Ratings of trigeminal stimulation in patients with olfactory loss*

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To the Editor:

Human nasal trigeminal sensitivity relates to the detection of irritants, to the sense of smell, and to subjective nasal patency [(1)]. These functions have attracted attention for centuries. It is known that patients with either olfactory dysfunction (OD) [(2)] or subjective nasal obstruction typically have reduced intranasal trigeminal functions [(3)]. Trigeminal sensations like freshness, coolness, tickling and stinging modulate the perception of odours [(1)], and the perception of nasal airflow is mediated by intranasal trigeminal nerves. For nasal patency, it is important to know whether subjective nasal obstruction is due to anatomical characteristics or decreased trigeminal sensitivity. In addition to nasal endoscopy or rhinomanometry testing of trigeminal function may provide information for the diagnosis and choice of proper treatment. Hence, by examining intranasal trigeminal sensitivity it appears possible to obtain more information about OD or subjective nasal obstruction.

In this first exploratory, retrospective study, we examined whether trigeminal intensity ratings (TrIRa) to intranasal ammonium relate to parameters of olfactory function and whether this simple screening test could contribute to the diagnosis made. We examined the use of intensity ratings in response to ammonium vapor known to stimulate trigeminal receptors, e.g., the transient receptor potential channel subfamilies V1 (TRPV1) [(4)] and A1 (TRPA1) [(4, 5)]. In order to screen for intranasal trigeminal function, the stimulus was presented in a commercially available lipstick-like container, also used as a "smelling salt" (AmmoLa®, Devesa Dr. Reingraber GmbH, Muggensturm, Germany). The ammonium stimulus is bimodal, stimulating both cranial nerves I and V. In addition to the odor of ammonium AmmoLa® contains traces of lavender which is perceptually dominated by the strong irritation induced by ammonium. Transient receptor potential cation channel subfamily M, member 8 (TRPM8) receptors have been shown to be associated with nasal patency. For other receptors including TRPV1 and TRPA1 this is less clear. Because most trigeminal irritants typically activate several types of receptors [(1, 4)] it is likely that the presently employed stimulus also provides information about subjective nasal obstruction [(6)]. Hence, by using AmmoLa® probe, a certain spectrum of the patient's nasal trigeminal function can be tested. We obtained TrIRa from OD patients using Visual analogue Scale (VAS) and correlated the results with detailed measures of olfactory sensitivity.

TrIRa correlated positively with measured olfactory sensitivity (T, D, I, TDI score) and the severity of olfactory function (Tables 1, S1). Across the entire group, but also specifically in postviral cases, the D score showed a significant, positive correlation to TrIRa. Odor discrimination ability might partly rely on nasal trigeminal stimuli.

These results emphasize that intranasal trigeminal function is related to olfactory sensitivity [(7)]. This is important in terms of the nasal warning function in the detection of potentially harmful gases so that patients with olfactory loss are more prone to respective accidents. As mentioned above, it also may have implications for the clinical assessment of nasal airflow [(8, 9)] contributing to the impression of nasal blockage in a certain group of patients.

In the present study, we investigated a screening test. Compared to other trigeminal tests it clearly is less reliable, for example the lateralization test or electrophysiological measures. Still, the TrIRa test, in all its simplicity, may be helpful in three ways. It could be useful 1) to support the medical interview with the patients, for example, with regard to nasal patency. As mentioned above, intranasal trigeminal function relates to subjective nasal patency. Patients without anatomical nasal blockage complaining of decreased nasal patency could be screened by TrIRa. Patients with positive test results can be tested in more detail, which would probably inform the decision about performance of nasal surgery.

TrIRa may also provide a screening 2) to uncover possible low olfactory sensitivity [(2)], especially when considering the high in-

