

Original Article

Olfactory Impairment in Chronic Rhinosinusitis Using Threshold, Discrimination, and Identification Scores

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Accepted 5 July 2016.

Abstract

Differences in testing modalities and cut-points used to define olfactory dysfunction contribute to the wide variability in estimating the prevalence of olfactory dysfunction in chronic rhinosinusitis (CRS). The aim of this study is to report the prevalence of olfactory impairment using each component of the Sniffin' Sticks test (threshold, discrimination, identification, and total score) with age-adjusted and ideal cut-points from normative populations. Patients meeting diagnostic criteria for CRS were enrolled from rhinology clinics at a tertiary academic center. Olfaction was assessed using the Sniffin' Sticks test. The study population consisted of 110 patients. The prevalence of normosmia, hyposmia, and anosmia using total Sniffin' Sticks score was 41.8%, 20.0%, and 38.2% using age-appropriate cut-points and 20.9%, 40.9%, and 38.2% using ideal cut-points. Olfactory impairment estimates for each dimension mirrored these findings, with threshold yielding the highest values. Threshold, discrimination, and identification were also found to be significantly correlated to each other ($P < 0.001$). In addition, computed tomography scores, asthma, allergy, and diabetes were found to be associated with olfactory dysfunction. In conclusion, the prevalence of olfactory dysfunction is dependent upon olfactory dimension and if age-adjusted cut-points are used. The method of olfactory testing should be chosen based upon specific clinical and research goals.

Key words: olfaction, prevalence, sinusitis, Sniffin' Sticks

Introduction

Impaired olfaction is a cardinal diagnostic feature of chronic rhinosinusitis (CRS) according to current clinical guidelines (Fokkens et al. 2012; Rosenfeld et al. 2015). Considering its prevalence across North America, Europe, and Asia, CRS is one of the principal conditions contributing to olfactory loss worldwide (Hastan et al. 2011; Soler et al. 2012; Shi et al. 2015). Olfactory dysfunction in CRS results in significant declines in health related quality-of-life (QOL);

patients commonly complain of a lack of interest in food, decreases in social interaction, and may be at a greater risk for clinical depression (Blomqvist et al. 2004; Smeets et al. 2009; Croy et al. 2014).

The prevalence of CRS-related olfactory loss has been variably reported across studies, using both patient-reported and psychological assessments, with estimates ranging from 20% to 80% (Klimek et al. 1998; Jiang et al. 2008; Rudmik and Smith 2012; DeConde et al. 2014). The variability in this prevalence estimate is

likely multifactorial but could include differences in demographic features that impact olfaction, such as age or gender. Other factors might include disease features such as the presence/absence of polyps, presence of medical comorbidities, or the overall disease severity of a particular cohort. Differences in testing modalities exist as well, with some studies focusing on isolated domains of psychophysical olfaction, such as threshold, identification, or discrimination, whereas others focus on patient-reported metrics. Lastly, cut-offs utilized to define normal (normosmic) versus abnormal (hyposmic/anosmic) smell would also directly influence prevalence estimates.

The current study seeks to comprehensively explore olfactory loss in a patient population satisfying diagnostic criteria for CRS. The main goal was to provide internally valid estimates of olfactory impairment across different psychophysical olfactory domains using cut-points from population norms. Secondary goals were to explore disease specific factors that impact olfaction in this population and investigate the relationship between threshold, identification, and discrimination domains within CRS.

Materials and methods

Enrollment

Adult patients (≥ 18 years) who satisfied diagnostic criteria for CRS according to the European Position Paper on Rhinosinusitis (EPOS12) (Fokkens et al. 2012) were enrolled from Rhinology clinics at the Medical University of South Carolina in a prospective, cross-sectional fashion. Each patient was required to have at least 2 cardinal symptoms for greater than 3 months and objective evidence of inflammation on both sinonasal endoscopy and computed tomography (CT) scan. Patients were enrolled irrespective of perceived olfactory ability. Patients were excluded if they had been prescribed short-term oral corticosteroids within the last month or had sinonasal surgery within the last 6 months. Participants were able to complete all study questions in English. The MUSC Institutional Review Board approved this study, and all subjects provided written, informed consent. This study complies with the Declaration of Helsinki for Medical Research involving Human Subjects.

