Orthonasal and retronasal olfactory function in olfactory cleft obstructions

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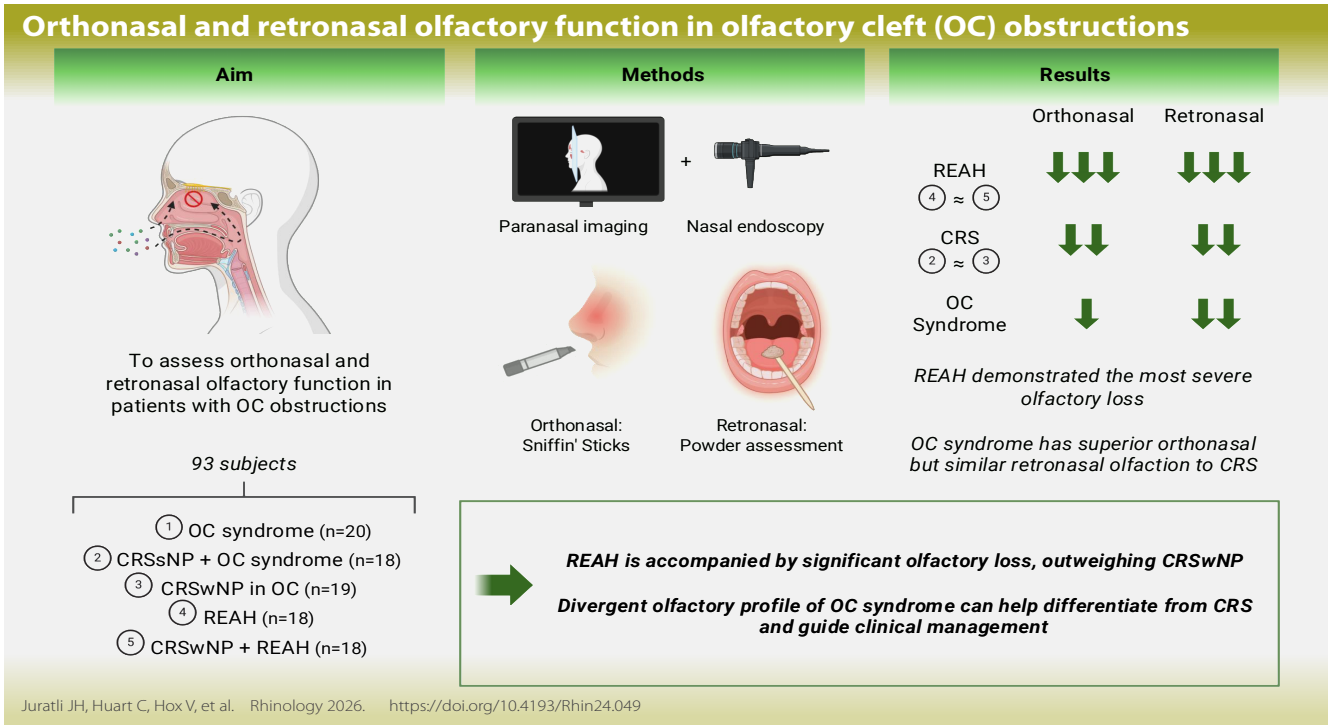

Abstract

Background: A healthy olfactory cleft is critical to normal olfactory function. The aim of this study was to explore the differential orthonasal and retronasal olfactory functions in patients with olfactory cleft (OC) obstructions including a combination of OC syndrome, chronic rhinosinusitis with or without nasal polyps (CRSwNP or CRSsNP), and respiratory adenomatoid epithelial hamartoma (REAH).

Methods: Patients (n = 93) presenting to an ENT clinic with OC obstruction underwent nasal endoscopy, chemosensory event-related potential (ERP) recordings, and radiologic assessment, and were subsequently diagnosed with OC syndrome, CRSsNP with OC syndrome, CRSwNP in the OC, REAH, and CRSwNP with REAH. Orthonasal and retronasal function were assessed using the complete Sniffin' Sticks test and a set of 30 powders, respectively.

Results: Orthonasal function was lower in patients with REAH and CRSwNP+REAH compared to CRSwNP in OC patients. Retronasal function was similarly diminished in REAH compared to CRSwNP in OC. Patients with OC syndrome alone had higher orthonasal scores than those with CRSsNP plus OC syndrome and CRSwNP in OC but not statistically different retronasal function. There was no significant difference in orthonasal or retronasal scores in REAH patients based on concurrent CRSwNP.

Conclusions: REAH corresponded with greater orthonasal and retronasal olfactory loss compared to other olfactory cleft obstructions, indicating a greater effect on the olfactory mucosa beyond disrupting airflow. The difference between CRS and OC syndrome is more pronounced orthonasally than retronasally.

