Development of a new psychophysical method to assess intranasal trigeminal chemosensory function*

C. Huart[1,2], T. Hummel[3], C. Kaehling[3], I. Konstantinidis[4], V. Hox[1], A. Mouraux[2], P. Rombaux[1,2]

[1] Department of Otorhinolaryngology, Cliniques universitaires Saint-Luc, Brussels, Belgium

[2] Institute of Neuroscience, Université catholique de Louvain, Brussels, Belgium

[3] Smell and Taste Clinic, Department of Otorhinolaryngology, TU Dresden, Dresden, Germany

[4] Second Academic Otorhinolaryngology Department, Papageorgiou Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece

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Abstract

Background: The aim of this study was to develop a new psychophysical test to assess intranasal trigeminal chemosensory function.

Methodology: The test is similar to the Sniffin' Sticks test, but using pens impregnated with substances preferentially activating trigeminal afferents. Our test comprises detection threshold, discrimination, identification and lateralization tasks. In a first study, we evaluated healthy controls. In a second study, we evaluated the potential usefulness of this test in patients with rhinological conditions.

Results: Study 1: 86 controls were included. Threshold, identification and lateralization performance decreased with age. Test-retest reliability was similar to that of olfactory tests. Study 2: results of the controls group were compared to those of 59 patients (14 allergic rhinitis, 11 chronic rhinosinusitis with nasal polyps (CRSwNP), 9 without nasal polyps (CRSsNP), and 25 with an olfactory disorder (OD)). Controls had 1) lower detection thresholds compared to CRSwNP, CRSsNP and OD, 2) better discrimination and identification scores compared to OD, and 3) better lateralization scores compared to CRSwNP and CRSsNP.

Conclusions: Our test allows to identify age-related changes in trigeminal chemosensory function. Trigeminal function seems to be differently affected in different pathologies. Further studies are necessary to validate our results and evaluate the impact of olfactory co-activation on the observed results.

Key words: nose, olfaction, sinusitis, smell, trigeminal

Corrected Proof

Introduction

The nose is a complex sensory organ, ensuring diverse functions that are essential for our survival. For that purpose, the nose relies on a double innervation by olfactory and trigeminal chemosensory systems [(1)]. The trigeminal system is involved in the perception of odorants [(1)] and nasal airflow [(2-3)], as well as in nasal inflammation, and activation of the autonomic nervous system [(4-6)]. Activation of trigeminal fibers by irritants, allergens or bacteria leads to protective reflexes, whose aim is to avoid inhalation of potentially dangerous substances and to trigger their expulsion [(7)]. Essentially, the trigeminal chemosensory system constantly screens the environment for potential threats and when activated, it leads to a series of physiological reactions intended to protect the upper and lower respiratory airways. Hence, it must be considered as a sentinel of the airways, ensuring a first line defense mechanism against a diverse array of noxious agents [(4-6)].

It has been shown that trigeminal sensitivity is decreased in patients with olfactory loss [(8,9)] and it is thought to be affected in several rhinological conditions [(10)]. Yet, in current clinical practice, the trigeminal system receives relatively little attention. The impact of rhinological diseases on the trigeminal system has been poorly investigated as well as the impact of dysfuncti-

onal trigeminal system has on the airways. This lack of interest in trigeminal sensitivity may, at least partially, be explained by the lack of simple, validated and easy ways to measure trigeminal sensitivity in clinic [11].

The evaluation of trigeminal chemosensory function is particularly challenging due to the close interaction between the olfactory and trigeminal systems [12]. Several methods have been described to assess intranasal trigeminal chemosensory function, including psychophysical or electrophysiological testing [11,13-15]. However, up to this day, there is no standardized or preferred tool for the evaluation of trigeminal chemosensory function in clinical practice. Recently, some authors have introduced new devices to selectively activate trigeminal afferents using gaseous CO_2 [14,15]. Although they demonstrated a high test-retest reliability and an investigator-friendly use, these devices are not available for purchase. Consequently, their availability is limited.

The aim of this study was to develop a simple and practical tool to evaluate trigeminal chemosensory function in patients. For that purpose, we designed a test similar to the Sniffin' Sticks test for the psychophysical evaluation of olfactory function [16].

Materials and methods

The aim of a first study was to develop and validate the test in a healthy population. A second study aimed at evaluating the potential usefulness of this test in a subset of patients suffering from diverse rhinological conditions. All experimental procedures were explained and demonstrated in full detail to the subjects who provided informed written consent. The study was performed in accordance with the Declaration of Helsinki. Experiments were performed in three different centers (Brussels (Belgium), Dresden (Germany) and Thessaloniki (Greece)), following a standardized protocol.

Trigeminal probes

Chemicals were presented in commercially available felt-tip pens (Burghart Medical Technology, Wedel, Germany), similar to the pens used in the Sniffin' Sticks test [16]. The pens were filled with chemicals dissolved in propylene glycol, to a total volume of 4 ml. To present the chemicals at the patient, the investigator removed the cap for ~3 s, and then held the pen's tip approximately 2 cm in front of both nostrils.

