	0.72	0.09
SF	r_s	0.27	0.27	0.2	0.2
	95% CI	0.13–0.39	0.14–0.4	0.06–0.33	0.06–0.33
	P	.0001	< .0001	.005	.004

CI = confidence interval; D = discrimination, I = identification; OD = olfactory dysfunction; SF = self-assessment of flavor perception; SO = self-assessment of olfactory performance; ST = self-assessment of taste; T = threshold; TDI = Sniffin' Sticks test score.

Table III.
Factors Associated With Changes in Self-Assessment of Olfactory Function in Patients With OD.

	Model 1			Model 2		
Variables (Reference)	OR	95% CI	*P* Value	aOR	95% CI	*P* Value
TDI	1.25	1.17 to 1.35	<.001	1.23	1.15–1.33	< .001
Gender (male)				0.58	0.26–1.24	.16
Age				1.0	0.97–1.03	.97
Reason for OD (posttraumatic)						
Postinfectious				1.61	0.40–8.31	.53
Idiopathic				1.83	0.42–10.01	.44
Sinonasal				2.92	0.68–15.68	.17

Multivariate analysis was performed using ordered logistic regression models, adjusted for gender, age, olfactory function (TDI), and reason for OD.

aOR = adjusted odds ratio; CI = confidence interval; OD = olfactory dysfunction; OR = odds ratio; TDI = Sniffin' Sticks test score (sum of T, D, and I: threshold, discrimination, identification).

Modified Pearson χ^2: model 1, *P* = .14; model 2, *P* = .15.

