Automated assessment of intranasal trigeminal function*

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Abstract

Background: The intranasal trigeminal system is a key player in the perception of intranasal airflow. Why it has not been studied very well may be due to the lack of techniques that allow for fast, reliable and inexpensive routine investigation of the system. The basis of the current study is the notion that – within limits - the intranasal trigeminal system detects the overall mass of a stimulus and not just its concentration. Thus, changing the duration of the stimulus at a given concentration has a similar effect as changing its concentration.

Methodology: Ninety-nine normosmic subjects participated [48 women and 51 men; mean (range) age = 45 years (20-88 years)]. In addition, 50 patients with olfactory loss were investigated once (28 women, 22 men; mean age 58 years, SD = 14 years; age range 24-88 years; causes of olfactory loss: viral infections n = 22, head trauma n = 8, chronic sinunasal disease n = 3, idiopathic n = 17). CO_2-stimuli with various durations (multiples of 50 ms) were presented through a standard bilateral nasal cannula at an interval of 10 s; stimulus duration was increased by 50 ms from one stimulus presentation to the next, until the subject pushed a button indicating a painful sensation. This was the basis for automated assessment of CO_2-pain responsiveness.

Results: This current study had four main findings: (1) Using the new, automated device CO_2 pain responsiveness can be measured reliably, (2) CO_2 pain responsiveness correlates with olfactory function, (3) as with olfaction, women are more sensitive to CO_2, and CO_2 - pain responsiveness also correlates with aging, (4) CO_2 - pain responsiveness is lower in patients with olfactory loss compared to normosmic, healthy controls, even when controlling for age.

Conclusion: We have demonstrated that the current approach is a reliable and valid measure of intranasal trigeminal function.

Key words: smell, nose, olfaction, trigeminal system, CO_2

Introduction

Most odorants stimulate, at least at high concentrations, both the olfactory and the trigeminal nerves [1-3]. Thresholds for trigeminal sensations, such as burning, cooling, stinging, and fullness, are generally higher than thresholds for olfactory sensations [4]. Clinically, the trigeminal system has received little attention. This is despite the fact that the sensation of airflow is mediated through the trigeminal nerve, which is nicely illustrated with menthol lozenges. When they are sucked on, menthol activates receptors in the respiratory epithelium and, consecutively, the nasal airflow is perceived as stronger. This is, in turn, interpreted as a widening of the nasal cavity, which is not the case [5,6]. In fact, it has been suggested that nasal airflow perception is related to cooling of the nasal mucosa rather than, for example, to obstruction of the nasal passages [7,8]. An alternative example is local anesthesia of the nasal cavity that produces a strong feeling of stuffiness. Based on the finding that patients receiving sinus surgery are typically less sensitive to trigeminal stimuli than controls [9,10], it has been speculated that some patients may receive nasal surgery because of a decreased sensation of airflow, not because of a significant nasal congestion.
A number of psychophysical techniques have been introduced to study the function of the nasal trigeminal nerve [11]. Among these is the stimulation with CO_2 gas, which is thought to be a

specific trigeminal stimulant that has little or no smell [12]. Other techniques involve the lateralized presentation of chemical stimuli with the subjects' task to identify the nostril that had been stimulated. This is based on the idea that lateralization of intranasal chemical stimuli is only possible through the trigeminal nerve [(1,4,13-15), but see also (16)].

The basis of the current study is the notion that the trigeminal system detects the overall mass of a stimulus rather than its concentration [17]. Thus, changing the duration of the stimulus at a given concentration should have the same effect as changing its concentration. Therefore it should be possible to apply the irritant CO_2 at relatively low flows, but with pulses of 100% concentration and different durations. After building an apparatus that provided these stimuli, we investigated the test-retest reliability of these responses, their relation to age and sex of the subjects, and their clinical applicability in patients with olfactory loss.

Materials and methods

The study was conducted at the Smell & Taste Clinic, Department of Otorhinolaryngology of the TU Dresden (protocol number EK156052012). It was approved by the Ethics Committee of the Medical Faculty at the TU Dresden. All chemosensory measurements were carried out in well-ventilated rooms by the same investigator (CK).

Subjects

Ninety-nine normosmic subjects participated [48 women and 51 men; mean (range) age = 45 years (20-88 years)]. All of these subjects maintained that they had a normal sense of smell. Olfactory function was assessed by the "Sniffin' Sticks" package which included assessment of phenyl ethyl alcohol odour thresholds, and an extended odour identification test consisting of 32 items [18,19]. Normosmia was defined as a test result of 23 and more points on the 32-item odour identification test [20-22]. Exclusion criteria were neurological or rhinological conditions associated with olfactory disorders, including major septal deviations, as assessed with nasal endoscopy and acoustic rhinometry. Subjects were asked to refrain from smoking, eating, or drinking anything other than water for at least one hour prior to testing.

