

Monitoring olfactory function in chronic rhinosinusitis and the effect of disease duration on outcome

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Background: Our primary aim in this study was to determine which of the “Sniffin’ Sticks” subtest components (threshold, discrimination, or identification) best reflect overall change in olfactory function during treatment for chronic rhinosinusitis (CRS). Our secondary aim was to determine whether duration of CRS affects olfactory outcomes after treatment.

Methods: A retrospective cohort study was performed. Sniffin’ Sticks test scores from patients medically treated for CRS at our center from 1999 to 2016 were analyzed. Only patients with 2 test scores available were included.

Results: Results from 408 patients were included (mean age, 56 years; male:female ratio, 217:191). There was a statistically significant improvement in threshold (T), discrimination (D), and identification (I) scores as well as the composite “TDI” score between the two testing sessions. Controlling for age, there was a significantly greater improvement in composite TDI score in patients with CRS of ≤ 24 months duration. As expected, we found statistically significant correlations between change in overall

composite TDI score and change in threshold, discrimination, and identification, between sessions. Of the individual subcomponents, change in discrimination correlated best with change in composite TDI score ($r = 0.82$, $p < 0.0001$). This relationship was maintained irrespective of duration of CRS.

Conclusions: In patients with CRS, odor discrimination appears to best reflect overall changes in olfactory function, as determined using the composite TDI score. Furthermore, olfactory outcomes are better when treatment is started sooner. © 2018 ARS-AAOA, LLC.

Key Words:

chronic rhinosinusitis; duration; functional anosmia; hyposmia; olfaction; testing

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Chronic rhinosinusitis (CRS) is a common inflammatory condition of the nose and paranasal sinuses, and can be classified into phenotypic subtypes, including those with and without polyps. It has been shown to affect 10.9%

of the European population, increasing to almost 30% in some areas.¹ Disease burden is significant: CRS patients have worse social functioning and more bodily pain than those with congestive heart failure, back pain, or chronic obstructive pulmonary disease.²

One of the cardinal diagnostic symptoms of CRS is quantitative olfactory dysfunction, in the form of hyposmia or functional anosmia.³ Olfactory dysfunction is thought to affect 61%-83% of patients, irrespective of subtype,⁴ rising to 95% in those with polyps.⁵ Furthermore, olfactory impairment is independently associated with reduced quality of life, manifest through social and environmental anxiety, depression, and nutritional disturbances.⁶⁻¹⁰ Accordingly, CRS patients should be routinely assessed for smell impairment.

With regard to clinical assessment, it is increasingly acknowledged that subjective ratings of olfactory function correlate poorly with more objective psychophysical tests. This has been demonstrated in healthy participants,^{11,12}

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general Ear, Nose and Throat (ENT) patient populations¹³ and in patients with CRS.¹⁴ Despite this, uptake of psychophysical testing in secondary care remains poor: a 2007 survey by McNeill et al found that, although 97% of consultant ENT surgeons regularly managed olfactory dysfunction in the UK, <6% routinely tested for impairment.¹⁵ Moreover, the 2012 European position paper on rhinosinusitis and nasal polyps describes subjective olfactory assessment as correlating “significantly” with tests of odor threshold.³

In response to these and other potential shortcomings in the diagnosis and management of smell disorders, the recently published 2017 position paper on olfactory dysfunction (PPOD) outlines preferred methods of clinical assessment.¹⁶ Accordingly, it is recommended that subjective assessment not be performed in isolation but rather combined with psychophysical testing. With regard to the latter, a variety of psychophysical tests are available, commonly employing either odor identification alone, or some combination of identification (I), discrimination (D), and/or threshold (T). The PPOD guidelines state that testing should include at least 1 of these subcomponents, although assessment of 2 or 3 would be “ideal.” Composite testing in this way increases diagnostic sensitivity,¹⁷ and the pattern of subtest result may provide diagnostic information regarding underlying disease etiology.¹⁸ However, full “TDI” testing (eg, as used in the “Sniffin’ Sticks”) can take up to 30 minutes to perform, which is prohibitively long in some busy clinic environments.

