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Direktor: Herr Prof. Dr. med. Dr. h.c. Thomas Zahnert

Investigating the intranasal trigeminal system and its interactions with olfaction and nasal airflow / obstruction based on psychophysical and objective airflow tests

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Anna Kristina Malabag Hernandez, MD, MM-PM

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List of Abbreviations

AAR	Active anterior rhinomanometry
B	Bilateral
Ca	Calcium
CO_2	Carbon dioxide
CRS	Chronic rhinosinusitis
CN	Cranial nerve
EPOS 2020	European Position Paper on Rhinosinusitis and Nasal Polyps 2020
ERP	Event related potential
H_2S	Hydrogen sulfide
ISI	Interstimulus interval
MRI	Magnetic resonance imaging
Na	Sodium
OB	Olfactory bulb
OD	Olfactory dysfunction
PG	Propylene glycol
PNIF	Peak nasal inspiratory flow
PET	Positron emission tomography
SD	Standard deviation
SNOT-20 GAV	Sinonasal Outcome Test - 20 German Adapted Version
SNO	Subjective nasal obstruction
SPSS	Statistical Package for the Social Sciences
TLT	Trigeminal lateralization test
TRP	Transient receptor potential
tERP	Trigeminal event related potential
VAS	Visual analogue scale
v/v	Volume per volume

Definition of Terms

Anosmia *	Quantitatively reduced olfactory function to the extent that the sense of smell is not useful in daily life
Bimodal stimulus	Stimulus that activates both the olfactory and trigeminal systems (e.g., eucalyptol, menthol); also referred to as *mixed olfactory-trigeminal stimulus*
Dysosmia	Olfactory dysfunction, in general; but is not regarded as synonymous to *parosmia*
Hyposmia *	Quantitatively reduced olfactory function
Normosmia *	Quantitatively normal olfactory function
Stimulus mixture	A combination of 2 or more stimuli which are co-presented, with each component having distinct individual qualities (olfactory stimulus + trigeminal stimulus); NOT synonymous with *mixed olfactory-trigeminal stimulus* or *bimodal stimulus*

*Adapted from (Hernandez et al., 2023a)

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Hernandez AK, Walke A, Haehner A, Cuevas M, Hummel T. 2023. Correlations between gustatory, trigeminal, and olfactory functions and nasal airflow. Eur Arch Oto-Rhino-Laryngology 280(9):4101–4109. doi:10.1007/s00405-023-07962-6

Hernandez AK, Hummel T. 2023. Intranasal trigeminal function in chronic rhinosinusitis: a review. Expert Rev Clin Immunol 19(8):921-938. doi:10.1080/1744666X.2023.2231149

Hernandez AK, Uhl C, Haehner A, Cuevas M, Hummel T. 2024. Objective nasal airflow measures in relation to subjective nasal obstruction, trigeminal function, and olfaction in patients with chronic rhinosinusitis. Rhinology 62(4):394-402. doi:10.4193/Rhin23.270

Introduction

The nose is a unique organ that plays a crucial role in respiration and sensory perception. It optimizes the air we breathe by warming and humidifying it and it also filters out pathogens and reflexively reacts and alerts us to potential respiratory dangers (Ottaviano and van Gerven, 2021; Shusterman, 2023). In everyday life, we use our nose to understand and interact with our environment. It helps us discriminate between harsh, intense and unpleasant smells and warm, pleasant, and calming aromas.

Most of the stimuli we experience through our noses involve at least two chemosensory systems –trigeminal and olfactory— and the respiratory system. For instance, when we inhale, volatile odorant molecules travel into the nose along with the airflow and stimulate sensory neurons of the olfactory system. More so at higher concentrations, these odorant molecules can also stimulate the nerves of the trigeminal system (Doty, 1975; Cometto-Muñiz and Simons, 2015).

This thesis explores the relationship and interaction between trigeminal function, olfaction, and nasal airflow in both healthy individuals and those with impairments in these systems.

The Trigeminal Nerve

The trigeminal nerve (named after its three branches; tri: three, geminus: twin – in this case triplet) is the fifth cranial nerve (CN V) and is also the thickest (Frasnelli et al., 2007; Hummel et al., 2017a; Laing et al., 2021), connecting to the brainstem at the level of the pons (Hummel and Frasnelli, 2019). While it has both sensory and motor functions (a mixed type), the sensory nerve is much larger than the motor nerve and is distally divided into three main branches: the ophthalmic nerve (CN V1), the maxillary nerve (CN V2), and the mandibular nerve (CN V3) ((Hummel and Frasnelli, 2019), Figure 1).

Figure 1. Innervation to the Nose and the Nasal Cavity. A: The trigeminal nerve and the 3 main branches (from (Ferneini, 2021)[1]); B: Innervation of the nasal septum; C: Innervation of the lateral nasal wall; Pink: Ophthalmic branch of the trigeminal Nerve (V1), Blue: Maxillary branch of the trigeminal nerve (V2) (modified from (Lang, 1989)[2] *using Biorender.com).*

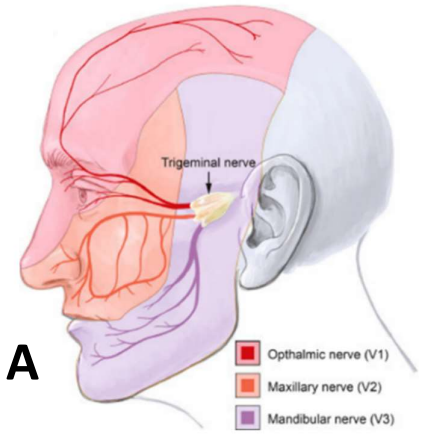

Figure 1B shows the intranasal trigeminal nerve distribution in the nasal mucosa of the lateral nasal wall and nasal septum.

For legal reasons, the figure may not be published online.

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The nasal cavity is innervated by two cranial nerves. The first 2 branches of CN V innervate the anterior (CN V1: anterior ethmoidal nerve, infraorbital nerve) and the posterior (CN V2: posterior superior medial nasal nerve, nasopalatine nerve) nasal cavity (Lang, 1989; Hummel and Frasnelli, 2019); while the olfactory nerve (CN I) innervates the superior nasal cavity, specifically at the area of the olfactory neuroepithelium, and its nerve fibers synapse to the olfactory bulb (OB). Additionally, it has also been shown that trigeminal collaterals innervate both the nasal mucosa and the OB in rats (Schaefer et al., 2002).

The Trigeminal System

The trigeminal nerve, along with the central nervous system, forms the trigeminal system. This system is responsible for somatosensation in the scalp and the entire face, including the mucosa of the eyes, nasal cavity, paranasal sinuses, and oral cavity (Gingras-Lessard and Frasnelli, 2016; Hummel and Frasnelli, 2019; Shusterman, 2023).

The intranasal trigeminal system also responds to chemicals from the environment (Cometto-Muñiz and Simons, 2015) and is involved in the perception of pain and temperature (Hummel and Frasnelli, 2019). This leads to sensations of irritation, tickling, burning, warmth, cooling, and stinging (Doty and Cometto-Muniz, 2003; Hummel and Frasnelli, 2019). This system also triggers nasal reflexes that protect the airway from harmful substances or pathogens causing reactions like sneezing, mucus production, nasal congestion, and changes in respiration patterns (Gingras-Lessard and Frasnelli, 2016). Some odorants are potent trigeminal activators (e.g., eucalyptol, acetic acid (Laska et al., 1997; Saunders et al., 2013)), while others require considerably higher concentrations before triggering trigeminal sensations (e.g., phenyl ethyl alcohol). Almost all odorous molecules can stimulate the free nerve endings of CN V in the nasal cavity at higher concentrations (Doty et al., 1978; Doty and Cometto-Muniz, 2003; Wysocki et al., 2003; Gingras-Lessard and Frasnelli, 2016; Hummel et al., 2016). Furthermore, intranasal trigeminal chemosensation influences the perception of food (e.g., peppermint, spicy jalapenos or wasabi, sparkling water or soda) and aids in odor localization. Unlike cutaneous input, which crosses over at the brainstem level, intranasal trigeminal sensory information is processed ipsilaterally (Iannilli et al., 2008; Hummel and Frasnelli, 2019).