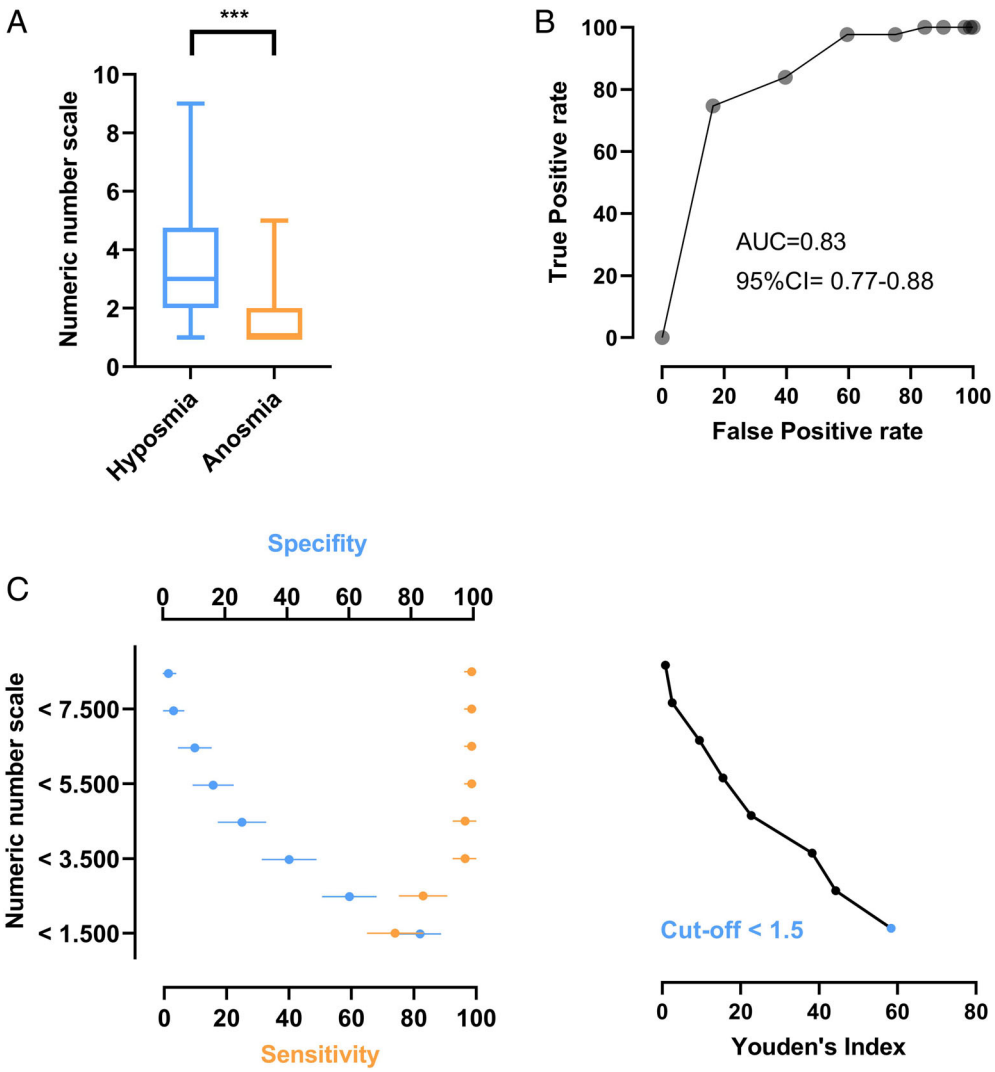

Fig. 2. Diagnostic accuracy of the self-assessment of olfactory performance scale in patients with olfactory dysfunction. (A) Comparison of self-assessment of olfactory performance scores in patients divided into hyposmics and anosmics according to TDI test scores. (B) Area under the receiver operating curve for discrimination between hyposmics and anosmics using the self-assessment of olfactory performance scale. (C) Sensitivity and specificity for different cutoff scores (respective percentage and 95% CI). The optimal cutoff score is indicated by the blue plot on the right. ***P < .001, Mann–Whitney U test. AUC = area under the curve; CI = confidence interval; TDI = Sniffin' Sticks test score (sum of T, D, and I: threshold, discrimination, identification). [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

Low Correlation Between Self-Reported Flavor Perception and Olfactory Test Results in Patients With OD

To assess correlations between SO, ST, and SF with TDI, we performed bivariate correlation analysis in patients with OD.

The detailed results are shown in Table II. SF was weakly correlated with TDI (r_{203} = 0.27, P < .001) and its subscores (r_{203} for T = 0.27, D = 0.20, I = 0.20, all P < .001). Moderate correlation was found between SO and TDI (r_{203} = 0.64, P < .001) and its subscores (r_{203} for T = 0.54, D = 0.47, I = 0.56, all P < .001).

Because SO not only differed from SF but also correlated moderately with a well-established test for overall OF (TDI) in patients with OD, it also seemed interesting to assess these associations in a multivariate regression model.

Higher TDI Is Associated With Odds of Higher Self-Perceived Sense of Smell

To determine which olfactory-related variables (TDI, age, gender, reason for OD) were associated with changes in SO and SF (hierarchical categories of "impaired," "average," and "good"), ordered logistic regression models were computed.

The first model (unadjusted) revealed a significant association between TDI and SO with an odds ratio (OR) of 1.25 (95% confidential interval [CI]: 1.17–1.35). After including "olfactory-related" variables age, gender, and reason for OD (postinfectious, posttraumatic, idiopathic, and sinonasal) into the second model, TDI still remained the only independent factor associated with higher odds of SO with an adjusted odds ratio of 1.23 (95% CI: 1.15–1.33). Modified Pearson χ^2 confirmed that both models were appropriate and fit the data well (Table III) (both P > 0.05). Contrariwise, ordered logistic regression analysis revealed both SF models not to be appropriate and fit the data (both P < .001).

Hence, TDI seemed to be only associated with odds of higher SO in our cohort of patients with OD. In the next step, we assessed the diagnostic accuracy of SO (as predictor) to discriminate between hyposmic and anosmic patients.

SO Cutoff Score to Discriminate Between Anosmia and Hyposmia

In the last step, patients with OD were classified into hyposmic (reduced olfactory function) and anosmic (loss of olfactory function) according to the score achieved in the Sniffin' Sticks test (TDI). Differences in SO and SF between both groups were calculated based on Mann–Whitney-U test. To evaluate the potential of SO to discriminate between hyposmics and anosmics, a ROC curve was first computed following the calculation of the AUROC. The optimal cutoff score was determined using the Youden index, giving equal importance to sensitivity and specificity.

SO was significantly lower in anosmic compared to hyposmic patients (P < .001) (Fig. 2A). The AUROC of 0.83 (95% CI: 0.77–0.88) (Fig. 2B) reflected good diagnostic accuracy to identify patients with anosmia. Subsequently, optimal cutoff score was determined as < 1.5 (sensitivity: 0.75, specificity: 0.84) using the Youden index (Fig. 2C).

DISCUSSION

Medical history taking usually represents the first step in a physician–patient interaction. Considering the possible causes of OD (e.g., sinonasal diseases, head traumas, and upper airway infections), obtaining relevant information from anamnesis and asking patients for self-reported chemosensory function remains a cornerstone in treatment and counseling of patients with chemosensory disorders. In the present work, we compared SO, ST, and SF with olfactory test results and found a significant difference between self-assessment of smell and flavor perception in our group of patients with OD. Furthermore, we demonstrated a weak correlation between SF and TDI, whereas a moderate correlation was found between SO and TDI. In multivariate analysis, higher TDI was associated with odds of higher SO. However, applying a similar model on flavor perception failed to describe the association between self-reported and olfactory test results.

The uniqueness of the sense of smell lies in its dual-representation pathway, including orthonasal smell (defined as odor molecules travelling via the nose) and retronasal smell (i.e., odor molecules reaching the olfactory epithelium via the nasopharynx).[13] It has been proposed that all human senses contribute to our multisensory flavor system, including visual, auditory, somatosensory, gustatory, olfactory, and autonomic perception. Of these, the human sense of smell (particularly retronasal smell) has since been identified as the major contributor.[2,26] Understandably, it is commonly assumed that flavor perception should be affected in addition to the sense of smell in patients presenting with quantitative olfactory dysfunction.[12,27] Previous studies on brain imaging and olfaction have suggested that the human brain responds differentially to single-modal taste and smell stimulation compared to a combined, bimodal taste, and smell (retronasal) approach. The latter additionally activates areas that would not be identified through simple addition of the taste and smell pathway alone.[28,29] Thus, one explanation that SO and SF can differ significantly leans on the residual olfactory function, which might enhance central activation during retronasal perception even in OD. This difference may provide a new reference point from which to consider neuroimaging studies in patients with OD but subjectively normal flavor perception.