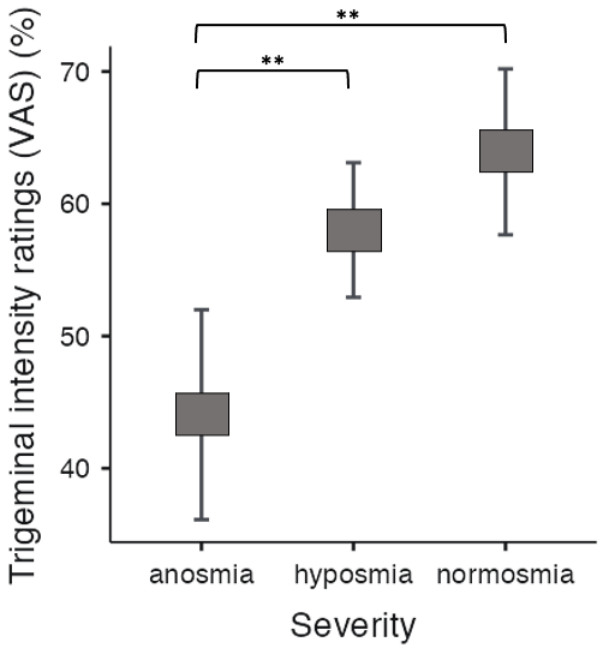

Figure 1. Comparison between trigeminal intensity ratings (median, IQR) and severity of olfactory dysfunction based on TDI scores.

crease of OD in post COVID-19 patients in case it can be proven that there is a significant difference between normosmic people and OD patients in TrIRa. This thought is based on the significant differences between patients with normosmia and patients with anosmia but not between hyposmia and normosmia. Instead, we used the 10th percentile as a cut-off score to distinguish normal from abnormal intranasal trigeminal function. When the TrIRa is below 15%, the test subject may have trigeminal dysfunction and might also have OD.

Finally, AmmoLa® may provide information 3) to find possible discrepancies between trigeminal and olfactory function. If TrIRa is below the 10th percentile (VAS of 15%), the patient is likely to have not only trigeminal dysfunction but also OD. When the trigeminal rating is above the 90th percentile (VAS of 94%), the patient is less likely to have trigeminal dysfunction or severe OD. If a patient has either hyposmia or anosmia, with trigeminal ratings above 94%, this should initiate more detailed investigations, e.g., for isolated congenital anosmia, and psychiatric or neurological issues, as they are reported to be less likely to have intranasal trigeminal dysfunction.

In conclusion, the present study showed that there is a positive correlation between rated intranasal trigeminal sensations and olfactory function, even when screened with a very simple trigeminal probe. The screening test appears to be useful as a practical tool for the clinical assessment of patients with olfactory loss in clinical routine. However, building on the present pilot study, numerous questions need to be explored further, including the question of the test's reliability and the correlation with other more sophisticated tests of trigeminal function.

Abbreviations

OD, olfactory dysfunction; TrIRa, trigeminal intensity rating; TRPV1, Transient receptor potential cation channel subfamily V, member 1; TRPA1, Transient receptor potential cation channel subfamily A, member 1; TRPM8, transient receptor potential cation channel subfamily M, member 8; TTS, Taste test score; VAS, Visual analogue Scale.

Authorship contribution

RS performed the analysis and drafted the paper and edited the final manuscript. AH provided the data and total project administration and supervision. ML and EM reviewed our study and discussed critically and also edited the final manuscript. TH provided the data and performed the analysis, methodology, resources, project administration and supervision.

Conflict of interest

No conflicts of interest exists.

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Table 1. Correlation between trigeminal intensity ratings and Age, Duration T score, D score, I score, TDI score, Severity or OD, TTS, Parosmia degree and Phantosmia degree.

		Age	Duration	T	D	I	TDI	Severity	TTS	Parosmia	Phantosmia
All subject	Spearman's rho	0.09	0.09	0.20	0.24	0.26	0.23	0.24	0.02	0.00	0.05
	p-value	0.17	0.19	0.00*	<.001*	<.001*	<.001*	<.001*	0.78	0.99	0.43
Postviral	Spearman's rho	0.02	-0.09	0.10	0.18	0.15	0.15	0.19	0.01	-0.05	0.06
	p-value	0.79	0.31	0.25	0.03*	0.07	0.07	0.02*	0.87	0.54	0.49

All factors are analysed with the ρ-value and p-value using Spearman's test. A p-value < 0.05 indicates significance. Abbreviation: OD, olfactory dysfunction, TTS, taste spray score.

Ethical considerations

This retrospective study was performed in accordance with the guidelines of the Declaration of Helsinki on Research Involving Human Subjects. Its design was approved by the Ethics Committee of the Faculty of Medicine at the TU Dresden.

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This manuscript contains online supplementary material

SUPPLEMENTARY MATERIAL

Methods

The data were collected during the first half of 2021 at the Smell and Taste Clinic of the Department of Otorhinolaryngology of the Technical University of Dresden.