The conduction of trigeminal signals may vary based on axon diameter and the degree of myelination in different types of sensory nerve fibers (Figure 2). The nerve fibers that primarily relate to intranasal trigeminal chemosensation include (Shusterman, 2023):

- **small-diameter myelinated A-delta (Aδ) fibers,** which transmit sensations like sharp pain or stinging and cold sensations quickly

- **small-diameter unmyelinated C fibers,** which transmit dull pain and heat or burning sensations more slowly

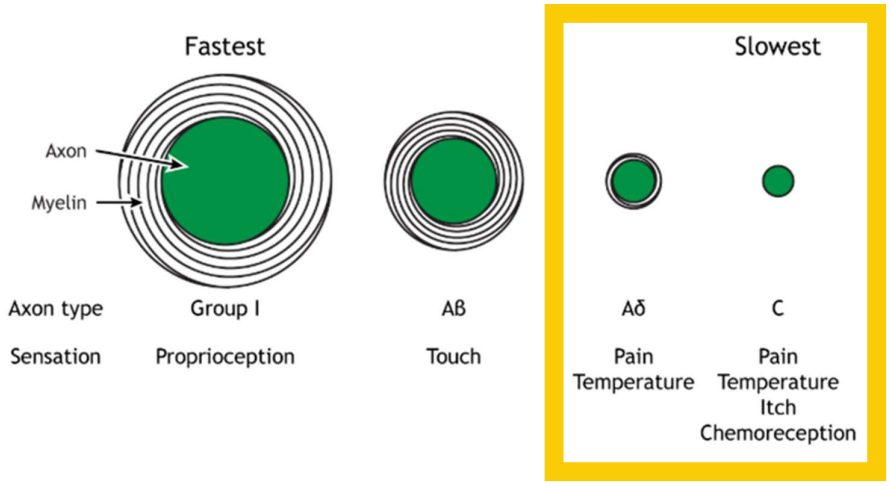

Figure 2. Types of Sensory Nerve Fibers (from (Henley, 2021)[3]*).*

Different types of sensory nerve fibers reach their maximum intensity at different times. For C-fibers, the overall intensity ratings of sensations increase when stimuli are applied at short intervals (≤ 3 seconds). In contrast, for Aδ-fibers, the intensity of stinging sensations decreases when stimuli are applied at short intervals (< 20 seconds for Carbon dioxide, CO_2), (Hummel et al., 1994; Hummel, 2000; Hummel and Frasnelli, 2019). In the skin, myelinated Aδ-fibers also adapt quickly and activate only during actual irritation; while non-myelinated C-fibers adapt slowly and communicate dull, burning, and persistent difficult to locate perceptions that may outlast acute pain.

Transient Receptor Potential (TRP) Ion Channels

Various ionotropic receptors, which open ion-channels to allow specific ions to flow in and out of a cell (Abuin et al., 2011), are key to trigeminal sensations.

When a TRP ion channel is activated, it results in the transition from a closed to open pore configuration, allowing cations to enter the cell at physiologic resting membrane potentials. This increases the intracellular concentrations of sodium (Na^+) and calcium (Ca^{2+}). Once these ions accumulate and reach the threshold, the cell membrane depolarizes and trigeminal signals are then transmitted through the nerves to the brain.

[3] 'Somatosensory Axon Types' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License (https://creativecommons.org/licenses/by-nc-sa/4.0/).

Various types of TRP ion channels responds to a specific range of temperatures (Gingras-Lessard and Frasnelli, 2016):

- **TRPV1** (Vanilloid) is the most common and is sensitive to temperatures above 43 degrees Celsius, resulting in painful burning sensation. Agonists include capsaicin, eugenol, and CO_2.
- **TRPV3** is activated by temperatures above 39 degrees Celsius, resulting in feelings of warmth, typically elicited from oregano or thyme.
- **TRPM8** (melastatin, also cold and menthol receptor 1 [CMR1]) is sensitive to cold temperatures between 8 to 25 degrees Celsius, yielding to cool and fresh sensation from substances such as menthol and eucalyptol.
- **TRPA1** is activated by extremely cold temperatures below 17 degrees Celsius and plays a role in nociceptive pain perception and can result in dull, painful sensation. Known agonists include mustard oil and wasabi.

Psychophysical Intranasal Trigeminal Assessment

There are many ways to measure intranasal chemosensory trigeminal function, including electrophysiologic (event related potentials [ERP], negative mucosal potentials) and imaging (functional magnetic resonance imaging [fMRI], positron emission tomography [PET]) modalities. However, psychophysical methods are easy to perform, accessible, practical and are often used for patient testing in the clinical setting. Here are some examples of previously published psychophysical intranasal trigeminal assessment methods:

Subjective Intranasal Trigeminal Intensity Rating

This test involves the presentation of a trigeminal stimulus (in some publications ammonium was contained in a lipstick-like container (AmmoLa®, Devesa Dr. Reingraber GmbH, Muggensturm, Germany, (Garefis et al., 2024; Juratli et al., 2024); in another it was CO_2 (Burghardt et al., 2023)). Participants then rate the stimulus intensity from varying ranges of scores (i.e., Ammola®: 0 [no sensation] to 100 [very strong sensation]; CO_2: 0 [not intense] to 10 [extremely intense]).

Trigeminal Lateralization Test

The trigeminal lateralization test (TLT, sometimes odor lateralization or odor localization test or task) is a widely-used clinical test to assess trigeminal function. It centers on the principle that humans are unable to lateralize a pure odorant when presented to only one nostril, but with the addition of a trigeminal component, this task then becomes possible (Schneider and Schmidt, 1967; Kobal et al., 1989;

Negoias et al., 2013; Croy et al., 2014b). It typically involves the presentation of a bimodal stimulus (often eucalyptol or menthol) and a neutral stimulus (air or solvent). A participant is then required to identify which side of the nose received the trigeminal stimulus by raising the corresponding arm. The stimuli is typically presented a total of 20 to 40 times.

Trigeminal Sticks Test

Based on the work of Huart et. al. (Huart et al., 2019), a trigeminal test similar to the "Sniffin' Sticks" olfactory test was developed. The trigeminal sticks are filled with bimodal stimuli that activate different TRP ion channels (TRPM8: menthol, eucalyptol, and camphor; TRPA1: diallyl sulfide; and TRPV1: ethanol and propanol). The conduct of testing is similar, such that the examiner uncaps each pen for around 3 seconds and presents the tip of the pen approximately 2 cm in front of both nostrils. The test has 3 subtests: threshold, discrimination, and identification.

A. Threshold

Ten dilutions of menthol (highest concentration at 50%, at 1:2 dilutions in propylene glycol) is presented in a 3-alternative forced choice ascending staircase method with 7 reversals. Pens are presented in triplets, where one pen contains menthol and the two others contains the solvent. Participants must identify the pen containing menthol, focusing on the trigeminal sensation (i.e., stinging, burning, irritating or cool sensation). The presentation of the three pens lasts around 10 seconds, with an inter-triplet interval of 30 seconds. The average of the last 4 reversals make up the score, similar to the "Sniffin' Sticks".