Demographics and comorbidities

Demographic information and medical comorbidities were specifically collected from the patients and included age, gender, race/ethnicity, smoking status (yes/no), and prior sinus surgery (yes/no). The presence of medical comorbidities was determined by patient-report of a prior, existing physician diagnosis for all conditions except allergic rhinitis, which required prior positive objective testing (skin prick or in vitro testing). Diabetes was defined as those with type 2 diabetes mellitus only as there were no patients with type 1.

CRS disease severity

Sinusitis-specific disease severity was assessed based on endoscopy, imaging, and patient-reported QOL. Rigid sinonasal endoscopy was performed on each patient and scored according the Lund–Kennedy algorithm (range 0–20; higher scores indicate greater disease) by the enrolling physician (Lund and Kennedy 1997). Patients were further categorized as those without polyps (CRSsNP) and those with visible polyps (CRSwNP). CT scans performed during the course of clinical care were graded by the enrolling physician according to the Lund–Mackay scoring system (range 0–24; higher scores indicate greater disease) (Lund and Mackay 1993). Sinus-specific QOL was assessed using the 22-item Sino-Nasal Outcome Test (SNOT-22) (Hopkins

et al. 2009). The SNOT-22 contains 22 questions (total score range, 0–110), with higher scores representing more severe QOL impact.

Olfactory testing

Quantitative olfactory testing was performed using the “Sniffin’ Sticks” test (Burghardt) (Hummel et al. 1997). All tests were performed by the same clinical research coordinator who was blinded to all other study responses. The test battery included odor threshold, odor discrimination, and odor identification. The threshold test was performed using dilutions of *n*-butanol in a single-staircase, triple-forced choice procedure. The discrimination test used triplets of pens presented in random order with 2 containing the same odorant and the third a different odorant. The identification test utilized 16 odorants presented at suprathreshold intensity using multiple-choice procedure. All subjects were blindfolded to avoid visual identification of odorant-containing pens. The 3 test scores were reported independently. Discrimination and identification were scored from 0 to 16, and threshold was scored from 1 to 16. The overall results were also combined for an overall score called the “composite threshold-discrimination-identification score” (TDI), which ranged from 1 to 48 with higher scores indicating superior olfactory performance.

Statistical analysis

Statistical analyses were performed using a commercially available software application (SPSS v. 22; IBM Corporation). Descriptive statistics (means, standard deviations [SDs], percentages, etc.) were used to characterize the study cohort with respect to all collected measures, including demographics, comorbidities, and CRS-specific disease severity measures. The influence of these measures on olfactory function was first examined with bivariate analysis. Measures with a *P*-value ≤ 0.10 were included in multiple regression analysis to explore the independent association of these measures on olfaction. Measures that were not significant ($P \geq 0.05$) were removed in a backward selection stepwise procedure. Models explored the association of the correlates with total TDI scores, as well as individual olfactory domains. Continuous variables were compared between 2 groups using independent-samples *t*-tests or Mann–Whitney *U* tests, and categorical variables were compared using the Pearson chi square test or Fisher’s Exact test. Pearson correlations were used to determine associations between 2 continuous variables.

Age-adjusted prevalence

The prevalence of olfactory loss was then determined for the overall cohort using “age-adjusted” cut-offs. Age adjusted cut-offs were determined using data from a large population of normal subjects reported previously by Hummel et al. (2007). Subjects were placed into 16–35, 36–55, and >55 year age groups. Total TDI scores were broken into normosmic, hyposmic, and anosmic categories. For individual olfactory domains (threshold, discrimination, identification), subjects were classified as having impaired olfaction if their individual scores was ≤ 10 th percentile based on their age group.

Prevalence based on ideal olfaction

The prevalence of olfactory loss was then determined for the overall cohort using “ideal” cut-offs. We defined ideal cut-offs as the scores that would be expected for normal subjects aged 16–35 years, using expected TDI values for into normosmic, hyposmic, and anosmic categories. For individual olfactory domains (threshold, discrimination, identification), subjects were classified as having impaired olfaction if their individual scores was ≤ 10 th percentile based on the 16–35 year age group (Hummel et al. 2007).