Where logistically limited to 1 or 2 tests, choice of subcomponent should include those aspects of olfaction that most closely reflect both impairment and improvement in sinonasal disease. As mentioned, cross-sectional studies have assessed subcomponent test use with regard to diagnosis. However, to our knowledge, no previous longitudinal studies have addressed which of odor threshold, discrimination, or identification best correlate with overall changes in olfactory function (as determined by composite TDI) after treatment in CRS. The primary aim of this study was therefore to determine which individual subcomponent of the Sniffin’ Sticks test battery correlates most closely with change in composite TDI after conservative treatment for CRS. We hypothesize that odor threshold will best reflect change in olfactory function after treatment in this group.

Our secondary aim was to determine whether olfactory outcomes are affected by the duration of CRS prior to initiation of treatment. It has been suggested that early intervention may lead to better outcomes in CRS with respect to health-care provider attendances and disease-specific medication use.¹⁹ Furthermore, histopathological evidence suggests that the olfactory neuroepithelium may undergo remodeling with more established disease.²⁰ However, there is some heterogeneity in the literature, with several studies showing no correlation between disease duration and olfactory function.^{21,22} To investigate this further, we aimed to determine whether disease duration affects olfactory

outcomes. We hypothesize that shorter duration of disease is associated with greater improvement in olfactory function.

Patients and methods

Experimental design

A retrospective cohort analysis of patients with CRS attending the ENT Department of the Technische Universität Dresden between 1999 and 2016 was performed. Anonymized demographic information, self-reported disease duration, and olfactory test scores were collected.

Participants

Participants included were patients with CRS for whom at least 2 full olfactory test scores had been recorded during their course of treatment in secondary care. Duration of disease was self-reported, and categorized according to clinic questionnaire into <3 months (acute, excluded), 3–24 months, and >24 months.

Treatment for CRS

All treatment was conservative, including systemic and topical corticosteroids, systemic antibiotic treatment, and nasal saline washes. From 2007 onward, medical management was in accordance with the European position papers on rhinosinusitis and nasal polyps from 2007 and 2012.^{3,23}

Olfactory testing

All participants underwent birhinal orthonasal olfactory testing using the Sniffin’ Sticks test battery (Burghart Messtechnik, Wedel, Germany). This is a commonly used reliable and validated psychophysical test of odor threshold, discrimination, and identification.^{17,24}

The testing procedure was undertaken as previously described.^{18,25,26} In brief, odor threshold (T) is the concentration of odorant at which the participant is able to correctly identify the target pen from 2 blank distractors, during 50% of trials. A higher score indicates a better odor threshold; that is, the ability to smell odors at lower concentrations. Odor discrimination (D) is the participant’s ability to discriminate between odors of different quality. During this test, the participant is asked to identify which of 3 suprathreshold odors differs from the other 2 odors. Again, higher scores indicate better odor discriminatory ability. Finally, odor identification (I) tests the participant’s ability to correctly identify an odor from a choice of 4 written/picture cues, with higher scores indicating better function. Diagnoses of impairment and improvement are based on composite “TDI” scores^{24,27}: functional anosmia, = TDI ≤16.5; hyposmia, TDI >16.5 and ≤30.3; normosmia, TDI >30.3; clinically significant improvement, increase ≥5.5.

Statistical analysis

Statistical analysis was performed using GraphPad Prism version 6 (GraphPad Software, LaJolla, CA) and SPSS

TABLE 1. Strength of correlations

Correlation coefficient (<i>r</i> value)	Strength of association
0.5-1.0	Strong
0.3-0.49	Moderate
0.1-0.29	Weak
0-0.99	Negligible

TABLE 2. Demographic information

Age	56 ± 11 (14-86) years
M:F (n)	217:191
Body mass index	26.15 ± 4.15 (18.13-40.75)
Duration of olfactory dysfunction (number of patients)	
3-24 months	140
> 2 years	248
Unknown	20
Interval between olfactory tests	28.4 ± 60.9 (0.9-463.4) weeks

Data expressed as mean ± standard deviation (range) unless noted otherwise.

version 24.0 (IBM SPSS, Inc, Armonk, NY). Statistical significance was attributed where $p < 0.05$. Data were assessed for normality and parametric or nonparametric tests used as appropriate. Strengths of correlation are assumed, as shown in Table 1. Unless otherwise specified, data are given as mean ± standard deviation (SD).