Key words: hamartoma, rhinosinusitis, endoscopy, olfactory mucosa, nasal polyps

Introduction

Chemosensory perception relies on the activation of olfactory sensory neurons (OSNs) situated in the olfactory mucosa, housed within the olfactory cleft (OC) [1,2]. The integrity of the OC is essential for normal olfactory function [1]. The OC may be blocked by tumors explaining the decrease of olfactory function. These tumors may be benign (e.g., schwannoma and inverted papilloma) or malignant (e.g., adenocarcinoma and esthesioneuroblastoma). In cases of anosmia without mechanical blockage, the OC may be locally inflamed in patients with chronic rhinosinusitis (CRS) which can be reversed through local or systemic administration of glucocorticoids, indicating the critical role of the inflammatory process [3].

CRS with nasal polyps (CRSwNP) has been extensively studied with regard to olfaction [3]. CRS is one of the most common causes of quantitative olfactory dysfunction, and the prevalence of olfactory dysfunction in CRS has been estimated at 78% [4]. CRS can be explained by a mixed conductive and inflammatory process, with both a swollen nasal mucosa and inflammatory markers affecting OSNs and supporting cells [5]. Respiratory epithelial adenomatoid hamartomas (REAH), first defined by Wenig and Heffner in 1995 [6], are another classification of OC obstructions characterized by glandular proliferation from the surface epithelium and believed to be produced secondary to inflammation [6,7]. The prevalence of olfactory dysfunction in REAH is not established but has been reported in numerous cases and warrants further characterization [8,9].

The complex landscape of OC obstructions underscores the utility of differential orthonasal and retronasal olfactory effects in diagnosis. It has been demonstrated that patients with nasal polyposis had relatively greater preservation of retronasal compared to orthonasal olfaction [10,11], a pattern also observed in healthy subjects whose OC was experimentally blocked [12]. A similar study found a correlation between retronasal and orthonasal scores in CRS patients but did not report the practical difference between CRSwNP and CRSsNP patients [13]. This pattern has been observed in CRS but has not been segmented by various other classifications of OC obstruction [14]. For example, CRS can present with and without nasal polyps (NP) and may include inflammation in the OC. Bifurcated olfactory function between CRS and OC syndrome – an olfactory disorder arising from local inflammation of the OC and diminished airflow first described by Biacabe and colleagues [15] – could provide insights into their effects on the OC. Therefore, the aim of this study was to examine differences in orthonasal and retronasal olfactory function across various OC obstruction diagnoses including REAH, CRS, NP, and OC syndrome.

Materials and methods

Demographics

Subjects were retrospectively recruited from patients at Saint Luc University Hospital in Brussels (Université Catholique de Louvain) presenting with olfactory dysfunction who were diagnosed with an OC obstruction at the endoscopic evaluation between 2012 and 2022 and were willing to undergo psychophysical testing. Other causes explaining the olfactory dysfunction - such as postinfectious, posttraumatic, toxic or medication-related, neurologic, or congenital olfactory loss - were ruled out by a thorough history [16].

A total of 93 eligible subjects were categorized into five different conditions: OC syndrome (n = 20; 7 female), OC syndrome with endoscopic and radiological signs of chronic sinusitis in the ethmoid sinus (CRSsNP+OC; n = 18; 11 female), chronic rhinosinusitis with nasal polyps in the OC (CRSwNP in OC; n = 19; 9 female), REAH (n = 18; 4 female), and chronic rhinosinusitis with nasal polyps and REAH (CRSwNP+REAH; n = 18; 9 female). All subjects consented to participation in the study, and appropriate ethics approval was obtained from UC Louvain (2025/20JUI/246).

Diagnosis

OC syndrome (OC; first group) was diagnosed in patients complaining of an olfactory dysfunction when a close contact between the middle and/or superior turbinate and the septum was confirmed by endoscopic examination and radiological evaluation (CT scan, and MRI to assess intracranial structures) with or without mucosal swelling [17].

The second group of patients (CRSsNP+OC) was defined in patients who reported at least two of the following symptoms - nasal obstruction, facial pain/pressure, mucopurulent discharge, and olfactory dysfunction - for at least 12 weeks, according to EPOS 2020 guidelines [18]. Additionally, the OC syndrome was associated with an opacification in the ethmoid cells at the radiological evaluation or when an endoscopic evaluation demonstrated edema, secretions, and inflammation in the middle meatus, and optionally in the superior meatus. As described for the olfactory bulb and the olfactory sulcus [19], an appropriate location to diagnose the close contact between the medial aspect of the middle turbinate or of the superior turbinate with the septum is the plane posterior to the tangent to the eyeball (PPTE). The third group was represented by patients having stage 2 or 3 CRS (stage 1 and 4 excluded) with bilateral nasal polyps in the OC (CRSwNP in OC). Nasal polyps were identified according to the following classification: I = polyp above the inferior limit of middle turbinate; II = polyp at the inferior limit of middle turbinate; III = polyp below the inferior limit of middle turbinate; IV = polyp reaching the nasal floor.