Relationship between psychophysical olfactory domains

The relationships between threshold, discrimination, identification, and total TDI scores were then assessed in a quantitative fashion using Pearson's correlation coefficients. Additionally, using ideal cut-offs, patients were categorized into normal versus abnormal olfaction for each metric and 4 × 4 tables were compared across olfactory measures.

Results

A total of 110 patients with CRS were enrolled of which 40.1% were CRSsNP and 59.9% CRSwNP (Table 1). The average age of the cohort was 52.7 years (SD = 16.1), with just over half female (55.5%). Asthma and allergic rhinitis were present in 48.1% and 56.4% of the cohort, respectively, with greater prevalence seen in the CRSwNP subgroup. Overall, the cohort had a high degree of disease severity with mean CT score of 12.1 (SD = 6.8), endoscopy score of 6.3 (SD = 3.8), and average SNOT-22 of 46.5 (SD = 21.0). As expected, the CRSwNP subgroup had worse CT and endoscopy scores ($P < 0.020$ for both). The overall mean TDI score for the cohort was 21.1 (SD = 9.1), with lower scores seen in the CRSwNP

cohort as compared with CRSsNP (18.2 ± 7.9 vs. 25.3 ± 9.2 ; $P < 0.001$) (Table 1).

The relationship between olfaction and demographic, comorbidity, and disease severity factors was then explored with bivariate analysis. Nasal polyps, CT score, and endoscopy score were significantly associated with total TDI scores, as well as each individual subdomain. Asthma was significantly associated with total TDI scores, threshold, and discrimination. Allergy and diabetes were associated with identification and discrimination, respectively. Those factors found to be independent predictors on multivariate regression are reported in Table 2. Lund–Mackay CT scores were a consistent independent predictor across all olfaction measures, such that the higher the CT score, the worse the total TDI scores ($\beta = -0.75$; $P < 0.001$). The presence of asthma was similarly predictive for lower threshold and identification scores. Diabetes (type 2) was associated with worse total TDI and discrimination scores, whereas the presence of allergy was associated with improved identification scores. It should be kept in mind that there is colinearity among some of these measures, such as CT score and polyp status. Although polyp status was predictive on bivariate analysis, when CT score is added, it dropped out of the model.

Table 1. Baseline demographics and QOL measures

	All CRS (<i>n</i> = 110)	CRSsNP (<i>n</i> = 45)	CRSwNP (<i>n</i> = 65)	<i>P</i> -value for differences between CRSwNP and CRSsNP
	Mean (SD) count (%)	Mean (SD) count (%)	Mean (SD) count (%)	
Demographic or QOL measure				
Age	52.69 (16.07)	53.68 (16.30)	52.01 (16.00)	0.594
Sex				
Male	49 (44.55)	16 (35.56)	33 (50.77)	0.114
Female	61 (55.45)	29 (64.44)	32 (49.23)	
Race				
White	78 (70.91)	38 (84.44)	40 (61.54)	0.018
African American	30 (27.27)	7 (15.56)	23 (35.38)	
Asian	2 (1.82)	0 (0.00)	2 (3.08)	
Ethnicity				
Hispanic/Latino	2 (1.82)	1 (2.22)	1 (1.54)	1.000
Non-Hispanic/Latino	108 (98.18)	44 (97.78)	64 (98.46)	
Asthma	53 (48.18)	10 (22.22)	43 (66.15)	<0.001
ASA intolerance	11 (10.00)	3 (6.67)	8 (12.31)	0.520
Allergy by testing	62 (56.36)	21 (46.67)	41 (63.08)	0.088
COPD	8 (7.27)	3 (6.67)	5 (7.69)	1.000
Depression	20 (18.18)	10 (22.22)	10 (15.38)	0.361
Fibromyalgia	6 (5.45)	5 (11.11)	1 (1.54)	0.041
Immunodeficiency	2 (1.83)	1 (2.27)	1 (1.54)	1.000
Autoimmune disease	3 (2.73)	1 (2.22)	2 (3.08)	1.000
Steroid dependency	3 (2.80)	1 (2.33)	2 (3.13)	1.000
Diabetes	18 (16.36)	8 (17.78)	10 (15.38)	0.739
Prior sinus surgery	81 (73.64)	32 (71.11)	49 (75.38)	0.617
Smoking status (yes/no)	4 (3.64)	2 (4.44)	2 (3.08)	1.000
Alcohol use (drinks/week)	1.78 (3.48)	1.07 (2.44)	2.27 (3.99)	0.177
Lund–Mackay CT score	12.11 (6.78)	8.53 (5.74)	15.58 (5.89)	<0.001
Lund–Kennedy endoscopy score	6.32 (3.78)	5.36 (3.21)	6.98 (4.02)	0.020
SNOT-22 score	46.5 (21.0)	49.8 (17.1)	44.3 (23.2)	0.161
Severity of olfactory impairment				
TDI total score	21.13 (9.10)	25.28 (9.20)	18.26 (7.90)	<0.001
Threshold	2.96 (2.43)	3.91 (2.73)	2.30 (1.96)	0.001
Discrimination	8.75 (3.35)	10.20 (3.40)	7.74 (2.95)	<0.001
Identification	9.43 (4.45)	11.12 (4.21)	8.22 (4.23)	<0.001

CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps; ASA, acetylsalicylic acid; COPD, chronic obstructive pulmonary disease. Outcome test: T, threshold; D, discrimination; I, identification. Bold: $P < 0.05$ considered statistically significant.

The age-adjusted prevalence of olfactory dysfunction is shown in Table 3. Based on total TDI scores, 41.8% of the overall cohort was normosmic, 20.0% hyposmic, and 38.2% anosmic. When looking at individual domains, 75.5% of the cohort had threshold scores below the 10th percentile, as compared with 50.9% and 57.3% for discrimination and identification, respectively. When comparing the CRSsNP and CRSwNP subgroups, those with polyps had higher prevalence of dysfunction across all measures.

When evaluating the prevalence of olfactory dysfunction using ideal cut-offs, the overall prevalence of anosmia using total TDI scores remains exactly the same (Table 3). However, the prevalence of hyposmia increases relative to normosmia. When looking at the CRSsNP subgroup specifically, the prevalence of identification and discrimination loss are essentially the same as the age-appropriate cut-offs. The biggest difference is that a notably higher percentage of the CRSsNP has threshold loss when using ideal cut-offs compared with age-appropriate levels (82.2% vs. 66.7%; $P = 0.016$). When using ideal cut-offs in patients with CRSwNP, the prevalence of olfactory dysfunction increases by 14% and 20% in the threshold and discrimination domains, respectively, with a slight increase (6%) in the identification domain. Overall there was a statistically significant correlation between psychophysical olfactory measurements

(Table 4, Figure 1). The strongest correlation was between identification score and total TDI score ($R = 0.931$; $P < 0.0001$). Correlations among threshold, discrimination, and identification ranged from 0.621 to 0.697 and all were highly significant ($P < 0.001$). When examining 4×4 tables some relationships are readily apparent (Table 5). For the entire cohort, all patients with normal threshold also had normal identification scores. Similarly, 91% of patients with normal threshold also had normal discrimination. However, for those patients with abnormal threshold, 33% had normal identification and 30% had normal discrimination. On the contrary, 100% of patients with abnormal identification also had abnormal threshold, and 99% of those with abnormal discrimination also had abnormal threshold. Very similar relationships are seen when examining CRSsNP and CRSwNP subgroups specifically.

Discussion

This study cohort had a significant degree of olfactory dysfunction, which was predicted by polyp status, asthma, allergy, and diabetes. When CT scoring was considered in multivariate modeling, the importance of polyp status dropped out, but asthma, allergy, and even diabetes remained predictive depending on the specific olfactory domain. An association between olfaction and inflammatory conditions such as asthma is not unexpected. With regard to diabetes, there is at least one prior study showing an association between olfactory loss and diabetes, possibly a manifestation of microvascular disease (Vennemann et al. 2008; Gouveri et al. 2014). As expected, the prevalence of olfactory loss varied based on whether age-adjusted or ideal cut-offs were used to define normal and abnormal olfaction, with greater prevalence seen with ideal cut-offs to define normosmia.

The fact that olfactory function declines with age has been documented across a number of large, normative population studies (Doty and Kamath 2014). There is a temptation to consider this age-associated decline to be normal or “expected” and thus to report age-adjusted values. However, when one considers other senses, such as hearing or eyesight, “normal” is characterized in reference to the ideal level of function, typically defined as that seen in healthy, young adults. A simple corollary is the audiogram, which has an accepted range of normal independent of age. Just as one would consider it inappropriate to age-adjust an audiogram for an elderly patient with presbycusis, a similar argument can be made for olfaction.