Ethical considerations

This study was approved by the Ethics Committee at Technische Universität Dresden (protocol number EK122032011). It was conducted in accordance with the Declaration of Helsinki.

Results

Patients' demographics

Data were available from 408 patients. Demographic and disease-specific information is shown in Table 2. Data from 2 separate Sniffin' Sticks testing sessions were available for all patients. For all but 29 patients, the first of these sessions occurred at their first attendance to the ENT clinic. For all patients, the first olfactory testing session took place prior to commencement of treatment in secondary care.

Olfactory function

At the first testing session, 228 (55.9%) patients were functionally anosmic, 164 (40.2%) were hyposmic, and 16 (3.9%) were normosmic (Fig. 1). At the second testing session, 135 (33.1%) patients were functionally anosmic, 199 (48.8%) were hyposmic, and 74 (18.1%) were normosmic

(Fig. 1). With regard to clinically significant improvement, 174 (42.7%) patients improved in composite TDI score by ≥5.5 points.

Across all patients, overall mean composite and individual threshold, discrimination, and identification scores at testing sessions 1 and 2 are shown in Figure 2. There was a statistically significant improvement in composite TDI score between the 2 testing sessions (session 1 mean score: 16.5 ± 7.3 ; session 2 mean score: 21.8 ± 8.6 ; $p < 0.0001$), as well as in the individual subcomponents of threshold (session 1 mean score: 2.3 ± 2.2 ; session 2 mean score: 3.8 ± 3.1 ; $p < 0.0001$), discrimination (session 1 mean score: 7.5 ± 3.1 ; session 2 mean score: 9.5 ± 3.3 ; $p < 0.0001$), and identification (session 1 mean score: 6.7 ± 3.5 ; session 2 mean score: 8.4 ± 3.9 ; $p < 0.0001$).

The change in composite TDI, as well as individual T, D, and I scores between sessions 1 and 2 were calculated for each patient (where Δ score = session 2 score – session 1 score). Accordingly, overall mean change in olfactory scores across all patients are shown in Table 3.

Within the subgroup of patients whose TDI score improved ($n = 295$, 72.3% of total cohort), the overall mean change in score was 8.6 ± 7.0 . Within the subgroup of patients whose TDI score deteriorated ($n = 99$, 24.3% of total cohort), the overall mean change in score was -4.3 ± 4.2 .

To determine whether younger patients showed greater levels of improvement than their older counterparts, subgroup analysis was performed according to age. Although the median age within the cohort was 57 years, a lower cut-off age of 45 years was used to divide “younger” from “older” groups, given the possibility of age-related olfactory dysfunction closer to the median.²⁸ Accordingly, mean change in score in “younger” and “older” groups is shown in Table 4. Although there was greater improvement in olfactory test scores (for TDI, and T, D, and I) in the younger group, these differences did not reach statistical significance.

Effect of duration of CRS on change in TDI

A one-way analysis of covariance was performed to assess the effect of CRS duration on change in TDI score, controlling for the potential effect of age. A small but significant effect of duration was found [$F(1,384) = 5.145$, $p = 0.024$, partial $\eta^2 = 0.013$], where patients with CRS of ≤24 months duration had greater improvement than those with disease of >24 months duration at first testing (corrected change in TDI [mean ± standard error]: ≤24 months, 6.45 ± 0.68 ; >24 months, 4.50 ± 0.52).

Correlation between composite TDI and individual T, D, and I scores

As expected, the change in each of T, D, and I correlated significantly with change in TDI score, given that they are subcomponents of this composite score. The strongest

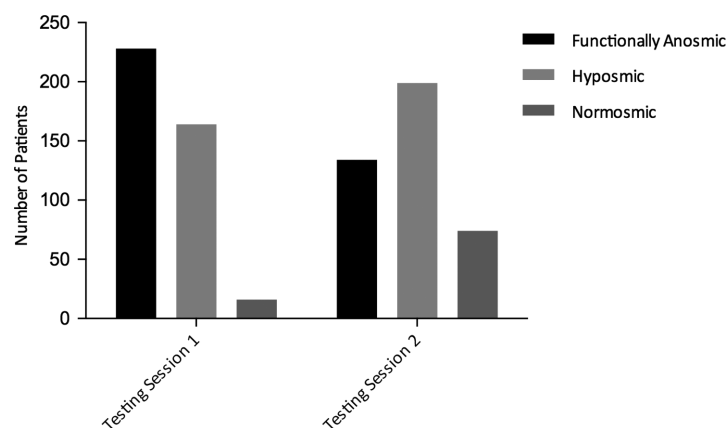


FIGURE 1. Frequency of patients with functional anosmia, hyposmia, and normosmia as determined by TDI score at testing session 1 and testing session 2. TDI: T = threshold; D = discrimination; I = identification.