Selection of chemicals

We selected six substances known to strongly activate trigeminal chemosensory afferents: menthol [1], eucalyptol [17], propanol [1], ethanol [1], camphor [18], diallylsulfide [19] (Merck chemicals; Overijse, Belgium). These substances are assumed to activate different kind of chemosensory receptor channels expressed by the trigeminal nerve fibers, i.e. transient receptor potential (TRP) TRPM8 for menthol, eucalyptol and camphor; TRPA1 for diallylsulfide, TRPV1 for ethanol and propanol [11].

Table 1. Description of the different odorants that were used in the discrimination test. Triplets of odorants consisted into one pen containing a substance activating the trigeminal system and two other containing substances activating the olfactory system.

Triplet	Trigeminal pen	Odorant pen (1)	Odorant pen (2)
1	Ethanol	Rose	Leather
2	Menthol	Apple	Liquorice
3	Diallylsulfide	Orange	Fish
4	Propanol	Lemon	Coffee
5	Camphor	Banana	Anise
6	Eucalyptol	Leather	Pineapple

Trigeminal thresholds

Trigeminal thresholds were assessed using menthol, dissolved in propylene glycol. Dilutions were established in a geometric series (1:2). The highest concentration was 50%. 10 dilutions were presented to patients, based on the results of the study of Frasnelli et al. [20].

Subjects were blindfolded to prevent visual identification. Three pens were presented to each subject in a randomized order: two contained the solvent and a third one the menthol solution. During this 3-alternative forced choice task the subjects were asked to identify the pen containing the menthol, focusing on the trigeminal sensation, that was described as a "stinging, burning, irritating or cool sensation". The presentation of the triplets lasted approximately 10s and there was an interval of 30s before presentating the next triplet. Pens were presented in an initially ascending staircase procedure with 7 reversals. The threshold was calculated as the average of the last 4 reversals of the staircase, similarly to the Sniffin' Sticks test [16].

Trigeminal discrimination

We evaluated the ability of subjects to discriminate between trigeminal and odorous sensations. Three pens were presented to each subject in a randomized order: two containing substances preferentially activating the olfactory system (selected from Sniffin' Sticks identification test battery) and one substance preferentially activating the trigeminal system (menthol, ethanol diallylsulfide, propanol, camphor, eucalyptol) (Table 1). Subjects had to identify the pen that gave the strongest trigeminal sensation, following a triple-forced-choice procedure. Participants were blindfolded to avoid visual identification. Presentation of triplets was separated by at least 30s. The interval between the presentation of individual pens was 3s. Stimuli were presented in a randomized order.

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Table 2. Descriptive statistics of normative values obtained in healthy subjects.

		Healthy subjects				Males				Females			
		T	D	I	L	T	D	I	L	T	D	I	L
Age group 1 <35 years													
N		36	36	30	36	13	13	10	13	23	23	20	23
Mean ± SD		8,71 ± 1,29	4,44 ± 1,13	2,70 ± 0,79	19,53 ± 3,78	8,40 ± 1,42	3,92 ± 1,44	2,40 ± 0,84	19,38 ± 3,07	8,89 ± 1,20	4,74 ± 0,81	2,85 ± 0,74	19,61 ± 4,19
Range		6,00-10,00	1,00-6,00	1,00-4,00	12,00-26,00	6,00 – 10,00	1,00-5,00	1,00-4,00	14,00-24,00	6,50-10,00	3,00-6,00	1,00-4,00	12,00-26,00
Percentiles	10	6,50	2,70	2,00	14,00	6,20	1,40	1,10	14,00	6,70	3,40	2,00	13,20
	25	7,81	4,00	2,00	16,25	6,87	2,50	2,00	17,50	8,00	4,00	2,25	16,00
	50	9,37	5,00	3,00	20,00	8,50	5,00	2,00	20,00	9,50	5,00	3,00	20,00
	75	9,94	5,00	3,00	21,75	9,62	5,00	3,00	21,50	10,00	5,00	3,00	22,00
	90	10,00	5,30	4,00	25,30	10,00	5,00	3,90	23,20	10,00	6,00	4,00	26,00
Age group 2 35-55 years													
N		24	24	22	24	12	12	11	12	12	12	11	12
Mean ± SD		8,42 ± 1,48	4,63± 1,27	2,45 ± 1,01	17,04 ± 2,61	7,58 ± 1,47	4,58 ± 1,38	2,64 ± 0,50	16,33 ± 2,50	9,27 ± 0,93	4,67 ± 1,23	2,27 ± 1,35	17,75 ± 2,63
Range		5,50-10,00	2,00-6,00	0,00-4,00	11,00-22,00	5,50-10,00	2,00-6,00	2,00-3,00	11,00-21,00	7,50-10,00	2,00-6,00	0,00-4,00	13,00-22,00
Percentiles	10	5,50	2,00	1,00	13,50	5,50	2,00	2,00	11,90	7,65	2,30	0,20	13,60
	25	7,50	4,00	2,00	15,25	6,00	4,00	2,00	15,25	8,50	4,00	1,00	15,25
	50	8,50	5,00	3,00	17,00	7,50	5,00	3,00	16,00	9,87	5,00	3,00	18,00
	75	10,00	5,75	3,00	18,75	8,87	5,75	3,00	17,75	10,00	5,75	3,00	19,75
	90	10,00	6,00	3,70	21,00	9,70	6,00	3,00	20,40	10,00	6,00	4,00	21,70
Age group 3 >55 years													
N		26	26	26	26	11	11	11	11	15	15	15	15
Mean ± SD		7,20 ± 2,47	4,12 ± 1,24	1,46± 0,90	17,63 ± 3,92	6,34 ± 2,75	4,00 ± 1,10	1,45 ± 0,52	16,36 ± 2,98	7,83 ± 2,13	4,20 ± 1,37	1,47 ± 1,12	18,69 ± 4,40
Range		1,00 – 10,00	1,00-6,00	0,00-3,00	9,00 – 24,00	1,00-10,00	2,00-5,00	1,00-2,00	9,00-19,00	3,25-10,00	1,00-6,00	0,00-3,00	10,00-24,00
Percentiles	10	3,10	2,70	0,00	11,50	1,35	2,20	1,00	10,00	4,00	2,20	0,00	11,20
	25	6,00	3,00	1,00	15,25	4,50	3,00	1,00	15,00	6,00	3,00	1,00	15,50
	50	7,37	4,00	1,00	18,00	6,75	4,00	1,00	17,00	8,50	4,00	1,00	19,00
	75	9,37	5,00	2,00	19,00	7,50	5,00	2,00	19,00	9,75	5,00	3,00	23,00
	90	10,00	6,00	3,00	23,50	10,00	5,00	2,00	19,00	10,00	6,00	3,00	24,00