B. Discrimination

Three pens are presented to each participant, two containing stimuli that activate the olfactory system preferentially, while one contains a bimodal stimulus (menthol, ethanol, diallyl sulfide, propanol, camphor, and eucalyptol). Participants must identify the pen that has the strongest trigeminal sensation in a 3-alternative forced choice method. Pens are presented in a randomized order with an inter-triplet interval of at least 30 seconds and interval of approximately 3 seconds between pens.

C. Identification

A total of 6 pens containing bimodal stimuli are presented to participants, who must identify the quality of the trigeminal component of the stimuli. Five cards

with verbal descriptors (1) pungent, astringent; 2) burning, warm; 3) scratching tickling, sneezing; 4) prickling, 5) cold, fresh) are presented and participants must choose the best descriptors for each stimulus (ethanol: “cold, fresh”, menthol: “cold, fresh”, diallyl sulfide: “pungent, astringent”, eucalyptol: “cold, fresh”; propanol and camphor were eventually excluded in the original article (Huart et al., 2019) as these stimuli had poor identification rates below 50%). Pens are randomly presented at an interval of at least 30 seconds between pens.

CO_2 Pain / Detection Threshold or Sensitivity Test

CO_2 is delivered using a portable device with a small CO_2 cylinder that is attached to a pressure reducer and a pressure regulator. Various stimulus presentation durations (in multiples of 50 milliseconds) are presented through a bilateral nasal cannula until the participant pushes a button indicating a (painful) sensation. After which, the stimulus duration is reduced until the participant no longer presses the button. This is then followed by a subsequent increase in stimulus duration. The interstimulus interval (ISI) is 10 seconds and the average of the last 4 turning points of this staircase method is referred to as the CO_2 pain threshold (when asking about pain) and CO_2 sensitivity (when asking about any sensation only). In Study 3, the value is multiplied by -1 to refer to sensitivity and for ease of interpretation (see Methodology).

A modified method of testing using air puffs at an ISI of 10 seconds has also been published, with a correct response corresponding to 2 correct detections, leading to a reversal, followed by another reversal after failure of detecting the stimulus (Yan et al., 2023). Compressed air is delivered by a portable air compressor (1.0 Gallon Air Tank, VIAIR, California, United States of America) that is connected to a pressure reducer and pressure regulator, as well as an airflow sensor (SFC5400, Sensirion AG, Stäfa, Switzerland) with a computer-controlled valve, allowing the release of different air volumes or durations at a total flow rate of 2 L/min and ISI of 10 seconds. The device is connected to a standard nasal cannula (the original article cited 20 gauge, Vasofix® Safety, Germany; but is probably more similar to an oxygen cannula, adult, curved tip, Asid Bonz, Herrenberg, Germany) attached to both nostrils of the participant. Velopharyngeal breathing is also instructed, which meant that participants should only breathe through their mouth lifting the soft palate which separates the nasal from the oral cavity.

Electrical Detection Threshold

Based on the article by Poletti et. al. (Poletti et al., 2017), electrical stimuli at a duration of 50 milliseconds and initial intensity of 0.05 mA is applied using a spherical electrode at three intranasal sites: 1) anterior nasal septum (1 cm from the nasal vestibule), anterior lateral nasal wall (1 cm), and the middle turbinate (4.5 cm). Electrodes are secured using a frame that resembles eyeglasses. The stimulus intensity is gradually increased by 0.05 mA until the participant detects the stimulus. This is followed by a decrease of 0.05 mA until the participant no longer detects the stimulus. After which, the stimulus intensity is again increased by 0.01 mA until the stimulus could be perceived again, and this point corresponds to the electrical detection threshold.

Interactions

Trigeminal sensation is anatomically bound to and functionally interrelated with olfaction and the other sensory modalities in the oral-nasal region (gustation, and nasal airflow; Figure 3). Nasal airflow helps transport odorant molecules to the olfactory cleft, where most olfactory neuroepithelium and receptors are located. Orthonasal (anterior to posterior direction of smelling, e.g., sniffing the external environment) and retronasal (posterior to anterior direction of smelling, e.g., from odors originating from the oral cavity, also flavor perception) olfaction largely depend on airflow. Retronasal olfaction and trigeminal perception are associated with flavor and taste perception. Odorous chemicals are also able to stimulate free trigeminal nerve endings in the nasal respiratory mucosa, causing sensations such as irritation or stinging, tickling, burning, warmth, and cooling (Hernandez et al., 2023b).

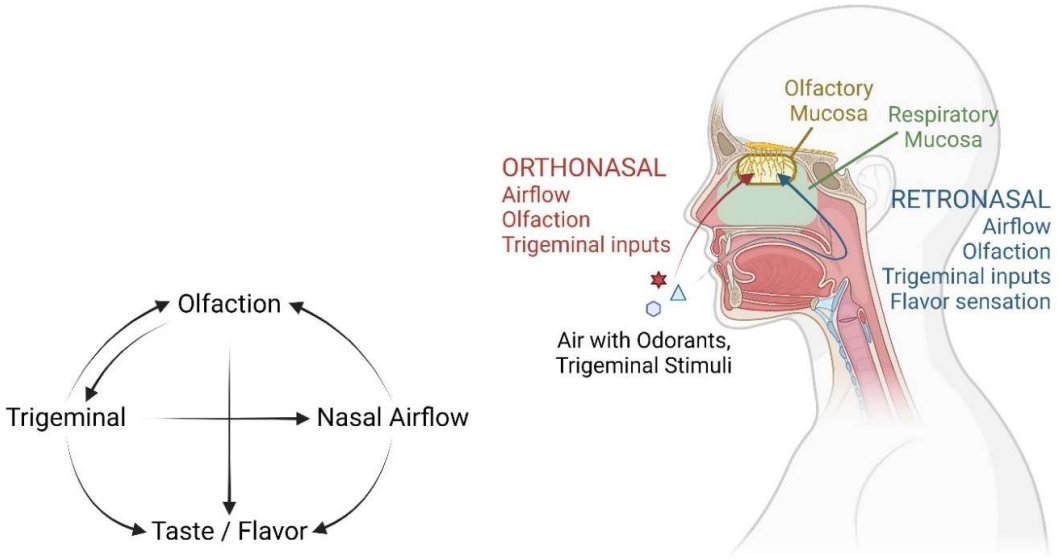

Figure 3. Anatomic Location and Functional Interaction of Trigeminal and Other Senses in the Head.

The interaction between intranasal trigeminal function and olfaction is evident not only in how odors can evoke trigeminal sensations and how certain chemical stimuli that evoke intranasal trigeminal responses can also provoke olfactory sensations. An exception is CO_2 which is not considered to be odorous (Fröhlich, 1851; Wysocki et al., 2003).

Furthermore, decreased trigeminal function has been observed in individuals with acquired olfactory dysfunction (OD) due to infectious, traumatic, sinonasal, and idiopathic causes (Hummel et al., 1996, 2003; Frasnelli et al., 2007). However, patients with olfactory loss related to neurodegenerative (Barz et al., 1997; Tremblay et al., 2019) or congenital causes have been found to have comparable trigeminal function to those with normal smell function (Laska et al., 1997).

Context

Despite the interactions between intranasal trigeminal function and other systems, research on this topic is relatively limited. A PubMed search conducted in May 2024 (Figure 4) using the search terms “intranasal trigeminal” yielded only 511 results, with the earliest English article dating back to 1943. In contrast, searches for “olfaction” and “gustation” returned 34,800 and 54,734 results, respectively with the earliest articles dating back to the early 1800s.