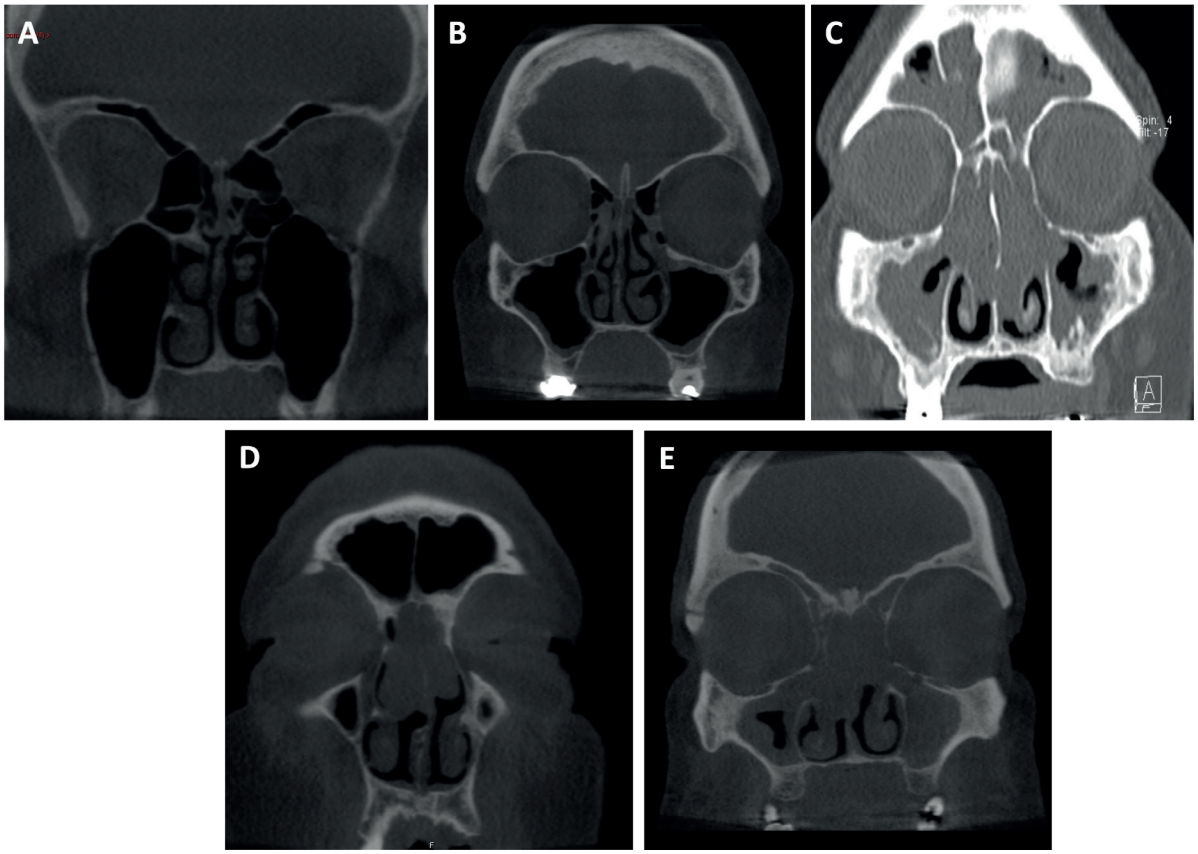

Figure 1. Coronal CT scans of patients with OC obstructions. A: OC syndrome, B: CRSsNP+OC, C: CRSwNP in OC, D: REAH, E: CRSwNP+REAH.

The fourth group of patients was the REAH group, defined as a mostly-bilateral, benign tumoral lesion of the OC [20,21]. Histologically, REAH is described as a polypoid proliferation of glands lined by ciliated respiratory (or in this case, olfactory) epithelium that appears to invaginate into the submucosa yet maintains direct continuity with the surface mucosa [22,23]. REAH was diagnosed when the endoscopic examination and the radiological evaluation revealed a bilateral polyp formation in the OC with the diagnosis confirmed at the histopathological examination. The fifth group encompassed patients with CRSwNP in the OC corresponding to a REAH (CRSwNP+REAH), also confirmed by histopathological examination.

Nasal endoscopy

In the present study, nasal endoscopy was employed as the primary method for the assessment of OC obstructions. This method involved the insertion of a 4mm flexible endoscope through the patient's nostrils, allowing for direct visualization of the OC. Images and videos obtained during the endoscopic procedure were reviewed by otolaryngologists to determine the type and extent of obstructions [24].

Radiologic assessment and biopsy

Radiologic assessment was done for all patients with computerized scanning of the nose, the paranasal sinuses, and the middle third of the face (Figure 1). In cases when a polypoid mass indicatory of REAH was visualized in the olfactory cleft, biopsies were taken under endoscopic control after administration of local anesthesia with xylocaine and naphazoline and were subsequently sent to histopathological review. Biopsies were taken after chemosensory tests were performed (Figure 2).

Orthonasal assessment

Psychophysical orthonasal function was assessed using the Sniffin' Sticks test battery (Burghart Messtechnik, Holm, Germany) [25]. This validated test allows a specific evaluation of phenyl ethylalcohol odor threshold, odor discrimination, and odor identification. For birhinal orthonasal testing, the pen's tip is placed approximately 2 cm in front of both nostrils. The corresponding subscores for threshold (T, maximum 16 points), identification (I, maximum 16 points) and discrimination (D, maximum 16 points) sum up to the composite TDI score between 1 and 48 points.