T: Threshold, D: Discrimination, I: Identification, L: Lateralization.

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Trigeminal identification

We evaluated the ability of subjects to identify the sensation induced by the trigeminal stimuli. Subjects were presented with 6 pens. To identify the quality of the substances, 5 cards with verbal descriptors were presented to the subjects. The cards were: 1) pungent, astringent, 2) burning, warm 3) scratching, tickling, sneezing, 4) prickling, 5) cold, fresh. These verbal descriptors were chosen from a list established by von Skramlik [21]. Each pen was presented in a randomized order with an interval of at least 30s.

Trigeminal lateralization

The ability to localize trigeminal stimuli was assessed using a test based on previous studies [22,23]. The device consisted of two parallel syringes (total volume 50 ml each) with their spouts angled so that the headspace from one syringe was presented to the left nostril and the headspace of the other to the right nostril. One syringe contained 20 ml of menthol diluted in propylene glycol (50%). The other contained 20 ml of odorless propylene glycol. Air from the headspace of the syringes was delivered in a uniform manner by pressing the joint pistons of the syringes. Subjects were stimulated passively and were blindfolded. They

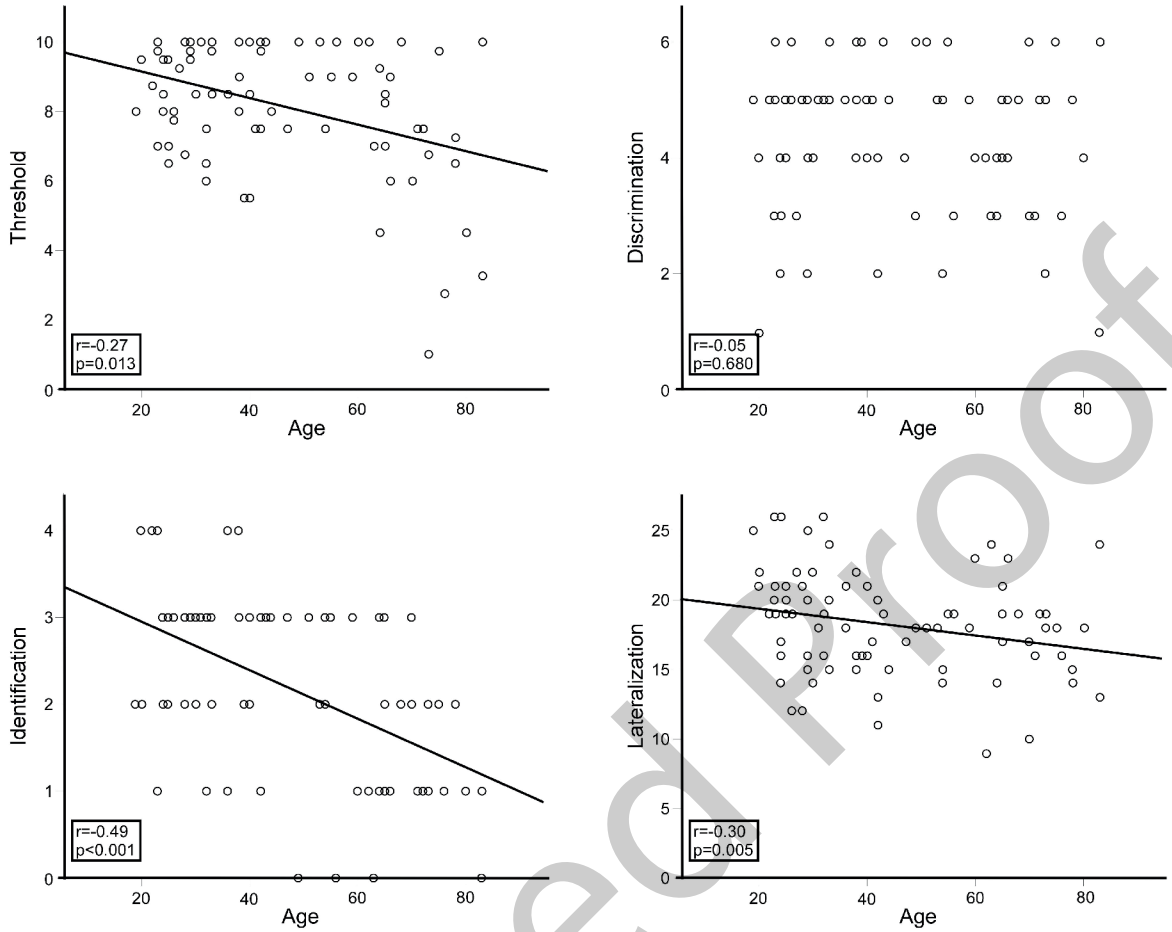

Figure 1. Correlation between trigeminal scores and age in healthy controls. Trendline is drawn for significant correlations.

received 26 stimuli, counterbalanced in a pseudorandomized sequence. Subjects had to indicate which nostril had been stimulated with menthol.

Study 1

Healthy controls were evaluated. All subjects had a self-declared normal olfactory function, did not present any sino-nasal symptoms and did not suffer from a neurological or psychiatric disease. 20 controls were also evaluated a second time, to check the test-retest reliability of our tests.

Study 2

In a second study, we investigated patients with diverse rhinological conditions. We evaluated patients with allergic rhinitis (AR), chronic rhinosinusitis with (CRSwNP) and without nasal polyps (CRSsNP), and patients with olfactory disorders (OD). Subjects who reported psychiatric or neurological disease were excluded from the study.

Statistics

Statistical analyses were performed using SPSS 21.0 (SPSS Inc, Chicago, IL, USA). The level of significance was set at $p<0.05$.