Patients

In addition, a total of 50 patients with olfactory loss were investigated once (28 women, 22 men; mean age 58 years, SD = 14 years; age range 24-88 years). All patients underwent a structured interview, a detailed otorhinolaryngological examination including nasal endoscopy by a specialized physician, and various tests of gustatory or olfactory function (e.g., "Sniffin' Sticks", taste strips, taste sprays, "Schmeckpulver" for retronasal olfactory testing, olfactory event-related potentials [23]). Structural brain imaging using MRI scans was performed whenever deemed necessary. Olfactory loss was caused by viral infections of the upper respiratory tract in n = 22, by head trauma in n = 8, by chronic sinunasal disease in 3 patients, and was of idiopathic cause in n = 17.

Trigeminal stimulus presentation device

The stimuli were delivered by a portable device containing a small CO_2 cylinder together with a pressure reducer and a pressure regulator. Stimuli with various durations (multiples of 50 ms) were presented through a standard bilateral nasal cannula; stimulus durations were regulated through a computer-operated valve.

Stimuli were presented at an interval of 10 s with the subjects being alerted to that by a small signal lighting up 3 s before stimulus presentation; stimulus duration was increased by 50 ms from one stimulus presentation to the next, until the subject pushed a button – indicating a painful sensation. Then the stimulus duration was reduced until the subject did not push the button anymore. Then the duration was increased again and so forth. The average of the last four turning points of this staircase (calculated by the microcomputer implemented in the stimulation device) was used as an estimate of the CO_2 pain threshold, further termed as CO_2 "responsiveness". Thus, patients only followed one instruction: "Push the button when you found the stimulus to be painful". In this way, the entire procedure was fully automated. In the present experiment, during each of the two sessions this procedure was repeated three times, and the average of the 3 measures per session was used for further statistical analyses. The entire procedure lasted about 5 min.

Statistical analysis

SPSS 21.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. T-tests and analyses of variance (for repeated measures) were used whenever appropriate. For post-hoc testing we used t-tests with Bonferroni-correction for inflated alpha. Pearson correlation coefficients were computed. The alpha-level was set at 0.05.

Results

No significant difference was found between trigeminal CO_2-pain responsiveness from sessions 1 and 2 ($t_{93} = 0.14$, $p = 0.89$). In contrast, there were significant correlations between results from sessions 1 and 2 ($r_{94} = 0.75$, $p < 0.001$) (Figure 1).

With regard to measurements in the control group, women were more sensitive than men (session 1: women: mean ± SEM 443 ± 59 ms, men: 627 ± 68 ms; $t_{92} = 2.03$, $p = 0.045$; session 2: women: 415 ± 58 ms, men: 645 ± 72 ms; $t_{92} = 2.48$, $p = 0.015$). Thresholds increased with age as indicated by significant coefficient of correlations obtained in session 1, but not in session 2 (session 1: $r_{94} = 0.25$, $p = 0.021$; session 2: $r_{94} = 0.12$, $p = 0.27$).

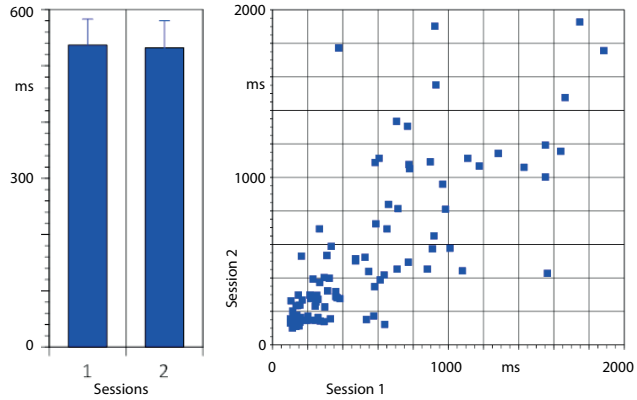

Figure 1. Left: Average pain responsiveness (in ms) for the first and second session. Right: Correlation between results from sessions 1 and 2. There was no significant difference between sessions 1 and 2 (the shorter the latency, the more sensitive the subject); results from the two sessions exhibited a good test-retest reliability.

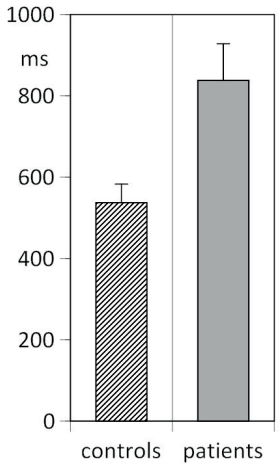

Figure 2. Average pain responsiveness (means, standard errors of means, in ms) for controls (left, n = 94) and patients (right, n = 47). Responsiveness was significantly less in patients (t139 = 3.30, p = 0.001)

In addition, CO_2 pain responsiveness exhibited a significant correlation with the 32-item odour identification test score (session 1: r94 = -0.29, p = 0.005; session 2: r94 = -0.21, p = 0.046) with subjects being more sensitive to CO_2 having higher scores in odour identification. Percentile distributions of results for the CO_2 pain responsiveness for session 1 are shown in Table 1. During session 1, eight people showed a consistent ceiling effect meaning that through all 3 trials per session they did not perceive CO_2 as painful with 3 of them being patients and another 5 being controls, which is 5.7% of the entire group tested. In these people data were not used.