Retronasal assessment

For retronasal olfactory testing, a standardized test was used based on the identification of odorized powders or granules presented to the oral cavity [26]. Thirty stimuli were selected: coffee, vanilla, cinnamon, cocoa, raspberry, orange, garlic, strawberry,

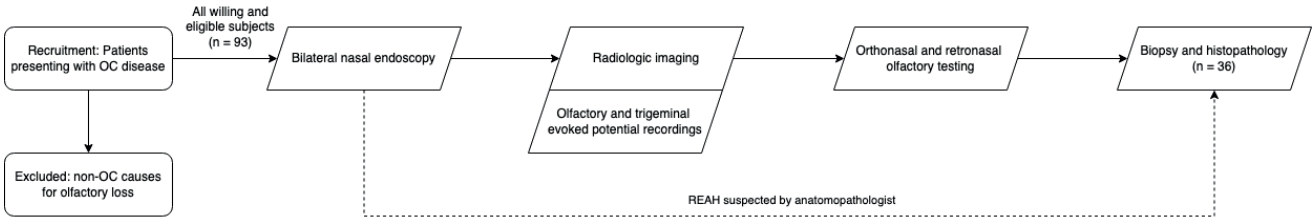

Figure 2. Study protocol flowchart.

cloves, nutmeg, onion, cheese, curry, milk, banana, mushroom, coconut, lemon, paprika, celery, leek, fish, parsley, black pepper, pizza, almond, tomato, apple, dill, and grapefruit. Stimulants were applied to the midline of the tongue. Participants were asked to identify the odor from a list of 4 items each. After administration of each powder, participants rinsed with tap water [11].

Chemosensory ERP recordings

ERP were recorded in response to olfactory (PEO) and trigeminal (PET) stimulation using a computer-controlled stimulator based on air-dilution olfactometry (Olfactometer OM2S; Burghart Medical Technology, Wedel, Germany) [11], allowing for the precise delivery of chemical stimuli while maintaining the nasal cavity's mechanical and thermal conditions. Thirty-three subjects did not have ERPs measured due to availability of the olfactometer. The stimuli were directed to the nasal cavity monorhinally through Teflon tubing inserted into a nostril beyond the nasal valve, pointing towards the OC. The total flow rate was 8 L/min (36°C; 80% relative humidity; stimulus duration, 200 ms; stimulus rise time, <20 ms). To prevent auditory evoked responses triggered by potential clicking sounds associated with the chemical stimuli, study participants listened to white noise delivered through headphones at a level of 60 to 70 dB. Study participants were asked to keep their eyes open and breathe through their mouth during the session [27]. Olfactory stimulation involved the use of phenylethyl alcohol (50% vol/vol), while trigeminal stimulation employed carbon dioxide (50% vol/vol). These two stimuli were presented 20 times each in a randomized sequence, with a 30-second interstimulus interval [11].

An electroencephalogram (EEG) was recorded from position Cz and referenced to linked ear lobes (A1/A2). EEG recordings that were affected by eye blinks and/or displayed activity exceeding 50 μV were discarded prior to averaging. EEG activity was averaged from 500 ms in the pre-stimulus period until 1500 ms in the post-stimulus period. All offline signal-processing procedures were performed using the LETSWAVE EEG toolbox (Université Catholique de Louvain) [28,29].

Statistical analysis

All quantitative data were summarized and analysed using R Statistical Software (v4.1.2; R Core Team 2021). Power analysis was conducted using the *pwr* package, with k = 5 groups, power = 0.8, and a significance level of 0.05. Effect size f was estimated at 0.4 based on Cohen's recommendations for a large expected effect [30]; this is equivalent to an eta-squared η^2 of 0.138. A minimum of 16 subjects per group was required to accomplish desired power.

Before conducting one-way analysis of variance (ANOVA), Levene's test for equality of variances found a significant difference in variances for TDI (W = 3.113, p = 0.019) but not for retronasal score (W = 1.374, p = 0.25) across disease groups. However, given similar sample sizes across groups (n between 18 and 20), ANOVA was still regarded to be suitable for analysis of TDI scores despite unequal variances. Subject age was adjusted for as a covariate using analysis of covariance (ANCOVA).

AN(C)OVA was performed to assess if there were significant differences in orthonasal and retronasal olfactory measurements across the subgroups of OC obstruction. Post-hoc analyses were conducted using Tukey's honest significance test through the package *multcomp* [31]. Assumptions of homoscedasticity and normality were met for all tests through the Scale-Location and Normal QQ plots, respectively. Analysis of the role of the binary variables PEO and PET on olfactory function were conducted using a two-way ANOVA.

Results

Orthonasal and retronasal correlations

TDI and retronasal olfaction scores were strongly correlated (r = 0.78; F = 139.6, p < 0.0001; Figure 3). This correlation applied to all disease subgroups – OC syndrome (r = 0.64, t = 3.53, p = 0.0024), CRSsNP+OC (r = 0.75, t = 4.52, p = 0.00035), REAH (r = 0.66, t = 3.55, p = 0.0027), CRSwNP+REAH (r = 0.60, t = 3.02, p = 0.0081) - except CRSwNP in OC (r = 0.38, t = 1.69, p = 0.11).