Interestingly, there has been a recent surge of interest in the chemical senses, where one-third of existing studies on olfaction, gustation, and intranasal trigeminal function have only been published in the last five years. However, given the relative paucity of studies in intranasal trigeminal function compared to the other chemical senses, this indicates a similar interest and a growing need for further research in this area.

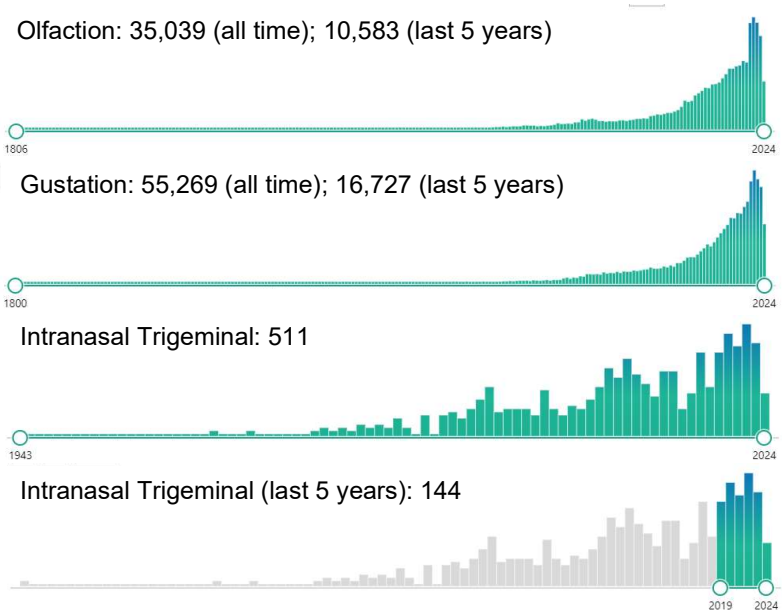

Figure 4. Results for Specific Search Terms in PubMed as of July 2, 2024.

Objectives

Considering the context outlined above, this thesis aims to address the following key questions:

- How is intranasal trigeminal function related to olfaction and nasal airflow in healthy individuals?
- What is the current understanding of intranasal trigeminal function in individuals experiencing both OD and nasal obstruction, such as patients with chronic rhinosinusitis?
- Is intranasal trigeminal function related to the perception of subjective nasal obstruction, objective nasal airflow measurements, and olfactory function in patients with sinonasal olfactory loss? Moreover, can psychophysical trigeminal function tests estimate measured nasal airflow in these patients?

Methodology and Results

Study 1: Correlations Between Gustatory, Trigeminal, and Olfactory Functions and Nasal Airflow

Methodology: Chemosensory and Objective Nasal Airflow Screening Tests and Visual Analogue Scale Ratings in Healthy Individuals

Study Design and Participants

This cross-sectional study involved participants aged 18 years and older, without chemosensory complaints, who presented for testing at a private dental clinic. A standardized structured history was taken, including data about participants' age, sex, height, weight, smoking history, alcohol consumption, exposure to occupational chemicals, head injuries, headaches, rhinologic symptoms, and co-morbid conditions. Subjective ratings (visual analogue scale [VAS] ratings for smelling / tasting ability and nasal airflow), composite sinusitis symptom and significance of olfaction questionnaire scores were also collected. Each participant was tasked to undergo five screening tests, namely: the TLT, Q-Sticks, Q-Powders, taste sprays, and peak nasal inspiratory flow.

The details of relevant outcome measures investigated are as follows:

Screening Tests

Trigeminal Lateralization Test

This test, based on a similar methodology published by Frasnelli et al. (Frasnelli et al., 2011b) involved using a device with 2 squeezable bottles (Figure 5) that delivered simultaneous air puffs into both nostrils for a total of 10 times, in a randomized manner ensuring each side received five stimulations. One of the bottles contained 20ml eucalyptol (order number C80601; Sigma Aldrich, Taufkirchen, Germany) and participants had to identify which nostril received the stimulus. The maximum score is 10.

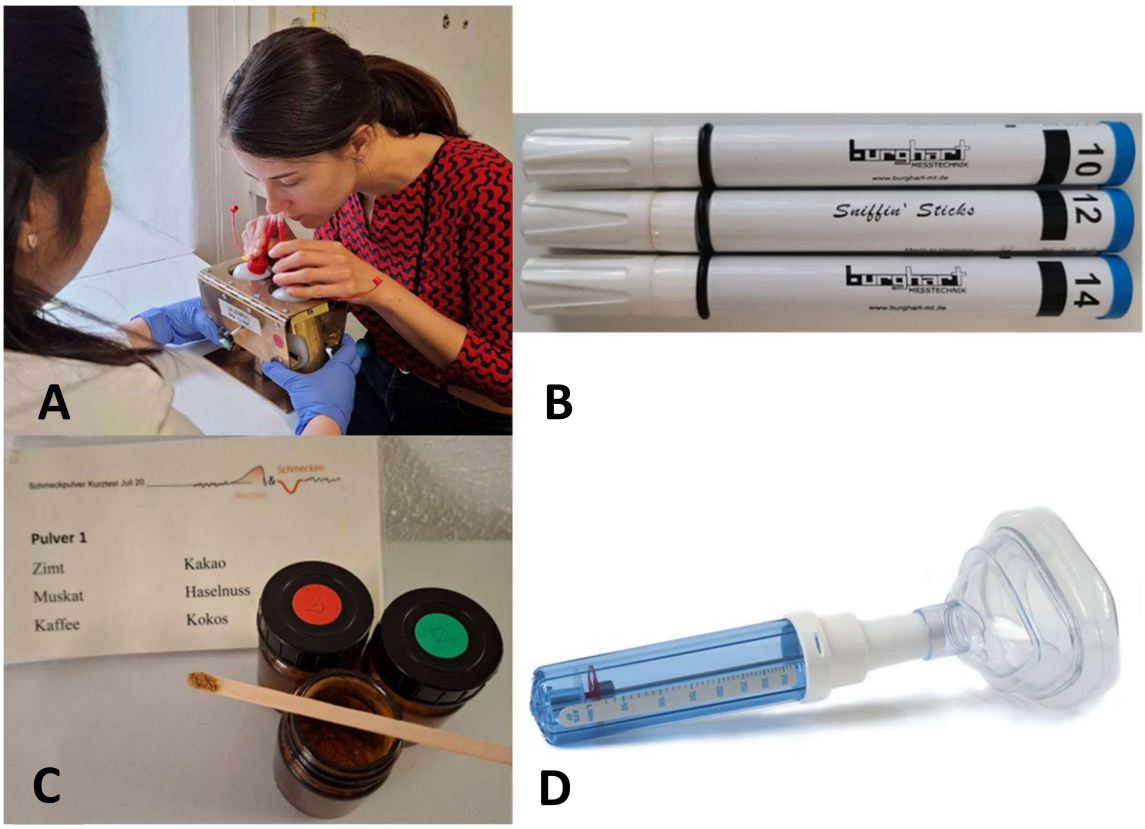

Figure 5. Study 1 Assessment Methods. A: trigeminal lateralization test; B: Q-Sticks (orthonasal olfactory test); C: Q-Powders (retronasal olfactory test); D: nasal inspiratory flow meter.

Q-Sticks

The Q-Sticks test is a three-item orthonasal odor identification test adapted from Sorokowska et al. (Sorokowska et al., 2019). Three odors (cloves, coffee, and rose, Figure 5) were presented in felt-tip pens similar to those used in the "Sniffin' Sticks" olfactory test (Hummel et al., 1997; Oleszkiewicz et al., 2019). These odors were selected as they are widely known and the ability to identify these odors was not strongly dependent on age (Hummel et al., 2010). Participants selected the correct answer from a list of four descriptors for each odor. The highest possible score is 3.