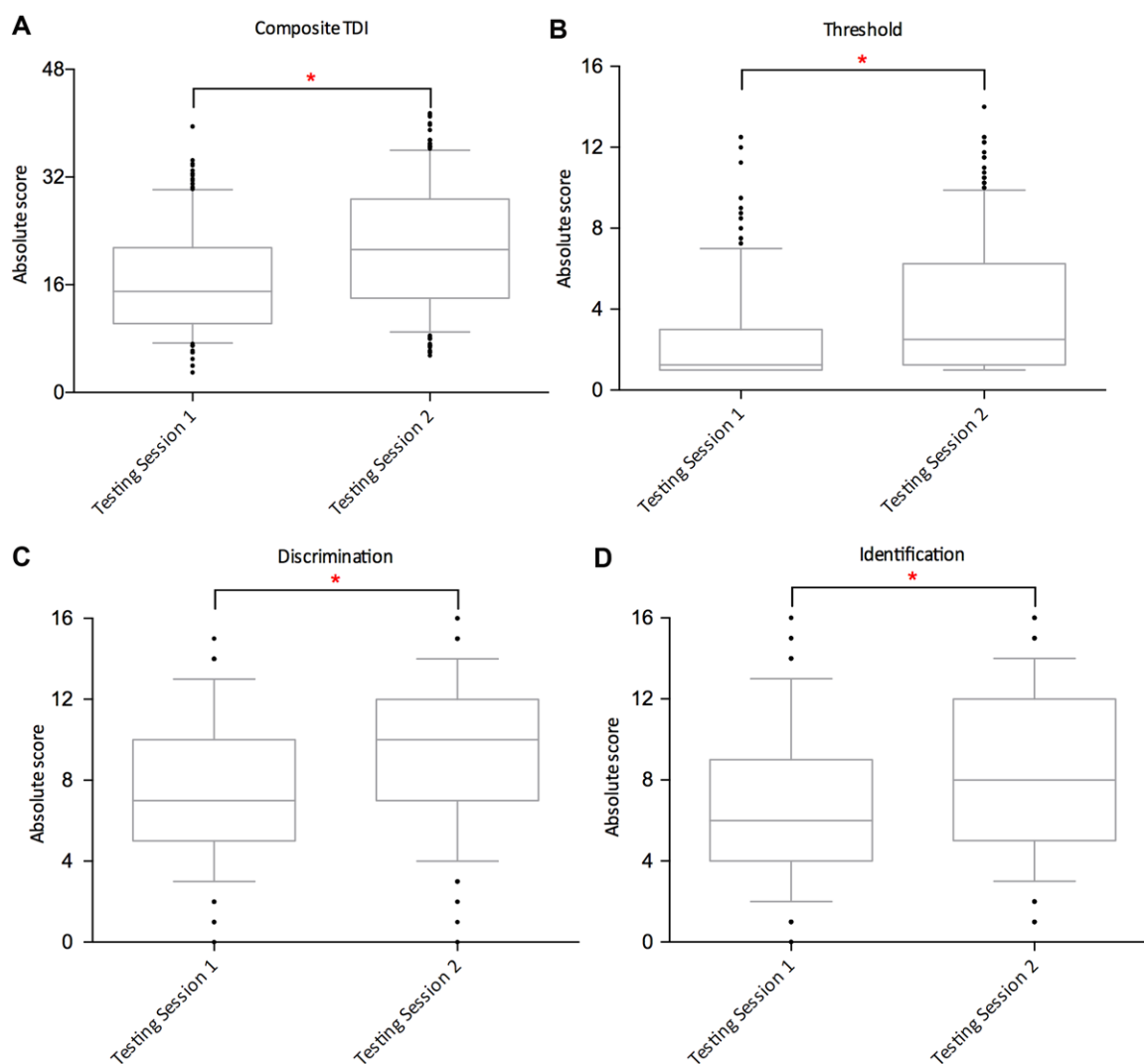


FIGURE 2. Overall mean composite (TDI) (A) and individual T (B), D (C), and I (D) scores at testing session 1 and 2, across all patients (error bars = 95% confidence interval). TDI: T = threshold; D = discrimination; I = identification.