Group comparisons of orthonasal and retronasal olfaction

Before controlling for any other variables, disease groups demonstrated significantly different TDI scores (F = 32.25, df = 43.49, p < 0.0001). The significance remained after adjusting for age (F = 18.4, df = 87, p < 0.0001). There were significant dif-

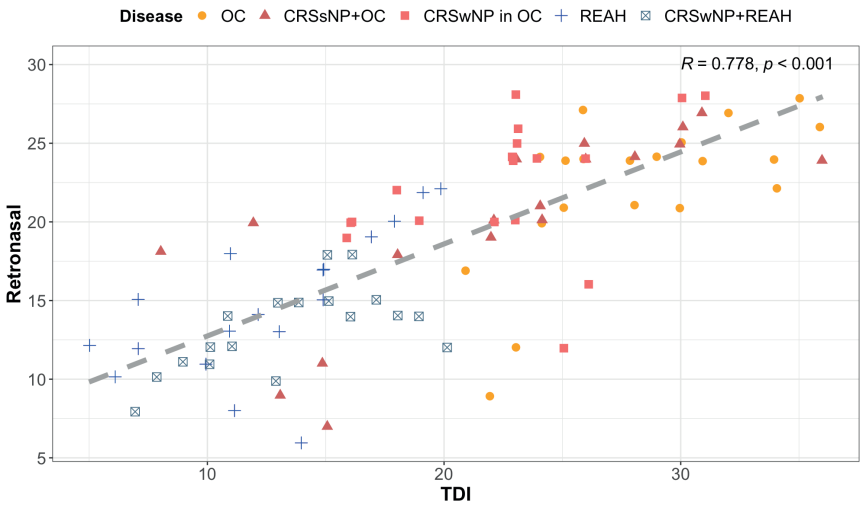

Figure 3. Scatterplot of the correlation between the composite TDI score and retronasal test score. The five cleft obstruction groups are differentiated by point color and shape.

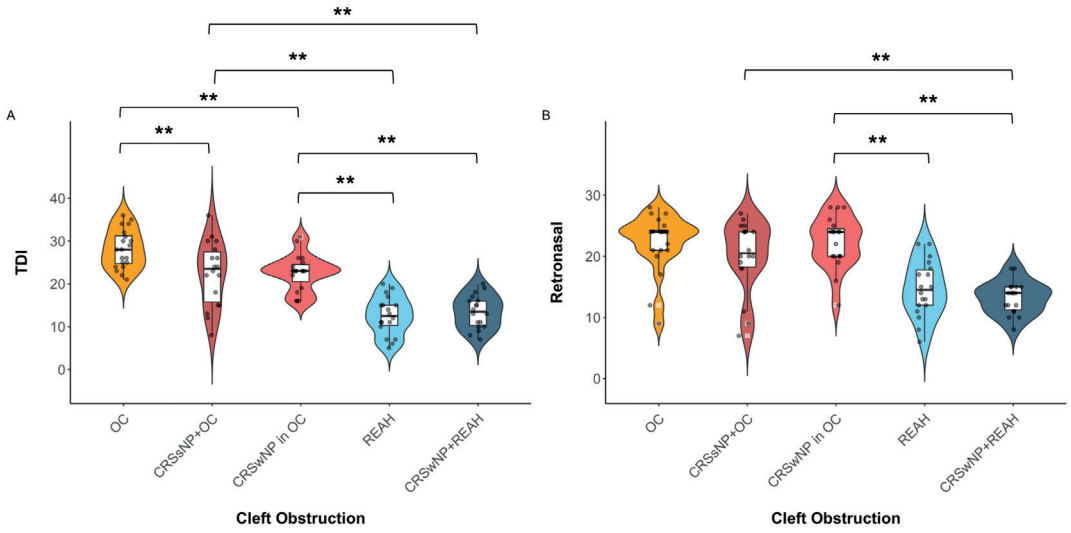

Figure 4. Pairwise comparisons of olfactory function by OC obstruction, shown by violin plots with overlaid boxplots and contributing data points. A: orthonasal olfactory function (TDI). B: retronasal olfactory function. Comparisons of interest are shown, with ** = significant ($p < 0.05$). Not all significant comparisons are shown; a complete comparison is shown in Table S1.

ferences between all possible group pairings except CRSwNP in OC vs. CRSsNP+OC ($p = 0.99$) and CRSwNP+REAH vs. REAH alone ($p = 0.97$; Figure 4A). The eta-squared (η^2) for Disease was 0.46, whereas η^2 for Age was 0.51, which indicates a large effect size for the disease groups on orthonasal TDI score.

All patients with REAH, either alone or in conjunction with CRS, had significantly worse retronasal scores than non-REAH patients before controlling for age ($F = 23.71$, $df = 43.10$, $p < 0.0001$). This remained true after controlling for age through ANCOVA ($F = 11.08$, $df = 87$, $p < 0.0001$), apart from retronasal function in REAH compared to CRSsNP+OC ($t = 2.604$, $p = 0.078$; Figure 4B). The age difference ($\bar{x} = 18.7$ years) between REAH and CRSsNP+OC patients was a predictor of the observed difference in retronasal function. There were no significant differences between any pairing of OC syndrome, CRSsNP+OC, or CRSwNP in OC; nor between REAH and CRSwNP+REAH (Figure 4B). Eta-squared for disease ($\bar{x} = 0.34$) indicates a large effect size of the disease groups on the retronasal score, with $\bar{x}$ for Age at 0.23.