Subjects

A total of 239 individuals (153 women and 86 men) with olfactory dysfunction (OD) participated in this study. The median age was 50 years (interquartile range, IQR=23.5, 18 to 86). Causes of olfactory loss were viral infections of the upper respiratory tract (n=142), idiopathic (n=44), traumatic brain injury (n=22), sinunasal disease (n=23), and congenital OD (n=8). The median duration in dysfunction was 9 months (IQR=18.0, 1 to 420 months); 79 patients had parosmia and 39 had phantosmia. The degree of parosmia and phantosmia (0 to 3) [10] was also collected.
All received a full ENT general examination including nasal endoscopy. Computed Tomography was done only if deemed necessary for the diagnosis. The cause of OD was mainly based on detailed and extensive history taking.

Sensory testing

AmmoLa® Riechstäbchen

We adopted the ready-to-use "AmmoLa® Riechstäbchen" (Devesa Dr. Reingraber GmbH, Muggensturm, Germany) for screening of nasal trigeminal function which was typically used as a "smelling salt" for fainting for decades. The device contains ampoules of ammonium with traces of lavender, dissolved in a watery isopropanol solute, lavender was added because of its hypothetical calming effect [11]. The ampoules are opened and placed inside the lip-stick size container from which the scent is released and it was exchanged daily. The aromatized ammonium is a colourless, pungent substance predominantly stimulating nasal trigeminal receptors [4,5]. The uncapped stick was presented 1 to 2 cm under the participant's nostril for approximately 2 seconds and participants were asked to sniff and rate the intensity of the trigeminal stimulus on a Visual Analogue Scale of 10 cm length (VAS; left hand end 0 units, "no irritation perceived"; right hand end 100 units, "extremely strong irritation").

Sniffin Sticks, TDI score

To evaluate olfactory function in detail the Sniffin' Sticks test battery was administered. Odour Threshold (T), Discrimination (D), and Identification (I) was examined as described elsewhere [12]. Based on the TDI score participants were classified as anosmic, hyposmic or normosmic [12].

Whole-mouth testing (WMT)

A WMT with taste sprays was performed in all participants. The WMT is described elsewhere [13,14].

Statistical analysis

The program jamovi (The jamovi project (2021). Jamovi (version 1.6) [Computer Software]. Retrieved from https://www.jamovi.org, Sydney, Australia) was used. Spearman statistics were used for correlational analysis (ρ, p). A linear regression was performed to examine the relation between trigeminal intensity ratings (TrIRa), T score, D score, I score and TDI score. Logistic regression was performed for the degree of parosmia, phantosmia and taste test score (TTS). TrIRa were investigated using analyses of variance with severity of olfactory loss (anosmia, hyposmia, normosmia) as between subject factor. We also performed a Mann-Whitney U test on differences in TDI scores between groups with low (≤10th percentile) and high (≥90th percentile) VAS ratings of the trigeminal stimulus. For post hoc analysis, Bonferroni tests were calculated. Mann-Whitney U test was also used to study differences between individuals. We examined 1) younger vs. older participants (median age at 50 years), 2) shorter and longer duration of OD (median duration at 9 months), 3) lower (0 to 2) vs. higher (3, 4) TTS, 4) with or without parosmia or phantosmia, respectively, and 5) lower vs higher TDI scores (median TDI score of 23), all with median split analyses. All statistics was done for either all subjects or postviral cases only because other OD subgroups had relatively small numbers of participants. Results are expressed as median, IQR or 95% confidence intervals (95% CI). P values < 0.05 were considered significant.

Results

Median VAS of AmmoLa® was 5.79 (IQR=4.69). Median TDI score was 23.0 (IQR=13.88). The 10th percentile of VAS was 15% and the 90th percentile was 94%. There were 66 patients with anosmia (27.6%), 107 with hyposmia (44.8%), and 66 with normosmia (27.6%). Median score of Taste Sprays was 4 (IQR=0).
For total subjects, TrIRa were positively correlated with olfactory test scores (T score ρ=0.20, p=0.003; D score ρ=0.24, p<0.001; I score ρ=0.26, p<0.001; TDI score ρ=0.23, p<0.001) (Table 1) and severity of OD (anosmia, hyposmia and normosmia) (ρ=0.24, p<0.001). TrIRa were lower in patients with anosmia compared to those with hyposmia (W=3.98, p=0.01) or normosmia (W=5.07, p<0.001). However, there was no difference between hyposmia and normosmia (W=2.15, p=0.28) (Table S1, Figure 1). Further, patients with TrIRa below the 10th percentile had median TDI score of 13.00 and it was significantly lower than the patients with TrIRa above the 90th percentile who had median TDI score of 24.75 (p=0.02) (Figure S1). Age of participants (ρ=0.09, p=0.17), duration of the dysfunction (ρ=0.09, p=0.19), degree of parosmia (ρ=0.00, p=0.99), degree of phantosmia (ρ=0.05, p=0.43) and TTS (ρ=0.02, p=0.78) showed no significant correlation with VAS (Table 1). No significant difference on VAS was observed between patients younger or older than the me-