TABLE 3. Overall mean change in score across all patients

	Δ score
TDI	5.2 ± 8.4
T	1.5 ± 3.1
D	1.9 ± 2.3
I	1.4 ± 2.1

TDI: T = threshold, D = discrimination, I = identification.

TABLE 4. Overall mean change in score in “younger” and “older” subgroups

	Δ score ≤45 (n = 63)	Δ score >45 (n = 345)
TDI	6.2 ± 10.3	5.0 ± 8.1
T	1.4 ± 3.5	1.6 ± 3.1
D	2.7 ± 4.0	1.8 ± 3.7
I	2.1 ± 4.4	1.6 ± 3.5

TDI: T = threshold, D = discrimination, I = identification.

correlation with overall change in TDI was seen with change in discrimination score, followed by identification and then threshold (Spearman $r = 0.82, 0.76$, and 0.68 , respectively; $p < 0.0001$). These results are shown in Figure 3.

A subgroup analysis was performed for patients of ≤24 months and >24 months duration. Within each group, the same pattern of correlation strength was seen, with D correlating best with composite TDI, followed by I and then T (Table 5).

Discussion

To our knowledge, this is the first study to investigate which of the individual subcomponents of the Sniffin’ Sticks test battery best reflect overall change in composite TDI score. In so doing, we have described psychophysical changes in olfactory function during conservative treatment for CRS, in the largest cohort of its type.

TABLE 5. Correlation coefficients for threshold, discrimination, and identification vs composite TDI score

	Correlation coefficient	
	≤24 months	>24 months
T	0.72 ^a	0.63 ^a
D	0.83 ^a	0.79 ^a
I	0.77 ^a	0.71 ^a

^aStatistically significant at $p < 0.0001$.
TDI: T = threshold, D = discrimination, I = identification.

Across all patients, we found modest, but significant improvements in test scores between session 1 and session 2. The overall mean improvement in composite TDI score was 5.2 ± 8.4 , whereas threshold, discrimination and identification mean scores improved by $1.5 \pm 3.1, 1.9 \pm 2.3$, and 1.4 ± 2.1 , respectively. As expected, larger improvements were seen within the subgroup of patients for whom olfactory function improved. In this group, mean TDI score increased by 8.6 ± 7.0 . Although correlation between subjective olfactory function and psychophysical test scores is poor,^{11,13,14} previous work from Gudziol et al has suggested that subjective improvement most commonly accompanies increases in composite TDI of ≥ 5.5 points.²⁷ Using this cut-off, the mean improvement across all patients falls just short of clinical significance, whereas the increase in score within the “improved” subgroup (72.3% of the total cohort) clearly reaches clinical significance. Furthermore, there was a greater level of improvement across all olfactory domains in younger as compared with older patients (using 45 years as cut-off age). However, this difference did not reach statistical significance.

Effect of disease duration on olfactory outcome

Controlling for age, we found a small but significant effect of duration on change in composite TDI score, where those patients with CRS for ≤2 years improved to a greater degree than those with disease of >2 years. Although there is some heterogeneity in the clinical literature, several in-vitro/vivo studies support the findings demonstrated here.