When comparing controls and patients, we found – on average - lower CO_2 - pain responsiveness in patients (controls: M = 537 ms, SD = 448; patients: M = 838 ms, SD = 619) (Figure 2). This effect was significant (t139 = 3.30, p = 0.001) although patients were also significantly older than controls (controls: M = 44 years, SD = 19; patients: M = 58 years, SD = 13; t139 = 4.37, p < 0.001). When only comparing participants older than 50 years, age was no longer significantly different between patients and controls (t79 = 0.17, p = 0.86) but pain responsiveness was (controls: M = 612 ms, SD = 522ms; patients: M = 928 ms, SD = 622 ms; t79 = 2.49, p = 0.015).

When only investigating the presence of a ceiling effect for CO_2 - pain responsiveness, we found that in healthy controls 5 of 100 participants (5%) exhibited a ceiling effect in all 3 measurements per session, whereas in patients this was the case in 3 of 50 patients (6%). Although group sizes became relatively small, there was no significant effect of the various causes of olfactory loss (acute infections, head trauma, sinunasal disease, idiopathic; F[3,43] = 1.53, p = 0.22) on CO_2 pain responsiveness.

Discussion

This current study had four main findings: (1) Using the new, automated device CO_2 pain responsiveness can be measured reliably, (2) CO_2 pain responsiveness correlates with olfactory function, (3) as with olfaction, women are more sensitive to CO_2, and CO_2- pain responsiveness also correlates with aging, (4) CO_2- pain responsiveness is lower in patients with olfactory loss compared to normosmic, healthy controls.

The most important result from this series of experiments is that the current approach allows to assess CO_2 pain responsiveness in a reliable manner. Although other techniques ultimately provide similar results (e.g., (17,24-27); for review see [11]) it is important to note that the current approach takes little time and is more or less self-organized by the subject. In addition, costs for producing such a device are low, especially as no dilution of CO_2 Is required but 100% v/v CO_2 is only presented in stimuli of various durations which simplifies stimulus control. The current approach is based on the assumption that – within a certain timeframe – the intranasal trigeminal system acts as an integrator to signal the overall number (mass) of stimulus molecules [17]. For a low concentration stimulus to be perceived as strong as a high concentration one, it has to be presented for a longer period of time (e.g., [25]).

Indicating its validity, results based on the current approach are related to sex and age, with trigeminal function being highest in young women. This reproduces previous work showing that women respond exhibit a higher sensitivity than men [15,28-30], and older people being less sensitive than younger ones [31-34]. In this context, it also seems to be important that the current

Table 1. Distribution of CO2-pain responsiveness data (in ms) in relation to three age groups (20-40, 41-60 and older than 60 years), separately for patients and controls.

age group		20-40 years		41-60 years		>60 years	
N		controls	patients	controls	patients	controls	patients
mean	0	46	6	23	17	25	24
SEM	1	466	606	448	790	749	931
		53	210	87	168	111	121
Percentile	10	121	104	134	107	126	173
	25	153	139	195	158	331	442
	50	283	517	296	596	591	761
	75	776	1018	550	1454	1210	1379
	90	957		1244	1891	1652	1911

work also provides first, tentative normative data which allow the rough gauging of trigeminal function on the basis of age-related values. However, here it has to be kept in mind that the current study is more a feasibility study than a validation study. The currently reported percentiles are likely to change the more subjects will be tested.

It is important to mention that – under the current circumstances - 5% of the tested population did not perceive CO_2 as painful. Thus, future studies should also investigate detection thresholds to overcome the current problem of missing data.

The current results indicate that trigeminal function is reduced in patients with olfactory loss, which is still the case when controlling for age; also the present results are correlated with results from odour identification tests. This relation has already been noted years ago [35], and then this was followed up in some detail [36]. The conclusion was that loss of olfactory function leads to changes both in the periphery and the central-nervous processing of trigeminal stimuli, which ultimately leads to a decreased trigeminal sensitivity in patients with acquired loss of function. Because the trigeminal system is involved in the perception of nasal airflow [5,37,38] it is also related to a sensation of a "congested nose". As already mentioned in the Introduction, it has been suggested that nasal airflow perception is related to cooling of the nasal mucosa, and much less so to congestion of the nasal passages [7,8] (compare [10]). This sensory component of nasal airflow perception could be a reason for the dissatisfaction of patients after septoplasty [39,40]. Furthermore, previous studies demonstrated a low correlation between subjective symptoms regarding nasal obstruction, and nasal anatomy [41,42]. Thus, the currently introduced, simple technique – provided its wider distribution - may help to shed some light on the above issue as it appears to be suited for the routine investigation of patients, e.g., before and after surgery.

Conclusions

In conclusion, we have demonstrated that the current approach is a reliable and valid measure of intranasal trigeminal function.

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Author contributions

Conceived and designed the experiments: TH, KH. Performed the experiments: NR, VB, AH, KH. Analysed the data: JL, AU. Wrote the paper: JL, TH.

Conflict of interest

The authors have declared that no competing interests exist.

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