Non-parametric tests using the Kruskal Wallis test and Mann-Whitney comparisons were used to compare the different trigeminal scores across the different age groups in Study 1; and across the different groups of subjects in Study 2. Bonferroni correction was used for multiple comparisons. A Chi square test was used to assess identification profile and to compare identification performance between the different age groups in Study 1. Correlations between the different scores and test-retest reliability were assessed using the Spearman's correlation coefficient.

Results

Study 1

86 healthy controls (mean age: 44.4±18.9 years, 36 men) were included in the study. For statistical analyses and, according to previous work (16), subjects were separated in three age groups (1-3): group 1: <35 years (36 subjects); group 2, 35-55 years (24 subjects); group 3 > 55 years (26 subjects). Detailed descriptive statistics are presented in Table 2.

Trigeminal thresholds

The threshold score was computed out of 10 (Table 2). Trigeminal thresholds were significantly different across the three

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Table 3. Percentage of identification for each individual trigeminal substance in healthy controls (aged <55).

	Pungent, astringent	Burning, warm	Scratching, tickling, sneeze	Prickling	Cold, fresh
Ethanol	3,8%	9,6%	15,4%	13,5%	57,7%*
Menthol	3,8%	1,9%	7,7%	11,5%	75,0%*
Diallylsulfide	75,0%*	5,8%	15,4%	3,8%	0,0%
Propanol	30,8%	19,2%	17,3%	11,5%	21,2%
Camphor	21,2%	21,2%	11,5%	5,8%	40,4%
Eucalyptol	13,5%	25,0%	1,9%	7,7%	51,9%*

Substances having an identification rate >50% (* asterisk), were considered to be suitable for testing. Others were dropped out.

groups (p=0.046). Post-hoc tests showed that threshold scores were significantly lower in group 3, compared to group 1 (p=0.018). We found a significant negative correlation between age and detection thresholds (r=-0.27, p=0.013) (Figure 1). Women had significantly better threshold scores (p=0.003).

Trigeminal discrimination

Each correct answer was granted by 1 point, leading to a discrimination score out of 6 (Table 2). The discrimination scores were not significantly different across the different age and sex groups (p=0.197 and p=0,271, respectively), and were not correlated with age (r=-0.05, p=0.680) (Figure 1).