Q-Powders

The Q-Powders test is a three-item retronasal odor identification test based on Pieniak et al. (Pieniak et al., 2021) and includes cinnamon, banana, and garlic odors (Givaudan Schweiz AG, Dubendorf, Switzerland, Figure 5). The odors were chosen based on a previous study that showed high identification rates for these odors (> 95%, (Croy et al., 2014a)). Before each stimulus was given, participants extended their tongue out and pinched their nostrils, after which the experimenter placed a small amount of each powder (around 0.05 g) using a

disposable drink mixer at the mid-dorsal area of each participant's tongue. Afterwards, the participants drew their tongues back into their mouths, nostrils were unblocked, and they were instructed to exhale through their nose. Participants then chose which word best described the flavor of each of the powders among six descriptors, presented as flash cards. The highest possible score is 3.

Peak Nasal Inspiratory Flow (PNIF)

PNIF is a measure of nasal airflow volume (in L/min) using a peak flow meter (Figure 5, nasal inspiratory flow meter, order number 3108750; Clement Clarke Int. Ltd., Harlow, United Kingdom). Participants were instructed to inhale deeply and rapidly with their mouth closed while a face mask was applied firmly around the nose and the mouth. The test was performed twice and the higher value of the two attempts was recorded.

Other Outcome Measures

Visual Analogue Scale (VAS) Ratings for Smelling Ability and Nasal Airflow

Each participant was asked to rate how well they can smell and how good the flow of air (nasal breathing) was through their nose from 0 to 10 (highest).

Statistical Analysis

Data analysis was done using Statistical Package for the Social Sciences (SPSS, Version 28.0; IBM Corp., Armonk, New York, United States of America). Pearson's r, Spearman's rho, and t-tests were performed, with a p-value of < 0.05 considered significant.

Results

A total of 400 participants (244 were women), aged 18-82 years (mean: 46 years, SD = 14.9) were included in the study. Trigeminal lateralization scores were positively correlated with Q-Powders ($r_{389} = 0.27$, $p < 0.001$) scores and PNIF ($r_{391} = 0.27$, $p < 0.001$), but not with Q-Sticks scores. VAS ratings for smelling ability and nasal breathing were not correlated with trigeminal lateralization.

Study 2: Intranasal Trigeminal Function in Chronic Rhinosinusitis: A Review

Methodology: Comprehensive Literature Search and Review in Chronic Rhinosinusitis Patients

Study Design and Literature Search

The review began with a comprehensive literature search across three databases (PubMed, Web of Science, and Scopus) on February 2, 2023. The search terms used were: ('trigeminal' [All Fields] OR 'trigeminal function' [All Fields]) AND ('chronic rhinosinusitis' (CRS) [All Fields] OR 'chronic sinusitis' [All Fields; Title-Abstract-Keywords for Scopus] OR 'nasal polyp' [All Fields; Title- Abstract-Keywords for Scopus] OR 'nasal polyposis' [All Fields; Title-Abstract-Keywords for Scopus]). Due to fewer number of studies found using 'trigeminal function', the term 'trigeminal' was retained. In addition, keywords such as 'chronic sinusitis', 'nasal polyp', and 'nasal polyposis' were added to expand the search.

Inclusion and Exclusion Criteria

All original articles with human participants, published in English, without date restriction were included in this review. Other types of study designs (reviews, case reports, or case series), formats (editorials, letters, conference papers, expert opinions, or guidelines), those whose samples did not include CRS patients, and studies not published in English were excluded.

Data Extraction and Collection

The primary author conducted the initial electronic database search and removed duplicates. References were compiled into a Microsoft Excel database (Microsoft Corp., Redmond, Washington, United States of America). Both authors independently screened the titles and abstracts, with inclusion of articles for full-text review after at least one author tags it as such. Full-text versions of these articles were subsequently reviewed independently by both authors. Again, articles considered relevant by at least one author were included in the final list of articles for review.

The following information were extracted from the articles: author, year, location, study design, participant groups, basis of CRS diagnosis, sample size, intervention, outcome measures (excluding intranasal trigeminal function testing), type of intranasal trigeminal function test used, and findings of trigeminal function in relation to: a) CRS, b) olfaction, c) nasal obstruction, d) demographics (age, sex), e) treatment modalities, and f) others.

Statistical Analysis

Frequencies, means, and qualitative summaries of the articles were tabulated and organized using Microsoft Excel.

Results

The initial search yielded 281 manuscripts, of which 16 underwent full-text review after removal of duplicates and screening of titles and abstracts. Nine studies were included in the final list, with a total of 659 participants. Among these, 208 were CRS patients, 223 were controls, and the rest had other conditions related to OD, such as post-traumatic, post-infectious or unspecified OD.

A summary of the included studies is provided in Table 1. The articles were published between 2006 to 2022, with most studies including patients with nasal polyps. Eight studies explicitly stated the basis for CRS diagnosis: either through clinical findings with nasal endoscopy, imaging, or adherence to clinical practice guidelines (European Position Paper on Rhinosinusitis and Nasal Polyps 2020 [EPOS 2020] (Fokkens et al., 2020), Canadian Guidelines for Acute and Chronic Rhinosinusitis (Desrosiers et al., 2011)). One study was later confirmed by the authors to have been based on clinical assessment (Huart et al., 2019). There were no randomized controlled trials in the included studies, as most were prospective cohorts or cross-sectional studies. Only six studies had clearly defined control groups, although one of these included a control group with 'little or no polyps', whose CRS diagnosis was uncertain (Minovi et al., 2008). Most studies had small sample sizes for CRS patients, ranging from 10 to 45, with a mean of 23.

		Participants (n)		
Author	Study design	CRS	Control	Total
Rombaux et al. (2006) [18]	Prospective comparative cohort	11	11	44
Minovi et al. (2008) [19]	Prospective comparative cohort	25	39	64
Savic et al. (2009) [20]	Cross-sectional study	12	12	24
Saliba et al. (2016) [21]	Prospective case-control	14	14	28
Poletti et al. (2017) [22]	Prospective	45	30	75
Huart et al. (2019) [23]	Cross-sectional study	20	86	131
Zhang et al. (2019) [24]	Cross-sectional study	40	0	40
Migneault-Bouchard et al. (2020) [14]	Cross-sectional study	31	0	178
Burghardt et al. (2022) [25]	Cross-sectional study	10	31	41

Table 1. Summary of Included Articles in Study 2. (Also Table 2 in (Hernandez and Hummel, 2023)*).*

Various methods were used to measure intranasal trigeminal function, including trigeminal event related potentials (tERPs), the TLT, negative mucosal potentials, CO_2 detection thresholds, electrical detection thresholds, air puff test, trigeminal threshold / discrimination / identification, 7-item olfactory-trigeminal test, PET, respiratory index, and self-ratings (see Table 3 in Study 2). Olfactory function was assessed using different methods such as: psychophysical ("Sniffin' Sticks" test battery, [(Rombaux et al., 2006; Huart et al., 2019; Zhang et al., 2019; Migneault-Bouchard et al., 2020; Burghardt et al., 2023), see also (Hummel et al., 1997; Oleszkiewicz et al., 2019)], odor identification test (Minovi et al., 2008), n-butanol or phenyl ethyl alcohol threshold tests (Savic et al., 2009), retronasal odor identification test (Rombaux et al., 2006)); electrophysiological (olfactory event related potentials (Rombaux et al., 2006; Zhang et al., 2019; Burghardt et al., 2023)); and imaging modalities (MRI (Rombaux et al., 2006), PET (Savic et al., 2009)). Nasal polyp grading was also used to estimate nasal obstruction (Lund Mackay (Minovi et al., 2008; Saliba et al., 2016), Lund Kennedy (Poletti et al., 2017; Zhang et al., 2019; Burghardt et al., 2023), and Lildholdt (Burghardt et al., 2023)). Subjective ratings for olfaction (Saliba et al., 2016; Poletti et al., 2017) and other nasal symptoms (nasal obstruction, smell loss (Zhang et al., 2019), nasal patency (Saliba et al., 2016)), as well as markers for inflammation (tissue eosinophil count (Zhang et al., 2019)) were noted in some studies.