dian age of 50 years (p=0.33), symptom duration shorter or longer duration than the median 9 month (p=0.26), a TTS of 0 to 2 and 3 to 4 (p=0.44), or presence or absence of parosmia (p=0.83) or phantosmia (p=0.47). Only participants who had lower than the median TDI score of 23 showed significantly lower TrIRa than patients with higher TDI scores (p=0.003).

For postviral cases, the 10th percentile of VAS was 17% and the 90th percentile was 92%. TrIRa correlated with D score (ρ=0.18, p=0.03) and the severity of dysfunction (ρ=0.19, p=0.02), but not significantly with T scores (ρ=0.10, p=0.25), I scores (ρ=0.15, p=0.07), or the combined TDI score (ρ=0.15, p=0.07) (Table1). Patients with anosmia had lower scores than normosmic patients (W=3.57, p=0.03), but patients with anosmia only showed a tendency for lower ratings than those with hyposmia (W=3.01, p=0.08) (Table S1). Similar to the analyses for the entire group of subjects, in postviral patients the age (ρ=0.02, p=0.79), duration of the dysfunction (ρ=-0.09, p=0.31), degree of parosmia (ρ=-0.05, p=0.54), degree of phantosmia (ρ=0.06, p=0.49) and TTS (ρ=0.01, p=0.87) was not significantly related to TrIRa (Table 1). No significant difference of TrIRa was observed between individuals aged younger or older than median 44.5 years old (p=0.68), symptom duration shorter and longer duration than a median of 7 months (p=0.14), the TTS of 0 to 2 or 3 to 4 (p=0.58), presence or absence of parosmia (p=0.39) or phantosmia (p=0.49). Participants who had a score lower and higher than the median TDI also had no significant difference in TrIRa (p=0.21). Participants who scored below the 10th percentile and higher than the 90th percentile of the distribution of the TDI scores did not show a difference in terms of the TrIRa (p=0.13) in postviral cases.

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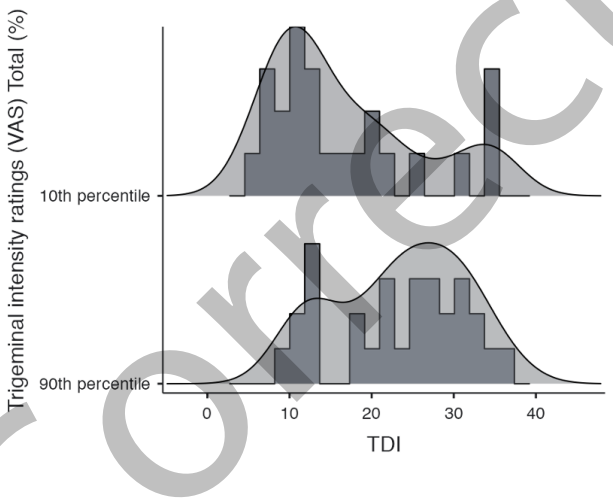

Figure S1. Distribution of TDI scores in participants with trigeminal intensity rating below the 10th percentile of the overall distribution of the TDI scores (top), and participants with trigeminal intensity rating above the 90th percentile of that distribution.

Table S1. Comparison of trigeminal intensity ratings between anosmia, hyposmia and normosmia.

Comparison		All subject		Postviral	
		W-value	p-value	W-value	p-value
anosmia	hyposmia	3.98	0.01*	3.01	0.08
anosmia	normosmia	5.07	<0.001**	3.57	0.03*
hyposmia	normosmia	2.15	0.28	1.07	0.73

All factors are analysed with the W-value and p-value using Kruskal-Wallis Test. df=2. A p-value < 0.05 indicates significance.