Trigeminal identification

Data were missing for 8 subjects. First, we determined, for each stimulant, which answer could be considered as correct. Because we assumed that chemosensory function is affected by age [22,24], we considered only subjects < 55 years. Ethanol was described as "cold, fresh" by 57.7% of subjects ($\chi2$= 48.2, p<0.001). Menthol was rated as "cold, fresh" by 75.0% of subjects ($\chi2$= 99.7, p<0.001). Diallylsulfide was described as "pungent, astringent" by 75.0% of controls ($\chi2$=70.9, p<0.001). Eucalyptol was described as "cold, fresh" by 51.9% of controls ($\chi2$=40.7, p<0.001). For propanol and camphor, the identification profile was blurred, and the identification rates were below 50.0%. Hence, we decided to leave them out (Table 3).
For the 4 remaining stimulants we evaluated identification performance with regards to age and sex.

Ethanol. "Cold, fresh" was the most-used descriptor in groups 1 and 2 (56.7% and 59.1%, respectively). In group 3, the most common was "pungent, astringent" (42.3%). There was a significant difference regarding the choice of descriptors among the 3 different groups ($\chi2$=24.6, p<0.001). Paired comparisons found a significant difference between groups 1 and 3 ($\chi2$=16.3, p=0.001) and between groups 2 and 3 ($\chi2$=10.1, p=0.039). We found no effect of sex on the response pattern ($\chi2$=3.4, p=0.488).

Menthol. The most commonly used descriptor was "cold, fresh" in groups 1 and 2 (76.7% and 72.7%, respectively). In group 3, although it was also the most frequently used, it was chosen by only 30.8% of subjects and was also frequently reported as "pungent, astringent" and "warm, burning" (19.2% each). The choice of descriptor was significantly different between the three groups ($\chi2$= 19.6, p=0.012), with a significant difference between groups 1 and 3 ($\chi2$=14.3 p=0.006); and between groups 2 and 3 ($\chi2$=10.9, p=0.028). Identification pattern was not affected by sex ($\chi2$=5.5, p=0.241)

Diallylsulfide. "Pungent, astringent" was the most-used descriptor in all 3 groups (76.7%, 72.7% and 65.4% in groups 1, 2 and 3, respectively). The identification pattern was neither influenced by age ($\chi2$=5.9, p=0.663) nor by sex ($\chi2$=4,7, p=0.324).

Eucalyptol. Eucalyptol was mainly described as "cold, fresh" by group 1 and group 2 subjects (60% and 40.9%, respectively), while group 3 subjects mainly reported it as "pungent, astringent" (34.6%). There was a significant difference regarding the identification pattern between the three groups ($\chi2$=24.1, p=0.002), with a statistically significant difference between groups 1 and 3 ($\chi2$=14.1, p=0.007) and groups 2 and 3 ($\chi2$=13.2, p=0.010). There was no significant effect of gender ($\chi2$=5.7, p=0.222).

From these results, we decided that correct answers would be "cold, fresh" for ethanol, menthol and eucalyptol, and "pungent, astringent" for diallylsulfide. Each correct answer is granted by 1 point, leading to a total identification score out of 4 (Table 2).

Using this scoring system, we found a significant negative correlation between age and identification performances (r=-0.49, p<0.001) (Figure 1). The identification score was not influenced by sex (p=0.428).

Trigeminal lateralization

Each correct answer was granted by 1 point, leading to a total identification score out of 26. We found significant differences in trigeminal lateralization performances between the three groups (p=0.014). Post-hoc tests showed that group 1 had higher lateralization scores as compared to groups 2 (p=0.007) and 3 (p=0.049). We observed a significant negative correlation between age and lateralization performances (r=-0.30, p=0.005) (Figure 1).