Trigeminal Function and Olfaction

Only seven studies analyzed the relationship of olfaction to trigeminal function (Table 2). Four studies used "Sniffin' Sticks (Rombaux et al., 2006; Huart et al., 2019; Migneault-Bouchard et al., 2020; Burghardt et al., 2023) while the others used odor identification tests (Minovi et al., 2008; Saliba et al., 2016) and PET scan (Savic et al., 2009).

Study	Trigeminal Test	Olfactory Test	Relationship of Olfaction to Trigeminal Function	Details
Rombaux et al., 2006 [18]	tERP	"Sniffin' Sticks" [27,28], 20-item Retronasal Powders Test [44]	Correlated	Significant correlation between orthonasal testing ($r = 0.21$, $p = 0.002$), but not retronasal testing ($r = 0.09$, $p = 0.05$), and N1P2 peak-to-peak amplitude after presentation with a trigeminal stimulus ($r = 0.21$, $p = 0.002$); normal trigeminal function may indicate good prognosis for recovery of olfaction
Minovi et al., 2008 [19]	7-item olfactory-trigeminal test	6-item odor identification test	Both decreased	Both olfaction and trigeminal function was decreased in patients with severe nasal polyps
Saliba et al., 2016 [21]	Trigeminal Lateralization	8-item odor identification test	Correlated	Trigeminal and olfactory functions were correlated ($r = 0.48$, $n = 28$, $p = 0.01$)
Huart et al., 2019 [23]	Mixed Olfactory-Trigeminal Threshold	"Sniffin' Sticks" [27,28]	Correlated	Trigeminal threshold scores significantly correlated with olfactory threshold ($r = 0.50$, $p = 0.012$), discrimination ($r = 0.660$, $p < 0.001$), and identification scores ($r = 0.70$, $p < 0.001$).
Migneault-Bouchard et al., 2020 [14]	Trigeminal Lateralization	"Sniffin' Sticks" [27,28]	Correlated	Olfactory and trigeminal scores were correlated, with age as covariate ($r = 0.25$, $p = 0.006$)

Table 2. Trigeminal Function Related to Olfaction. (Also Table 5 in (Hernandez and Hummel, 2023)*)*

Despite the differences in the trigeminal and olfactory function tests used, six studies supported the presence of a relationship between the two systems. Rombaux et al. reported a significant correlation between orthonasal ($r = 0.21$, $p = 0.002$), but not retronasal, olfaction and tERP (N1P2 peak-to-peak) amplitude. The sample size in this study, however, was only 44 (of which only 11 had nasal polyps) and may have affected this outcome (Rombaux et al., 2006). A correlation between TLT scores and olfactory scores was found by Migneault-Bouchard et al. ($r = 0.25$, $p = 0.006$) and Saliba et al. ($r_{28} = 0.48$, $p = 0.01$) (Saliba et al., 2016; Migneault-Bouchard et al., 2020). Huart et al. also found that trigeminal threshold scores were positively correlated with odor threshold ($r = 0.50$, $p = 0.012$), discrimination ($r = 0.66$, $p < 0.001$), and identification ($r = 0.70$, $p < 0.001$) scores (Huart et al., 2019). Although Burghardt et al. alluded to a possible interaction of trigeminal function and olfaction, they also suggested that results should be re-investigated in a larger sample given that their study only included 10 CRS patients with nasal polyps (Burghardt et al., 2023). Minovi found that severe nasal polyposis was associated with both olfactory ($r_{64} = -0.62$, $p < 0.001$) and trigeminal ($r_{64} = -0.41$, $p = 0.001$) loss, although a direct correlation between olfactory and trigeminal scores was not explicitly stated (Minovi et al., 2008). Only Savic et al., investigated the relevant brain regions that were activated by trigeminal and olfactory stimuli ((Savic et al., 2009), Table 3). Healthy controls had activations for olfactory stimuli (vanillin or androstadienone) in the amygdala, piriform cortex, agranular insular cortex, and fusiform gyrus. However, when acetone (a bimodal olfactory-trigeminal stimulus) was presented to these controls, additional areas, namely: the anterior cingulate, brainstem (trigeminal nucleus), thalamus (ventromedial nucleus and the pulvinar), sensorimotor cortex, and cerebellum, were also activated. Conversely, in anosmic patients, no activations for olfactory stimuli were observed. Only acetone elicited activations in similar areas as in controls (i.e. the anterior cingulate, brainstem, thalamus, and sensorimotor cortex), but not in the cerebellum. This finding suggests that, although there is an overlap in brain regions activated by olfactory and trigeminal stimuli, the absence or reduction of olfactory input leads to changes not only in areas associated with olfaction, but also in regions potentially related to trigeminal processing.

	Olfactory Stimulus [vanillin/ androstadienone]	Bimodal Stimulus [acetone]
Healthy	Amygdala Piriform cortex Agranular insular cortex Fusiform gyrus	Additional areas: Anterior cingulate gyrus Brainstem (trigeminal nucleus) Thalamus (ventromedial nucleus, pulvinar) Sensorimotor cortex Cerebellum
Anosmic Patients with Nasal Polyps (CRS patients)	No activations	Same as healthy, except: Amygdala Piriform Insula Cerebellum

Table 3. Location of Brain Activations for Olfactory and Bimodal Stimuli in Healthy Individuals and CRS Patients. (See also (Savic et al., 2009)*).*

Two studies that investigated trigeminal function also included individuals with other causes of olfactory loss. Although Huart et al., found that trigeminal function was affected in patients with CRS, as well as those with post-traumatic, post-infectious, and idiopathic OD (Huart et al., 2019), Migneault-Bouchard et al. did not (Migneault-Bouchard et al., 2020). Both studies had a low sample size of CRS patients (Huart et al.: 20, Migneault-Bouchard et al.: 31), and used bimodal stimuli, making any comparison between these findings inconclusive.

Huart et al. explored the possibility of a clinical intranasal trigeminal function test, similar to the 'Sniffin' Sticks" (Huart et al., 2019). However, results were difficult to isolate from the effects of olfaction as they used bimodal stimuli. Furthermore, the scores from their clinical intranasal trigeminal function test were not correlated with the TLT, which they attributed to the differences in methodology and the low sample size (n = 59, of which only 20 were CRS patients). This casts some doubt whether the both tests effectively measure trigeminal function or not. Although the authors emphasized their attempts at decreasing the influence of olfaction by specifically telling patients to focus on trigeminal sensations, this cannot be ascertained unless a purely trigeminal stimulus like gaseous CO_2 is used (Huart et al., 2019).