Patients with OC alone had better TDI scores than all other disease groups, with the most prominent differences existing against CRSwNP+REAH and CRSwNP in OC. Thus, all the separate components had a negative effect on orthonasal function: CRS, nasal polyps, and REAH. Patients with OC syndrome also

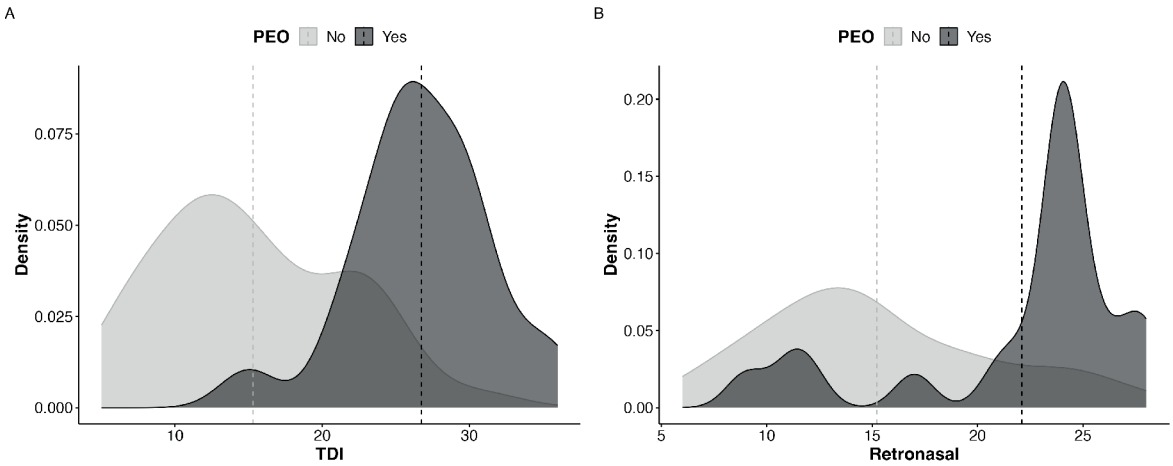

Figure 5. Density plots of (A) TDI and (B) retronasal test scores between subjects based on olfactory ERPs. Subjects who exhibited olfactory ERPs had greater orthonasal and retronasal scores than those without.

had better retronasal function than those with CRSwNP+REAH or REAH alone. However, there was not a significant retronasal difference between OC patients and the remaining CRS groups – CRSsNP+OC and CRSwNP in OC.

Role of event-related potentials

Next, the role of olfactory ERPs (PEO) and trigeminal ERPs (PET) on orthonasal and retronasal scores was investigated. Of the 93 subjects, 60 had reported values on the presence of PEO, so the data was subset to these subjects. The presence of PEO resulted in significant differences in TDI ($F = 50.0$, $p < 0.0001$) and retronasal score ($F = 20.7$, $p < 0.0001$) (Figure 5). Conversely, PET was insignificant for both TDI ($F = 0.02$, $p = 0.88$) and retronasal olfaction ($F = 0.42$, $p = 0.52$) as a part of these models.

Given the significant role of PEO on TDI score, PEO was added to the linear models to see if it accounts for the observed group differences. The presence of olfactory ERPs was insufficient in explaining the differences in TDI between REAH and OC syndrome ($t = 3.296$, $p = 0.0141$), CRSwNP+REAH and OC syndrome ($t = 2.923$, $p = 0.0382$), CRSwNP in OC vs. REAH ($t = 4.531$, $p < 0.001$), and CRSwNP+REAH vs. CRSwNP in OC ($t = 4.644$, $p < 0.001$). The adjusted R-squared of the model was 0.7018.

When PEO was included in the retronasal model, there remained a significant difference in retronasal scores in two pairings: CRSwNP in OC vs. REAH ($t = 3.590$, $p = 0.00611$) and CRSwNP+REAH vs. CRSwNP in OC ($t = 4.493$, $p < 0.001$). Both group pairings were also significantly different regarding TDI score. The remaining groups were not significantly different. The adjusted R-squared of the model was 0.469. PET decreased model fit and did not alter the results, so it was not included as a predictor in either model.

Discussion

Major findings of this clinical observational study were: (i) the OC syndrome with or without signs of CRS is similarly associated with an orthonasal - but not retronasal - olfactory dysfunction, (ii) patients with REAH with or without CRSwNP have worse olfactory function than the three other groups even when controlling for age, (iii) orthonasal and retronasal olfactory function strongly correlate for patients with OC diseases, and (iv) for these patients presence of olfactory event related potentials is associated with greater orthonasal and retronasal scores than for patients without.