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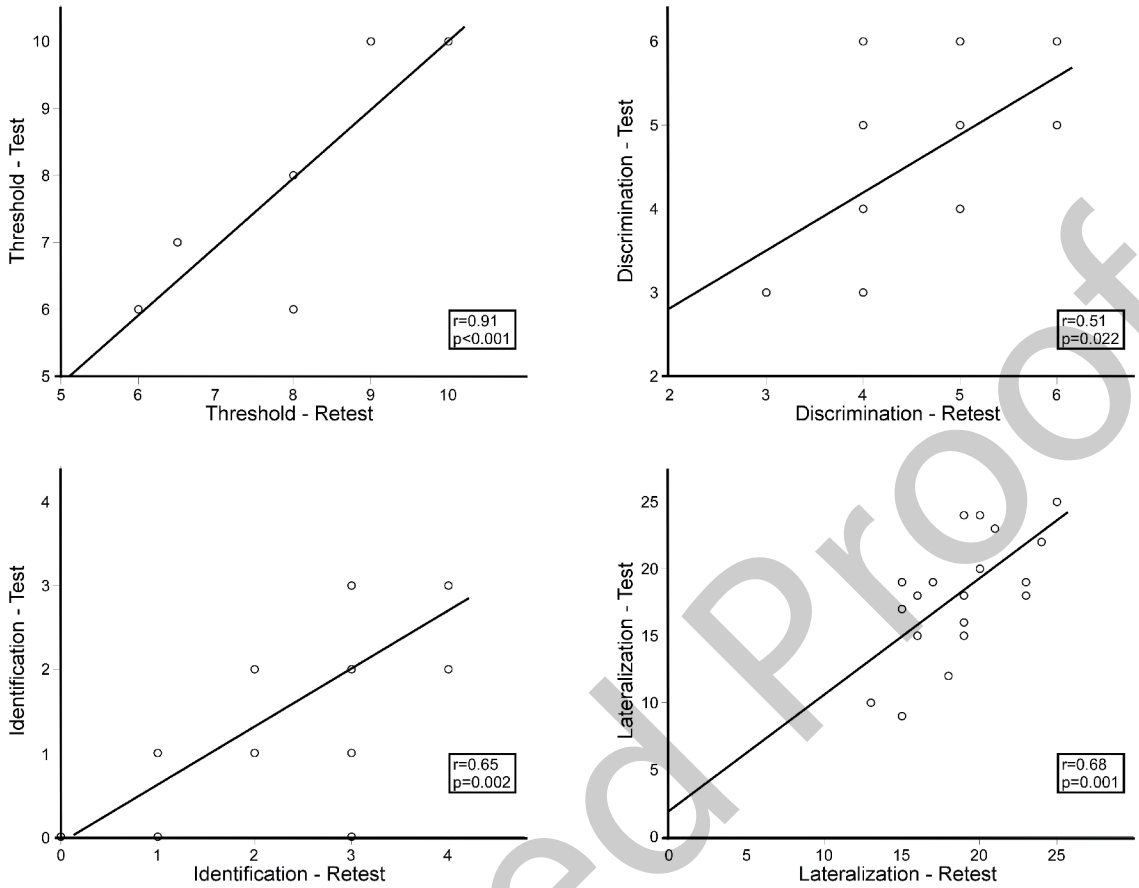

Figure 2. Correlational analyses between test and retest performances. Trendline is drawn for significant correlations.

The lateralization score was not influenced by sex (p=0.089).

Correlation between trigeminal tests

We found a small but significant correlation between discrimination and lateralization scores (r=0.225, p=0.048).

Test-retest

After the first testing (T1) 20 subjects were retested (T2) (mean interval: 7.1±1.7 days). The mean threshold scores at T1 and T2 were 9.35±1.38 and 9.37±1.24, respectively. These scores were not significantly different (p=1.000). The reliability coefficient between threshold scores at T1 and T2 was r=0.91 (p<0.001) (Figure 2). The mean discrimination score at T1 and T2 were 4.65±0.99 and 4.65±0.81, respectively. These scores were not significantly different (p=1.000). The reliability coefficient was r=0.51 (p=0.022) (Figure 2). The mean identification scores were 1.75±1.12 and 2.65±1.14 at T1 and T2 respectively. These scores were significantly different (p=0.001). The reliability coefficient was r=0.65 (p=0.002) (Figure 2). The mean lateralization scores were 18.15±4.45 and 18.00±5.05, respectively at T1 and T2. These results were not significantly different (p=0.366). The reliability coefficient was r=0.68 (p=0.001) (Figure 2).

Study 2

To evaluate the potential usefulness and feasibility of this test in a rhinology clinic, 59 patients were included in this study: 14 AR, 11 CRSwNP, 9 CRSsNP, and 25 OD (14 postinfectious, 5 posttraumatic, 6 idiopathic). Their results were compared those of the 86 controls from study 1. Regarding patients with OD, results of olfactory testing, using the Sniffin' Sticks test (16) were also recorded. There was no significant difference regarding age (p=0.134) and gender ($\chi 2$= 4.4, p=0.353) between the groups of subjects. Descriptive statistics are provided in Table 4.

Trigeminal thresholds

Threshold scores differed significantly between groups (p<0.001) (Table 4). Pairwise comparisons showed that patients with CRSwNP, CRSsNP and OD had significantly lower threshold scores as compared to healthy controls (p<0.001, p=0,024 and p<0.001, respectively) (Figure 3).

Trigeminal discrimination

Discrimination scores were significantly different between groups (p<0.001) (Table 4), with OD patients having significantly lower performances as compared to healthy controls (p<0.001)