Trigeminal Function and Nasal Airflow

Only two studies compared objective measurements of nasal airflow / breathing with trigeminal function measures. Savic et al. found that brain activations on PET scans, with acetone as the trigeminal stimulus, were slightly less pronounced in anosmic patients (including CRS patients) compared to controls. In addition, they also measured respiratory

patterns (using a strain gauge, based on recorded respiratory frequency [in breaths per minute] and amplitude during each scan) which did not differ significantly between the 2 groups (Savic et al., 2009). Two studies found that CRS patients rated their nasal patency as worse than controls (Saliba et al., 2016; Poletti et al., 2017). However, a study by Saliba et al., also found normal PNIF measurements among CRS patients, despite having worse self-ratings for nasal patency and significantly lower scores on the TLT compared to controls (Saliba et al., 2016). This finding supports the possibility of trigeminal dysfunction contributing to the subjective impression of nasal obstruction in CRS patients.

Study 3: Objective Nasal Airflow Measures in Relation to Subjective Nasal Obstruction, Trigeminal Function, and Olfaction in Patients with Chronic Rhinosinusitis

Methodology: Subjective and Objective Nasal Airflow Measures and Intranasal Chemosensory Tests in Chronic Rhinosinusitis Patients

Study Design and Participants

This cross-sectional study included adults aged 18 years and older, diagnosed with CRS according to the EPOS 2020 guidelines and admitted for surgery (CRS patients), as well as patients who consulted for non-nasal complaints (controls) at the University Hospital Dresden. Structured medical history was taken, including: age, sex, previous nasal surgery (including the number and types of previous nasal surgeries), rescue medication (intranasal corticosteroids ± biologics), CRS control (estimate of disease severity), and subjective nasal obstruction (SNO) ratings (see details later). Trigeminal function (TLT and CO_2 sensitivity), olfaction ("Sniffin' Sticks" odor identification test), and nasal airflow (PNIF and active anterior rhinomanometry [AAR, before decongestion and difference between after and before decongestion]) were also assessed.

Trigeminal Lateralization Test

As mentioned in Study 1, simultaneous air puffs were delivered into both nostrils using 2 squeezable polypropylene bottles pressed simultaneously using a device. For this study however, one bottle contained 10 ml of 99% eucalyptol (order number C80601; Sigma Aldrich, Taufkirchen, Germany) while the other bottle contained only air. Participants identified which nostril was presented with eucalyptol, for a total of 20 presentations with the stimulated nostril randomized for each presentation and an ISI of approximately 20 seconds. The score was based on the sum of correct lateralizations with a maximum score of 20 points.

CO_2 Sensitivity

Participants were presented with a trigeminal stimulus (100% CO_2) in both nostrils through a device providing a constant airflow of 200 ml/min via a nasal cannula. They were then instructed to press a button when they perceived the stimulus. The duration of the stimulus increased in 100-millisecond increments every 8 seconds until the participants signaled its perception. The maximum stimulus duration was set at 2000 milliseconds. The "CO_2 threshold" corresponded to the duration at which participants were able to perceive the trigeminal stimulus. This threshold was determined using a staircase method with seven turning points. To facilitate interpretation, the scores were multiplied by -1 and referred to as "CO_2 sensitivity", where a lower (more negative) number indicated poorer function.

"Sniffin' Sticks" 16-Item Odor Identification Test

In the "Sniffin' Sticks" odor identification test (Burghart Messtechnik, Holm, Germany (Hummel et al., 1997; Oleszkiewicz et al., 2019)), odors were contained in devices resembling felt tip pens. These pens were presented approximately 2 cm in front of participants' nostrils. Each participant was then prompted to identify the odor from a set of 4 descriptors. Scores were calculated based on the sum of correct answers, which may range from 0 to 16, with higher scores indicating better performance.

Peak Nasal Inspiratory Flow

As mentioned in Study 1, PNIF measures the volume of nasal airflow in liters per minute, using a peak flow meter (Inspiratory flow meter, order number 3108750; Clement Clarke Int. Ltd., Harlow, United Kingdom). Each participant was instructed to inhale deeply and rapidly with their mouth closed while a face mask was firmly applied around their nose and mouth. The test was done twice and the higher value of the two attempts was recorded.

Active Anterior Rhinomanometry

AAR evaluates nasal airway resistance based on airflow and pressure readings. However, for this study, only the airflow data was analyzed. The Rhino-Sys system (Figure 6, Happersberger Otopront GmbH, Hohenstein, Germany) was used, with a probe placed over one nostril while the nose and mouth were covered with a mask attached to the device. Measurements were taken in milliliter per second, following the manufacturer recommendations and correspond to the total volume of air through the left and right nasal cavities during the inspiratory phase of the respiratory cycle at a trans-nasal pressure difference of 150 Pa, before (AAR B Before Decongestion) and after decongestion with Xylometazoline hydrochloride. Only the pre-decongestion measurements and the difference between post- and pre-decongestion measurements (AAR B Change) were used in the analyses.

Figure 6. Active Anterior Rhinomanometry. Left to right, top to bottom: Otopront rhinomanometry device, anterior view, lateral view, nasal probe lateral view, nasal probe anterior view.

Nasal Cycle

To account for the influence of the nasal cycle, the measurements of nasal airflow were combined for both nostrils. A prior study by Gungor et al. (Gungor et al., 1999) found no correlation between VAS ratings for nasal patency and the nasal volumes or cross-sectional areas during the nasal cycle and that the sum of the left and right volumes and areas were quite consistent. Therefore, we adopted the same approach in this study to ensure consistency.

Subjective Nasal Obstruction Rating and CRS Control Score

Based on the work by Piccirillo et al. (Piccirillo et al., 2002), a validated German translation of the 20-item Sinonasal Outcome Test [SNOT-20 GAV, see Appendix] was administered to participants. This questionnaire assessed various rhinologic symptoms and overall quality of life. Participants rated each symptom on a scale of 0 (no problem) to 5 (problem as bad as it can be). For our analysis, we focused on the ratings for question 1 (SNO) and additionally for the CRS control score, including questions 3 (rhinorrhea), 10 (smell loss), 12 (facial pain/pressure), and 13 (sleep problems).

CRS control score

In order to determine the degree of disease severity of CRS among our participants, we opted to estimate disease control using the following variables based on the EPOS 2020 guidelines (Fokkens et al., 2020):

1) Nasal symptom count: Ratings for questions 1 (nasal obstruction), 3 (rhinorrhea), 10 (smell loss), 12 (facial pain/pressure), and 13 (sleep problems) of the Sinonasal Outcome Test-20 German Adapted Version (SNOT-20 GAV (Baumann et al., 2007),

see Appendix) were determined. Each item with a rating ≥ 3 (indicating a 'moderate problem') contributed 1 point.

2) Nasal polyp scores: Nasal polyps were evaluated using the Lildholdt or Lund Kennedy scoring systems, summed bilaterally. Scores ≥ 2, indicating diseased mucosa, contributed 1 point
3) Rescue medications: Participants using at least one course of rescue treatment (intranasal corticosteroids [mometasone or budesonide], with or without biologics), received 1 point.

Uncontrolled CRS was defined as a total score of ≥ 3 out of the 7 variables. A score of 1 to 2 indicated partly controlled CRS, while a score of 0 signified controlled CRS.

Statistical Analysis

Data were analyzed using SPSS (Version 28.0; IBM Corp., Armonk, New York, United States of America). Independent sample t-test, Pearson's r correlation, chi-square test, and Fisher's exact test were performed during data analysis, with a p-value of < 0.05 considered as significant.

Results

Sixty-nine participants were included (37 men, 32 women), aged 28 to 76 years (mean = 51 years, SD = 13.8).

CRS patients had worse SNO ratings ($t_{64} = 3.55$, $p < 0.001$), lower TLT scores ($t_{67} = 2.07$, $p = 0.04$), decreased CO_2 sensitivity ($t_{56.96} = 4.45$, $p < 0.001$), and lower odor identification scores ($t_{48.46} = 6.25$, $p < 0.001$) compared to controls. However, there were no significant differences in PNIF and AAR measurements between the groups.