Compared to patients with REAH alone or CRSwNP+REAH, patients with CRSwNP in OC showed better orthonasal and retronasal function, true even after controlling for age and presence of olfactory ERPs. There was no significant difference between REAH patients with and without CRSwNP. The impact on olfactory function thus appears dependent of the predisposing diseases (CRS, REAH), even if the OC syndrome per se negatively influences olfactory function.

REAH arises from the invagination of the surface epithelium and potentially attenuates the epithelial component, whereas nasal polyps generally emerge from the mucosal layer [6,32], although some nasal polyps associated with CRS can disturb the olfactory epithelium [33]. In addition, REAH typically occurs on the nasal septum, as opposed to the lateral nasal wall for inflammatory polyps [32]. These factors may elucidate restructuring in the olfactory epithelium and disruption of airflow to the OC, respectively. In an analysis of CRS cases, nasal polyp scores of the middle meatus and OC were predictors of REAH, suggesting greater polyposis and thickening of the mucous membrane in REAH [8]. NP may precede REAH in many cases, and this long-lasting previous inflammation may result in the severe olfactory loss

Table 1. Demographics and olfactory assessments by OC obstruction group.

		OC	CRSsNP+OC	CRSwNP in OC	REAH	CRSwNP+REAH	Total
Age	$\bar{x}$ (± SD)	39.50 (8.96)	45.44 (14.67)	45.26 (13.47)	64.11 (10.27)	52.06 (14.51)	49.02 (14.89)
TDI	$\bar{x}$ (± SD)	28.15 (4.51)	22.39 (7.55)	22.63 (4.23)	12.56 (4.49)	13.44 (3.85)	20.04 (7.81)
T	$\bar{x}$ (± SD)	5.45 (2.37)	4.17 (2.43)	3.68 (1.63)	1.56 (0.62)	2.28 (1.27)	3.47 (2.26)
D	$\bar{x}$ (± SD)	11.50 (1.61)	8.50 (2.98)	8.79 (2.37)	5.44 (2.45)	4.61 (1.42)	7.86 (3.33)
I	$\bar{x}$ (± SD)	11.20 (1.99)	9.72 (2.99)	10.16 (2.17)	5.56 (2.25)	6.56 (2.28)	8.71 (3.18)
Retronasal	$\bar{x}$ (± SD)	22.20 (4.81)	20.11 (5.84)	22.32 (4.19)	14.67 (4.55)	13.22 (2.69)	18.62 (5.87)
PEO	n/total (%)	11/12 (92)	6/12 (50)	3/12 (25)	0/12 (0)	0/12 (0)	20/60 (33)
PET	n/total (%)	12/12 (100)	11/12 (92)	11/12 (92)	10/12 (83)	9/12 (75)	53/60 (88)

observed. Associations between REAH and prior nasal polyposis have been reported [9,32,34,35], as with other indications of chronic inflammation beyond CRS [36,37]. Importantly, prior inflammation and nasal polyposis are not nearly present in every REAH case [21], lending to the idea that future analysis of REAH can be further segmented.

There was no observed difference between CRSwNP in OC and CRSsNP+OC across the gamut of analyses, for both TDI and retronasal scores. CRS and OC syndrome largely explain the olfactory dysfunction, with relatively less significance to nasal polyposis. Similar orthonasal and retronasal function further suggests an inflammatory rather than a conductive mechanism for CRS olfactory dysfunction. In a conductive model, polyps are likely to obstruct nasal airflow patency, diminishing orthonasal function more than retronasal function [10,12].

In contrast, sinonasal inflammation can result in sensorineural disruptions to olfactory sensory neurons or surrounding non-neuronal support cells. Levels of eosinophil markers have been found to be elevated in the superior turbinate and ethmoid bulla of CRS patients, with eosinophil expression inversely correlated to olfactory threshold and identification scores [38,39]. Olfactory function is negatively correlated with levels of cytokines IL-2, IL-5, IL-6, IL-10, and IL-13 in the OC and middle meatus [40,41]. Histological analysis of the olfactory mucosa reveals disruption to the pseudostratified epithelium and isolated inflammation in the lamina propria, adjacent to nerve bundles [33]. The eosinophilic reaction demonstrates the impact of the inflammatory mechanism on clinical olfactory dysfunction in CRS [42]. Future analysis should consider biopsies of the olfactory mucosa to generate an inflammatory profile in CRS patients who are candidates for surgery.

There is a lack of consensus about the clear definition of OC syndrome. The first descriptions from Biacabe and Trotier considered the syndrome as the presence of local inflammation of the soft tissue in the cleft together with a stagnation of secretions impairing air passage, leading to a conductive olfactory disorder [15,17]. It is the author's opinion that OC syndrome is present when a close contact between the septum and the superior or the middle turbinate - revealed by an endoscopic and/or radiological examination - exist with or without inflamed mucosa. In some patients, this may be attributed to a pneumatized middle turbinate (concha bullosa) and/or mucosal thickening [15]. In these circumstances, patients demonstrated an olfactory dysfunction as revealed by psychophysical testing and imaging data [15,17].