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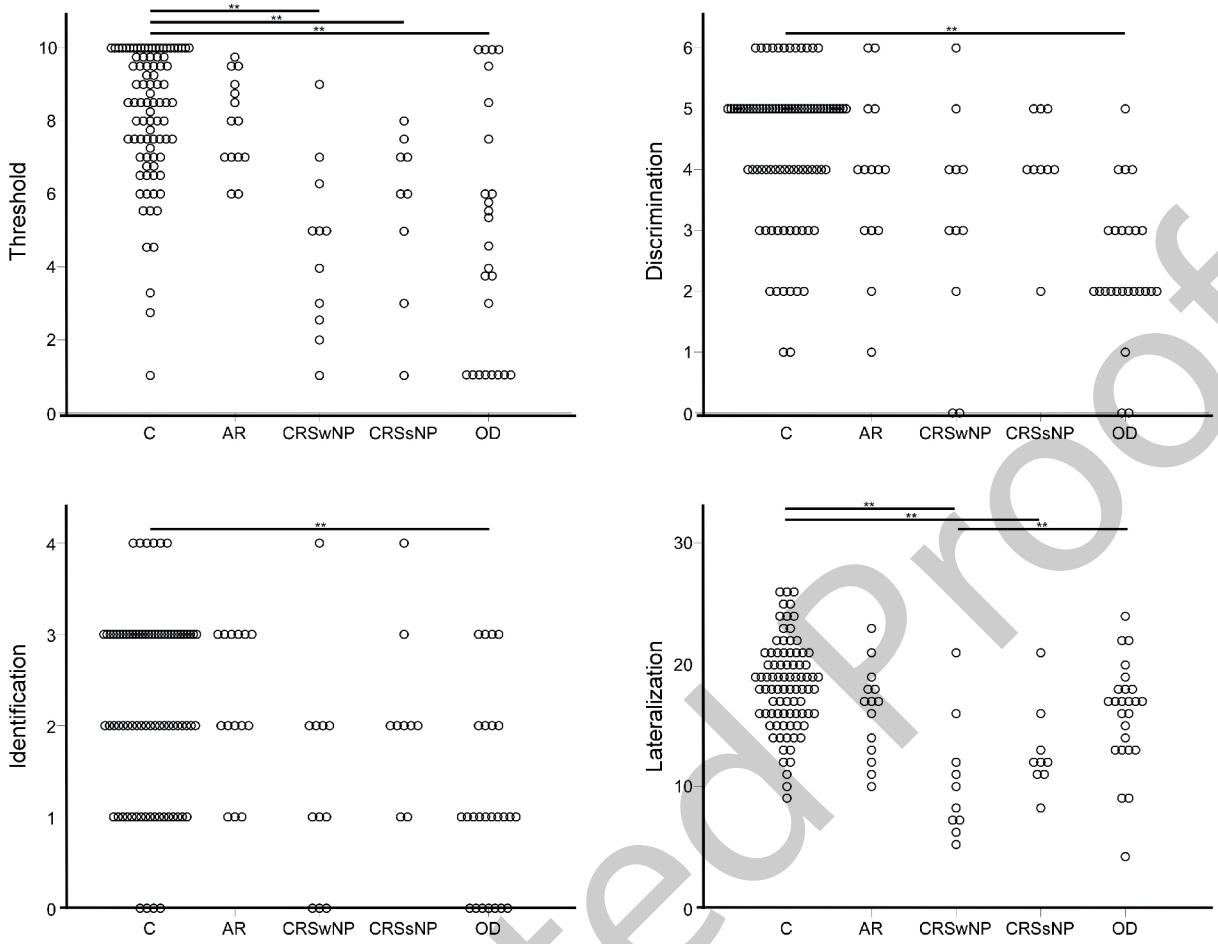

Figure 3. Swarm plots showing individual values of trigeminal threshold, discrimination, identification and lateralization performances in healthy controls (C), allergic rhinitis (AR), chronic rhinosinusitis with nasal polyps (CRSwNP), chronic rhinosinusitis without nasal polyps (CRSsNP) and olfactory disorder (OD) patients. (**p<0,01).

(Figure 3).

Trigeminal identification

The mean identification scores were significantly different between groups (p=0.001) (Table 4), with OD having lower identification scores as compared to healthy controls (p=0.001) (Figure 3).

Trigeminal lateralization

Lateralization scores were significantly different between groups (p<0.001) (Table 4). Patients with CRSwNP and CRSsNP had lower performances as compared to controls (p<0.001 and p=0.005, respectively) (Figure 3).

Correlation between trigeminal scores

At group level, we found a significant correlation between threshold and discrimination scores of all patients (r=0.38, p=0.009). Discrimination and identification scores were also correlated (r=0.43, p=0.004). No correlation was found between lateralization performances and other tests.

Correlation between olfactory and trigeminal performances

Correlation between olfactory and trigeminal performances was evaluated in the OD group. We found that trigeminal threshold scores significantly correlated with olfactory threshold (r=0.495, p=0.012), discrimination (r=0.660, p<0.001), and identification scores (r=0.700, p<0.001).

Discussion

In this study, we described a new tool to psychophysically assess the intranasal trigeminal chemosensory function and evaluated its potential usefulness and feasibility for clinical use.

Study 1

In a healthy population, our results show that trigeminal threshold, identification and lateralization performances decrease and correlate negatively with age. This finding is in line with previous reports, showing that older subjects have a decreased

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Table 4. Descriptive statistics of trigeminal scores.

	C	AR	CRSwNP	CRSsNP	OD
	n=86	n=14	n=11	n=9	n=25
T	8.17±1.86	7.92±1.28	4.52±2.35	5.61±2.28	4.76±3.50
D	4.40±1.20	3.86±1.41	3.09±1.86	4.11±0.93	2.40±1.15
I	2.22±1.04	2.21±0.80	1.36±1.21	2.11±0.93	1.20±1.04
L	18.27±3.66	16.14±3.76	10.30±4.99	12.89±3.69	15.92±4.39

Scores were obtained in healthy controls (C), patients with allergic rhinitis (AR), chronic rhinosinusitis with nasal polyps (CRSwNPs), chronic rhinosinusitis without nasal polyps (CRSsNPs) and olfactory disorder (OD) (mean±SD). (T: Threshold, D: Discrimination, I: Identification, L: Lateralization).

sensitivity to trigeminal stimuli [4,13,22,24-27]. Particularly, several authors have reported higher trigeminal thresholds [4,25,27], and decreased lateralization abilities [22] in older subjects.