As intimated above, the Sniffin' Sticks test (Burghart Medical Technology) was used to assess orthonasal olfactory function in the present study. Although ortho- and retronasal olfactory function are both processed at the same entity (i.e., olfactory bulbus), it has been reported that patients with smell loss periodically report about intact flavor perception.[9,30] Landis et al. demonstrated that patients of this subgroup with OD due to nasal polyps showed better retronasal than orthonasal olfactory function.[31] It was argued that these differences were likely due to the mechanical obstruction (nasal polyps) of the anterior olfactory cleft. Complementary to these findings, a previous

study of our working group demonstrated that patients of this subgroup with nonsinonasal smell loss also showed severe retronasal dysfunction.[9] However, testing of retronasal olfactory function is often not feasible due to time constrains in clinical practice, which likewise resulted in the lack of retronasal test results available for the current investigation. The paucity of literature on this topic again underlines the need for routine clinical examination of retronasal olfactory function based on validated and labor efficient methods.[21]

Regarding the moderate correlation between SO and TDI, this was commensurate with previous self-rating and objective test results in patients with OD.[8,22,32,33] Two studies found a moderate correlation between SO (assessed using visual analogue scales) and TDI in a predominantly anosmic group of patients presenting with olfactory complains.[8,33] Similarly, Kollndorfer et al. found a weak correlation between SO (9-point scales) and TDI scores in patients diagnosed with anosmia, whereas no relevant correlation was found in hyposmic patients.[32] Notable, one previous study on self-ratings (5-point rating scales) and olfactory test scores (using the 12-item identification screening test[34]) showed that approximately one-third of patients were unaware of their severe olfactory dysfunction. The heterogeneity in aforementioned measuring methods for self-reported olfactory performance highlights the need for consensus guidelines (frameworks) in chemosensory research to make results more comparable.

Another important result emerged from multivariate analysis on associations between SO and TDI, including demographic variables and causes of OD. Because previous studies on olfactory performance and self-assessment of olfaction have focused on bivariate correlations mostly,[8,22,32,33] our results expand these findings showing that SO and TDI also remain significantly associated after adjusting for possible confounding variables such as age and gender. Contrariwise, crude and adjusted ordered logistic-regression models, including SF and TDI, showed significant associations between SF and TDI. However, goodness-of-fit tests indicated that both models do not fit the data well. Taking into consideration that flavor perception is constituted by almost all of the senses, it is tempting to speculate that other sensory modalities partly undertake the previous task of olfaction in patients after olfactory loss, which might result in striking differences between SO and SF.[3]

On account of the smell and taste confusion, patients with OD regularly complain about their sense of taste during eating and drinking ("I have lost my sense of taste, my food tastes dull") when in fact they mean their sense of smell.[13,14] Consequently, specifying questions about self-assessment of the chemical senses (e.g., "basic sense of taste, such as sweet, sour, bitter and salty") should represent an integral part during the anamnesis. Because we asked specifically for basic taste perception, we did not expect ST to show any relevant correlation with TDI in patients with OD, which our results confirmed. The present findings again highlight the need for structured anamnesis when treating patients with OD.[10]

Interestingly, the SO scale showed good diagnostic accuracy in our cohort of patients with OD. When it comes to an applicable cutoff score, this was found to be < 1.5 on the numeric number scale. It is attractive to speculate that this cutoff score might be due to the awareness of functional anosmic patients about their olfactory impairment, thus marking the lowest number possible. Nevertheless, because we retrospectively calculated the diagnostic accuracy in a preselected cohort of patients with self-reported and objective smell loss, further work will be required to underpin the usefulness of these scales for different healthcare facilities and providers (e.g., primary, secondary, and tertiary care). This notwithstanding, it should be noted that the presented cutoff score should not be used alone in clinical routine and that validated olfactory test methods remain indispensable on an individual level.[7]

CONCLUSION

Taken together, this study contributes to the understanding of self-perceived chemosensory function and measured orthonasal olfactory function in patients with different causes of OD. Our results are commensurate with previous literature showing a moderate correlation between self-perceived and measured olfactory function. Findings also suggest that demographic variables and causes of OD do not influence SO in these patients to a large extent. We found that higher orthonasal olfactory performance was associated with odds of higher SO, even after controlling for olfactory-relevant factors. However, implementation of similar models for flavor perception failed to describe the relationship between subjective and orthonasal olfactory test results. Our results underline the importance to differentiate between smell, taste, and flavor perception during counseling of patients with smell loss.

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