In this cohort of patients, olfactory function was studied when the OC was virtually absent or filled with inflamed mucosa and/or polyp formation. The OC roof at the cribriform plate is very thin and the depth of the olfactory fossa may differ as expressed with the Keros type [43,44]. The width of the OC may be defined as the minimal distance between the septum and the superior or middle turbinate. Based on digital volume tomography, Savvateeva and colleagues found the average width of the OC on the right and left side to be 0.96mm and 0.89mm, respectively [43]. A computational fluid dynamics analysis of the OC found mean air flow volume, velocity, and flow ratio were positively correlated with olfactory function [45]. Based on these observations, it can be argued that if the OC is narrowed, airflow is diminished and olfactory function is compromised, cumulatively contributing to OC syndrome. That being said, it remains difficult to draw linear conclusions from the single symptom of a narrow olfactory cleft: these simplistic – and to some degree, mechanistic – relations between morphology and olfactory function have been repeatedly challenged by examples of preserved olfaction despite loss or reduction in olfactory bulb or cleft dimensions [46–48]. Morphology should not be overinterpreted to explain symptoms of an individual patient.

Cleft obstructions in this study were classified largely through qualitative assessment. Methods of staging cleft obstructions

may be endoscopic or radiologic and may directly measure polyp burden or sinus opacification [49]. A unified method may allow for clearer distinctions between CRSwNP and REAH across studies. Subsequently, it may enable further associations between the scale of nasal polyps and the effect on orthonasal and retronasal olfactory function. In examinations of the olfactory cleft, using a thinner endoscope (2.7mm) would be preferred over the 4mm endoscope utilized in the present study [3,50]. The lack of nasal patency data – through peak nasal inspiratory flow (PNIF), acoustic rhinometry, or rhinomanometry – precludes the investigation of the relationship between nasal anatomy and airflow in each condition. As such, further research into the differences between REAH and CRSwNP will promote investigation for their mechanisms of olfactory dysfunction as demonstrated in the present study.

Conclusion

This study found that of the studied OC obstructions, REAH had the most severe effect on orthonasal olfactory function, followed by CRSwNP and lastly, OC syndrome. The mechanism of REAH appears to include major olfactory epithelium remodeling, in addition to mechanical obstruction of the OC, given the relatively worse orthonasal and retronasal olfactory outcomes compared to CRSwNP patients. In contrast, CRS can be distinguished from OC syndrome by greater orthonasal olfactory loss but similar retronasal olfactory function. These findings can support in the differential diagnosis of OC obstructions beyond morphology of the blockage and provide insight into the mechanisms of olfactory loss.

Authors contributions

The authors confirm contribution to the paper as follows: study conception and design: PR, TH; data collection: CH, VH, PR; analysis and interpretation of results: JJ, TH; draft manuscript preparation: JJ, PR, TH. All authors reviewed the results and approved the final version of the manuscript.

Conflict of interest

Since 2021, TH collaborates/is supported by the following partners: Sony, Stuttgart, Germany; Smell and Taste Lab, Geneva, Switzerland; Takasago, Paris, France; Baia Foods, Madrid, Spain; Frequency Therapeutics, Farmington, CT, USA; Burghart, Holm, Germany. The remaining authors declare no conflicts of interest.

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SUPPLEMENTARY MATERIAL

Table S1. Pairwise comparisons of TDI and retronasal scores between disease groups, after controlling for age.

Cleft Obstructions		TDI ~ Disease	CRSsNP+OC
2-1	Mean (± SE)	-4.83 (± 1.55)	-1.73 (± 1.48)
	t-value	3.12	1.17
	p	0.020*	0.766
3-1	Mean (± SE)	-4.62 (± 1.53)	0.46 (± 1.46)
	t-value	3.02	0.32
	p	0.027*	0.99
4-1	Mean (± SE)	-11.75 (± 1.82)	-6.06 (± 1.74)
	t-value	6.44	3.48
	p	< 0.001*	0.0068*
5-1	Mean (± SE)	-12.75 (± 1.61)	-8.22 (± 1.54)
	t-value	7.90	5.35
	p	< 0.001*	< 0.001*
3-2	Mean (± SE)	0.21 (± 1.55)	2.19 (± 1.48)
	t-value	0.14	1.48
	p	0.99	0.57
4-2	Mean (± SE)	-6.92 (± 1.74)	-4.33 (± 1.66)
	t-value	3.97	2.60
	p	0.0014*	0.078
5-2	Mean (± SE)	-7.91 (± 1.60)	-6.49 (± 1.52)
	t-value	4.96	4.27
	p	< 0.001*	< 0.001*
4-3	Mean (± SE)	-7.13 (± 1.73)	-6.52 (± 1.65)
	t-value	4.13	3.96
	p	< 0.001*	0.0014*
5-3	Mean (± SE)	-8.13 (± 1.57)	-8.69 (± 1.50)
	t-value	5.16	5.78
	p	< 0.001*	< 0.001*
5-4	Mean (± SE)	-0.99 (± 1.65)	-2.17 (± 1.57)
	t-value	0.60	1.38
	p	0.97	0.64

Group 1 = OC syndrome; 2 = CRSsNP+OC; 3 = CRSwNP in OC; 4 = REAH; 5 = CRSwNP+REAH.