Table 2. Factors associated with olfaction on multivariate modeling

	β	SE	<i>t</i> -Statistic	<i>P</i> -value
TDI total score				
Diabetes	−6.29	2.49	−2.53	0.014
LM CT score	−0.75	0.14	−5.20	<0.001
Threshold				
Asthma	−1.13	0.53	−2.11	0.039
LM CT score	−0.10	0.04	−2.66	0.010
Discrimination				
Diabetes	−2.54	0.90	−2.82	0.006
LM CT score	−0.26	0.05	−5.02	<0.001
Identification				
Asthma	−2.02	0.95	−2.13	0.037
Allergy	2.24	0.92	2.43	0.018
LM CT score	−0.32	0.07	−4.56	<0.001

T, threshold; D, discrimination; I, identification; SE, standard error; LM, Lund–Mackay.

Table 3. Prevalence of olfactory dysfunction using age appropriate cut-offs

	Using age appropriate cut-offs			Using cut-off for 16–35 years old		
	CRS (%) (<i>n</i> = 110)	CRS (%) (<i>n</i> = 110)	CRSsNP (%) (<i>n</i> = 45)	CRSwNP (%) (<i>n</i> = 110)	CRSsNP (%) (<i>n</i> = 45)	CRSwNP (%) (<i>n</i> = 65)
T	75.5	75.5	66.7	90.0	82.2	95.4
D	50.9	50.9	35.6	63.6	37.8	81.5
I	57.3	57.3	40.0	60.0	37.8	75.4
TDI						
Normosmia	41.8	41.8	55.6	20.9	35.6	10.8
Hyposmia	20.0	20.0	22.2	40.9	42.2	40.0
Anosmia	38.2	38.2	22.2	38.2	22.2	49.2

T, threshold; D, discrimination; I, identification; CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps. Age appropriate cut-offs: Females (36–55 years old): T ≤ 5.50; D ≤ 10; I ≤ 12; TDI ≤ 28.75 (hyposmia); TDI ≤ 15 (anosmia); Males (36–55 years old): T ≤ 3.75; D ≤ 9; I ≤ 11; TDI ≤ 24.95 (hyposmia); TDI ≤ 15 (anosmia); Females (>55 yo): T ≤ 2.75; D ≤ 7.4; I ≤ 9; TDI ≤ 19.05 (hyposmia); TDI ≤ 15 (anosmia); Males (> 55 yo): T ≤ 2.25; D ≤ 7; I ≤ 9; TDI ≤ 19.75 (hyposmia); TDI ≤ 15 (anosmia). 16–35 year old cut-offs: Females: T ≤ 6.50; D ≤ 10; I ≤ 11; TDI ≤ 30.50 (hyposmia); TDI ≤ 15 (anosmia); Males: T ≤ 6.00; D ≤ 10; I ≤ 11; TDI ≤ 29.50 (hyposmia); TDI ≤ 15 (anosmia).

This seems particularly important if one considers the chronicity of CRS and the fact that repetitive and persistent inflammation related to CRS could contribute to or enhance age-related olfactory decline.

The prevalence of olfactory dysfunction varied across specific olfactory domains, with the greatest frequency of loss seen for threshold levels. When ideal cut-offs were used, 90% of the overall cohort had a threshold level below the 10th percentile, a finding which was relatively similar across CRSsNP and CRSwNP subgroups (82% and 95%, respectively). The overall prevalence of identification loss was only 60%, with a much greater disparity between CRSsNP (38%)

and CRSwNP (75%) subgroups. These findings suggest testing methods that only report identification scores might underestimate the degree of olfactory loss present in a CRS population, particularly those with CRSsNP.