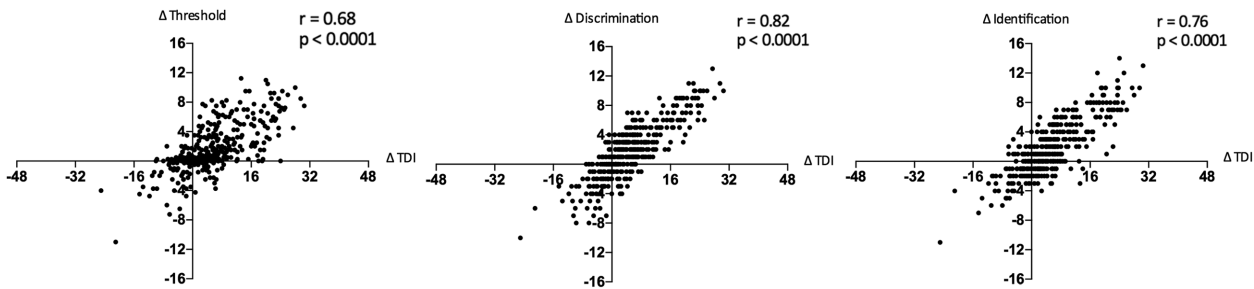


FIGURE 3. Scatterplots showing change in T (A), D (B), and I (C) subcomponent scores on the y-axis and change in TDI score on the x-axis, for each patient. Spearman correlation coefficient with associated p value is shown in the top right corner of each scatterplot. TDI: T = threshold; D = discrimination; I = identification.

In 2010, Lane and colleagues developed a transgenic mouse model in which a chronic inflammatory state was induced through temporary expression of tumor necrosis factor- α within the olfactory neuroepithelium.²⁹ They suggested that the initial olfactory dysfunction seen in their model could be attributed to reversible inflammatory cytokine-mediated receptor interference (which is in addition to known mechanical obstruction of odorant access to the olfactory cleft in CRS due to edema and polyp formation). However, as inflammation became more established, neuronal death occurred, coupled with subsequent impaired neuronal regeneration. The latter is in keeping with histologic findings from human olfactory mucosa biopsies, in which epithelial remodeling and replacement with respiratory or metaplastic squamous type epithelium has been shown to occur.²⁰ Extrapolating from these results, one may speculate that, when treatment is instigated before olfactory sensory neuron (OSN) death and associated epithelial remodeling has occurred, outcomes may be superior to treatment started once such histologic changes have begun.

With respect to clinical outcomes, several previous studies showed no correlation between duration of CRS and olfactory-related outcomes. This has been shown for subjective, psychophysical, and imaging-based studies.^{21,22} However, recent work from Hopkins and colleagues suggests that patients with CRS of longer duration prior to treatment (in this case endoscopic sinus surgery) incur significantly greater postoperative health-care needs, as defined by disease-specific medication use and health-care provider attendances.¹⁹ When considering such heterogeneity, one may argue that the lack of correlation demonstrated in some studies may be due to inconsistent reporting of disease duration, which is usually reliant on patient report. However, whereas such self-report has limitations, this is the accepted method through which disease duration is assessed in the clinic, and was the method used in our study.

In light of our results, combined with the histopathological evidence, we would suggest that patients undergo early treatment for CRS when olfactory outcomes are of concern.

Subtest correlation with composite TDI

Previous cross-sectional studies have addressed the diagnostic utility of Sniffin' Sticks subtest component scores. In 2010, Hedner et al showed that odor discrimination and identification, but not odor threshold, correlate significantly with tests of executive function and semantic memory.³⁰ This is in keeping with earlier findings in which cerebral pathology led to impaired odor identification but not threshold.^{31,32} Furthermore, in their cohort of 1226 patients, Whitcroft et al found that patients with olfactory dysfunction secondary to sinonasal disease had relatively poor odor threshold, but preserved odor discrimination and identification, when compared with non-sinonasal patients (ie, those with postinfectious, posttraumatic, or Parkinson-induced hyposmia).¹⁸ Combined, these results suggest that

odor threshold may best reflect peripheral olfactory function, whereas the suprathreshold tests of odor discrimination and identification preferentially reflect central olfactory processing.

Given the burden of disease within the neuroepithelium, one may therefore expect odor threshold to correlate best with change in olfactory function after treatment in CRS, as we hypothesized originally. However, it was surprising to find that change in TDI was best reflected by change in odor discrimination score (Spearman $r = 0.82$, $p < 0.0001$), not odor threshold (Spearman $r = 0.68$, $p < 0.0001$).