In the present study, we did not find that age affected discrimination performance, although Laska et al. [13] reported so. This can be explained by methodological differences between discrimination tasks used in these two studies.

We also found that women had significantly lower detection thresholds, compared to men. The higher chemosensory sensitivity of women has been previously reported in several studies [14,20,26,28,29,30].

We observed significant correlations between test and retest for all the subtests. The test-retest reliability of the threshold detection task was particularly good (r=0.91), and in the same range as what has been described for odor detection threshold with the Sniffin' sticks test (r=0.92) [31,32]. Identification task reliability appeared weaker (r=0.65), but value also within the range of what has been described for odor identification task (r=0.60-0.88) [31-33]. The reliability of the lateralization test-retest was in the same range (r=0.68). Finally, the discrimination task had the lowest test-retest reliability (r=0.56). This value was lower than what has been reported for the Sniffin' sticks (r=0.71-0.80) [31,32]. Hence, we concluded that our test is potentially suited for use in research and clinic, although it is mandatory to further investigate whether some measures are more reliable and useful than others.

Study 2

We found that trigeminal performance is affected in CRSwNP, CRSsNP and in OD. Interestingly, trigeminal performance seems to be relatively preserved in AR patients. In literature, findings regarding trigeminal sensitivity in AR patients are conflicting. Using trigeminal event-related potentials, it has been described that AR patients show an increased sensitivity [34]. In contrast, another study found that patients with seasonal AR had no increased sensitivity to ammonia exposure [35].

In OD patients, we found higher trigeminal thresholds, and lower discrimination and identification performances. This is congruent with previous findings showing that OD patients have decreased trigeminal abilities [9,36]. However, in the present study, we cannot rule out that olfactory function is involved in performing the trigeminal tasks because the stimulants that were used also have an olfactory component. Although it has previously been reported that patients with OD had also significantly lower lateralization performances [22,24], we found no significant difference between lateralization capacities of OD and healthy controls. This discrepancy could be partially explained by the fact that the methodology was different, and by the fact that we had a lower number of subjects in our study.

In CRSwNP and CRSsNP patients, we observed that trigeminal thresholds are higher, with lower trigeminal lateralization performances when compared to healthy controls. This is in line with previous findings. Indeed, it has been shown that patients undergoing sinus surgery are typically less sensitive to trigeminal stimuli than controls [37,38]. It has also been reported that abnormal trigeminal sensitivity could contribute to the sensation of impaired nasal breathing in CRS patients [39]. This result suggests that preoperative assessment of trigeminal sensitivity in patients that are candidates for nasal surgery probably deserves further attention [10,37]. Indeed, trigeminal impairment could be linked to a subjective impression of impaired nasal breathing; but also to dissatisfaction after surgery [37] and might play a role in the pathophysiology of the so called "empty nose syndrome" [10].

A major limitation of our study is that the trigeminal stimulants that were used also activate the olfactory afferents. Therefore, it is possible that olfactory stimulation contributed, at least partially to the patient's responses. We tried to decrease this bias by asking the patients to focus on trigeminal sensations. Nevertheless, the confusion of the trigeminal sensations with

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odorous impressions cannot be ruled out. However, confusion is considered to be unlikely for lateralization tasks because the ability to lateralize odorants is thought to depend exclusively on trigeminal activation [40,41]. In order to further investigate the selectivity of our tests for trigeminal chemosensory function, our results should be verified by tests using stimulation with gaseous CO_2, which is a pure trigeminal stimulus.
A second limitation is that we did not assess olfactory function in our subjects, except for those presenting with an OD. Parallel assessment of trigeminal and olfactory function should be performed in the future to investigate the interaction between olfactory and trigeminal systems.

Conclusion

In conclusion, our test allows to identify age- and sex-related changes of intranasal trigeminal chemosensory function, as well as group-level differences between patients and healthy controls, suggesting that it can be of value in clinical use practice. Further studies are needed to validate our results and to evaluate the impact of olfactory co-activation on the observed results.

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Author contriibution

CH, TH, IK, AM, PR participated in the study design. CH, TH, CK, IK participated in data collection and analysis. CH, TH, IK, VH, AM, PR participated in data interpretation. CH, TH, IK, VH, AM, PR participated in drafting the article. All authors revised and approved the final version of the article.

Conflict of interest

None.

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Caroline Huart
Department of Otorhinolaryngology
Cliniques universitaires Saint-Luc
Brussels
Belgium

Tel: +3227641949
Fax: +3227649042
E-mail: caroline.huart@uclouvain.be

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