Within this cohort there was a moderate to strong correlation between olfactory domains, a finding that has been reported across normative populations (Doty et al. 1994; Hummel et al. 1997; Hummel et al. 2007). In fact, the correlation between TDI and identification was incredibly strong ($R = 0.93$; $P < 0.0001$), such that knowing one essentially forecasts the other. However, focusing on these correlations alone obscures some of the important interrelationships. Within this cohort, essentially all patients with normal threshold testing also had normal identification and discrimination scores. Therefore, once a normal threshold is documented, further suprathreshold testing of identification or discrimination appears superfluous. On the contrary, patients with abnormal identification or discrimination scores nearly always also had abnormal threshold scores, indicating that further threshold testing in this population would also be superfluous. Those patients with abnormal threshold scores would benefit from further suprathreshold testing of

Table 4. Correlations between individual Sniffin' Stick components

	Discrimination	Identification	TDI total score
Threshold	0.621*	0.694*	0.835*
Discrimination		0.697*	0.875*
Identification			0.931*

T, threshold; D, discrimination; I, identification.
* $P < 0.001$.

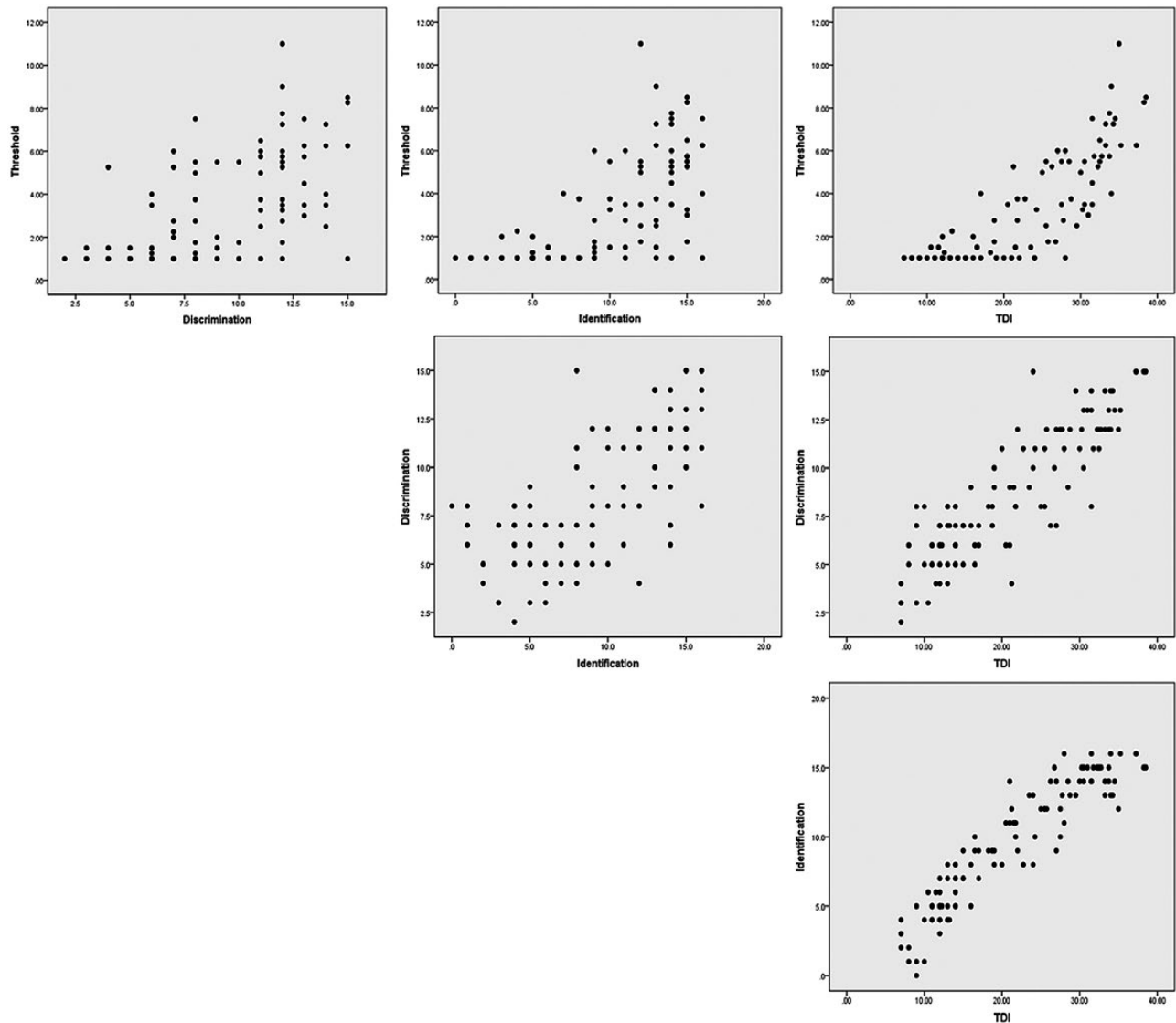


Figure 1. Scatter plots of correlations between individual Sniffin' Stick components.