Although short-term working memory and executive function are required for decision making in the odor discrimination task, perception of odor quality is also dependent on the peripheral olfactory system. As part of the mechanism by which odor quality is neurally encoded, each OSN displays 1 olfactory receptor (OR) type, due to monoallelic, mutually exclusive OR-gene expression.³³ However, each OR is capable of detecting multiple different odorants and, in turn, each odorant is recognized by multiple different ORs. Importantly, each odorant is detected by a unique combination of OSNs. This combinatorial encoding therefore creates a unique neural fingerprint for an odor.^{34–36} Furthermore, in mice, OSNs are distributed within the olfactory epithelium in distinct zones, according to OR type. Within each zone, a number of different OR-specific OSNs are distributed stochastically. Although the proportion of OR-specific OSNs may vary between zones, each zone contains a sufficient variety of OSNs, such that each odorant should be detected in multiple zones. This arrangement additionally contributes to the odor fingerprint: an odor's spatial code is transformed into a unique pattern of neural activation. Although the zonal distribution of OSN within the human olfactory neuroepithelium is unclear, some degree of topographic encoding has been demonstrated for odor hedonic quality.³⁷

Although patients with olfactory dysfunction secondary to CRS tend not to experience extreme distortions in odor quality (eg, they tend not to experience parosmia, which is more frequently seen in postinfectious dysfunction), it is possible that the underlying pathophysiology may subtly affect the odor fingerprint. For example, variable inflammation or remodeling within the neuroepithelium may distort the spatial distribution of OR activation. One may speculate that, where CRS disease state improves, there may be a generalized subtle difference in function across zones and therefore multiple ORs. It is possible that such changes are most sensitively reflected by odor discrimination, which is dependent on multiple odors and therefore multiple zones or ORs as described. Although odor threshold appears to be preferentially reduced during cross-sectional testing in sinonasal disease, as this test relies only on the perception of "something" (irrespective of quality), it may be less sensitive in detecting subtle change within the olfactory epithelium, as assessed in longitudinal testing.

It is also becoming increasingly apparent that olfactory dysfunction in CRS is related to structural alterations in

the brain. For example, Gudziol et al demonstrated reduced olfactory bulb volume in CRS patients compared with healthy controls, as well as improvement in such volumes with treatment.³⁸ Han and colleagues also demonstrated reduced gray matter volumes in the gyrus rectus, orbitofrontal cortex, thalamus, and insula in CRS patients with severe olfactory dysfunction, when compared with controls.²² Combined with results from Hedner et al, one may further speculate that small changes in odor threshold with treatment in CRS may lead to some form of amplified central reorganization, in turn manifest as improved odor discrimination. However, further work is needed to investigate this hypothesis.

When complete TDI testing is not possible, such as in the busy clinic environment, ideally, the subtest or tests used should accurately reflect both impairment and improvement. In the case of CRS, our results suggest that odor discrimination most accurately reflects overall change in olfactory function. Given that previous cross-sectional work has suggested odor thresholds are preferentially reduced in CRS, we would suggest that combined threshold and discrimination testing may best reflect static and dynamic disease state in this condition. Although change in odor identification also correlated strongly with overall change in TDI, such tests are culturally specific, and discrimination is therefore further advantageous in this respect.

Study limitations

Due to the retrospective design of this study, we were unable to control for timing of olfactory testing or

specific medication use. Therefore, we cannot comment on the efficacy of different treatment modalities within the “conservative” umbrella. With regard to systemic corticosteroids, it is possible that patients who had recently finished a course of such treatment at time of second testing may have achieved better scores than those who had either not received systemic corticosteroids or those who had done so less recently. Furthermore, although we are not aware of any evidence to support the differential effect of systemic corticosteroids on the individual subcomponents of threshold, discrimination, or identification, a priori, it is possible that odor threshold may benefit most from such treatment, due to its association with the peripheral olfactory system.¹⁸ Although the wide inter-test interval range in our data may serve to ameliorate any such potential effects, further prospective studies are needed to clarify these points.

Finally, information regarding etiologic CRS subtype (eg, presence of polyps, eosinophilia, or Lund-Mackay score) was not available. Future prospective work should also aim to determine whether olfactory outcomes after medical treatment differ between different CRS subtypes.

Conclusion

We suggest that, whenever composite TDI testing is not possible, threshold and discrimination should be used to assess olfactory function in patients with CRS. We would further urge health-care providers to start treatment for CRS as early as possible. 🌀

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