Table 5. Overlap between individual components of Sniffin' Sticks test

	CRS		CRSSNP		CRSwNP	
	Normal I	Abnormal I	Normal I	Abnor Abnormal I	Normal I	Abnor Abnormal I
Normal T	11	0	8	0	3	0
Abnormal T	33	66	20	17	13	49

	CRS		CRSSNP		CRSwNP	
	Normal D	Abnormal D	Normal D	Abnor Abnormal D	Normal D	Abnor Abnormal D
Normal T	10	1	8	0	2	1
Abnormal T	30	69	20	17	10	52

T, threshold; D, discrimination; I, identification; CRSSNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps.

identification and discrimination, which may or may not be affected. Similarly, those patients with normal identification and/or discrimination might benefit from threshold testing, as a large proportion would be expected to have declines. The exact order and scope of testing that should be performed depends on the underlying clinical or research goals. These findings may not hold true in other populations, particularly those with neurocognitive defects, like Alzheimer's disease, which might preferentially impact memory-dependent tasks like olfactory discrimination and identification (Hedner et al. 2010; Velayudhan 2015), or in Idiopathic Parkinson disease, in which all dimensions seem to be severely compromised upon clinical manifestation of disease (Lötsch et al. 2008). Further study on the longitudinal changes in CRS-related threshold, discrimination, and identification olfactory loss are also needed to support these findings.

This cross-sectional study was not designed to allow insights into mechanisms of disease. Presumably, the olfactory loss experienced by these patients relates to the underlying mucosal inflammation, which characterizes CRS (Klimek and Eggers 1997). Specific mechanisms might include diminished airflow into the olfactory cleft secondary to mucosal edema/polyps, direct inflammation of the specialized olfactory epithelium, alteration in olfactory mucus, or even replacement of olfactory epithelium with respiratory epithelium. The degree to which any specific process impacts individual domains of olfaction is unknown. It also remains unknown whether threshold declines are mechanistically different than suprathreshold declines or whether differences simply represent a continuum of disease severity. A similar argument can be made for hyposmic versus anosmic disease states. Answers to these questions will require more sophisticated study designs that directly explore olfactory-specific disease mechanisms.

Strengths of this study include a prospective design that recorded demographics, comorbidities, CRS-specific disease severity measures, and several psychophysical olfactory tests. This strengthens the internal validity of findings and allowed a comprehensive understanding of olfactory function within this individual cohort. However, it would not be appropriate to fully extrapolate these findings to all patients with CRS or across the spectrum of olfactory disorders, particularly absolute prevalence estimates. This patient cohort was small and enrolled from a tertiary referral center with severe disease burden, evidenced by a high prevalence of comorbid disease (asthma and allergic rhinitis), high CT/endoscopy scores, and 74% prior sinus surgery rate. Patient populations with less severe disease and a different constellation of patient-specific disease factors would probably have lower prevalence estimates.

Conclusion

Olfactory dysfunction is a common finding in patients with CRS, particularly those with polyps and asthma. Although correlations exist across olfactory domains in CRS, the prevalence of olfactory loss varies based on the domain of olfaction tested and whether age-adjusted or ideal normative values are used to define normal. The specific testing strategy utilized should be determined based on underlying clinical or research goals.

Funding

This work was supported by grants from the National Institute on Deafness and Other Communication Disorders (NIDCD), one of the National Institutes of Health, Bethesda, MD (R03 DC013651-01; PI: Z.M.S.). Z.M.S. is supported by grants from Entellus, Intersect, and Optinose, none of which are affiliated with this manuscript. R.J.S. is supported by grants from OptiNose, Entellus and IntersectENT, none of which are associated with this manuscript.

Conflict of interest

Z.M.S. is a consultant for Olympus, which is not affiliated with this manuscript. R.J.S. is also a consultant for Olympus, Meda, and Arrinex, which are not affiliated with this study. There are no disclosures for P.K. and K.A.S.

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