Trigeminal lateralization scores were not correlated with odor identification scores, PNIF, or AAR. CO_2 sensitivity was positively correlated with odor identification ($r_{66} = 0.33$, $p = 0.01$) and negatively correlated with SNO ratings ($r_{66} = -0.34$, $p = 0.01$).

SNO ratings were negatively correlated with CO_2 sensitivity ($r_{66} = -0.34$, $p = 0.01$), odor identification scores ($r_{63} = -0.38$, $p = 0.002$), and PNIF ($r_{65} = -0.26$, $p = 0.04$) but were not correlated with TLT scores and AAR (see Figure 1 in Study 3). Furthermore, SNO ratings, AAR B Change were also positively correlated with CRS control scores ($r_{34} = 0.64$, $p < 0.001$), as well as the number of previous surgeries ($r_{66} = 0.33$, $p = 0.01$).

Although CRS control scores were not significantly correlated with TLT scores or CO_2 sensitivity, they were negatively correlated with PNIF ($r_{33} = -0.36$, $p = 0.04$) and positively correlated with AAR B Change ($r_{29} = 0.49$, $p < 0.01$) and SNO ratings ($r_{34} = 0.64$, $p < 0.001$). In addition, the number of previous nasal surgeries was negatively correlated with CO_2 sensitivity ($r_{69} = -0.33$, $p = 0.01$), AAR B change ($r_{63} = -0.27$, $p = 0.04$), and odor identification ($r_{66} = -0.70$, $p < 0.001$), and positively correlated with SNO ratings ($r_{66} = 0.33$, $p < 0.01$).

Exploratory Subgroup Analyses (see Figure 2 in Study 3)

Low vs. Normal Trigeminal Lateralization Test Scores

When comparing participants' TLT scores and dividing them based on the cut-off of ≤ 15 as within the limits of chance performance and > 15 as performing better than by chance (Croy et al., 2014b), there were no significant differences for CO_2 sensitivity, odor identification scores, PNIF or AAR, SNO ratings, CRS control scores, or number of previous surgeries.

Low vs. Normal CO_2 Sensitivity

Based on a previous publication (Hummel et al., 2016), CO_2 threshold values greater than the 90th percentile (1556 milliseconds, n = 99) in their sample indicated poor CO_2 sensitivity and this was used to classify the participants into 2 groups (< -1556 milliseconds as low, ≥ -1556 milliseconds as normal). Those with low CO_2 sensitivity had lower odor identification scores ($t_{64} = 2.62$, $p = 0.01$), higher SNO ratings ($t_{64} = 3.17$, $p = 0.002$), and more previous surgeries ($t_{67} = 2.02$, $p = 0.047$). There were no significant differences for PNIF or AAR, or for TLT scores between the groups.

Low vs. Normal Odor Identification Score

Odor identification scores are regarded to be low if ≤ 10 (Oleszkiewicz et al., 2019). Those with low odor identification scores had worse CO_2 sensitivity ($t_{49.72} = 2.60$, $p = 0.01$), and more previous nasal surgeries ($t_{24.77} = 3.89$, $p < 0.001$). However, there were no significant differences for TLT scores, PNIF or AAR, between the groups.

Mild Nasal Obstruction vs. Severe Nasal Obstruction Ratings

When looking at participants who rated nasal obstruction as less problematic (0 to 1, n = 36) versus very problematic (4 to 5, n = 5), those who reported severe nasal obstruction had lower odor identification scores ($t_{38} = 2.86$, $p = 0.01$), worse CRS control ($t_{36} = 6.46$, $p < 0.001$) and more previous surgeries ($t_{39} = 2.35$, $p = 0.02$). However, there were no significant differences for any of the objective nasal airflow measures or trigeminal function tests between these groups.

Uncontrolled vs. Partly Controlled Chronic Rhinosinusitis

Only 12 patients had partly controlled CRS, 23 had uncontrolled CRS, while 2 had unknown control status. There were no significant differences for trigeminal function measures, AAR, and number of previous nasal surgeries. However, those with uncontrolled CRS had higher SNO ratings ($t_{35.71} = 4.16$, $p < 0.001$), lower odor identification ($t_{30.1} = 4.84$, $p < 0.001$) scores, and lower PNIF ($t_{13.24} = 2.42$, $p = 0.03$).

Severe Nasal Obstruction Patients: Described

Only five patients rated their nasal obstruction as 4. None of the patients rated their nasal obstruction as 5. One had a low TLT score (≤ 15 (Croy et al., 2014b)) score, four had low CO_2 sensitivity (low: < -1556 (Hummel et al., 2016)), three had low odor identification (low: ≤ 10 (Oleszkiewicz et al., 2019)), three patients had low PNIF (< 120 (Ottaviano et al., 2019)), four had low AAR B Before (taking the mean of measurements for both sides of the nose, (normal: ≥ 700, (Bermüller et al., 2008; Lara-Sánchez et al., 2017)), all had uncontrolled CRS, 4 were women, 4 had asthma, and all had at least 1 previous surgery with 3 having had previous nasal polyp surgery.

Publication 1: Correlations Between Gustatory, Trigeminal and Olfactory Functions and Nasal Airflow

Hernandez AK, Walke A, Haehner A, Cuevas M, Hummel T.

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Abstract

Purpose To determine the relationship of chemosensory screening and nasal airflow tests among the same set of participants, and to determine other factors that are related to the outcomes of these tests.

Methods Participants had no chemosensory complaints. Structured medical history was taken. Participants underwent 5 screening tests: Q-Sticks (orthonasal olfaction), Q-Powders (retronasal olfaction), trigeminal lateralization test, taste sprays, and peak nasal inspiratory flow (PNIF). Ratings of smell/taste ability and nasal airflow were obtained using visual analogue scale (VAS) ratings. Composite sinusitis symptoms and significance of olfaction questionnaire scores were also determined.

Results Four hundred participants were included in the study, 156 men, 244 women; aged 18–82 years (mean: 46). The Q-Powders and taste spray scores were weakly positively correlated with all the other chemosensory tests and PNIF. However, chemosensory test scores were not correlated with VAS ratings, composite sinusitis symptoms, and significance of olfaction questionnaire scores. Various tests showed significant decrease starting at specific ages (in years, PNIF and trigeminal lateralization: 40, Q-Powders: 60, and Q-Sticks: 70).

Conclusion Chemosensory screening tests and self-rated chemosensory function showed no correlation in participants without chemosensory complaints. In addition, gustatory function appeared to be correlated with olfactory and trigeminal function but also with nasal airflow, and nasal airflow was related not only to olfactory but also to trigeminal and taste function. Over all, the results suggest that chemosensory functions (orthonasal olfactory, trigeminal, retronasal olfactory, gustatory) and nasal airflow are correlated with each other, which we propose may be possibly mediated, at least in part, through central nervous system interactions.

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RHINOLOGY

Correlations between gustatory, trigeminal, and olfactory functions and nasal airflow

Anna Kristina Hernandez[1,2,3] · Antje Walke[1] · Antje Haehner[1] · Mandy Cuevas[1] · Thomas Hummel[1]

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Keywords Smell · Taste · Trigeminal · Olfactory · Chemosensory tests · Nasal airflow

Introduction

In recent years, there has been increasing interest on the chemical senses, particularly as they can be impaired in those with a history of COVID-19 infection. However, studies have focused more on the relationship between the various types of chemosensory dysfunctions [1–3]. Less is known about the relationship of the chemical senses with each other, especially in the absence of any chemosensory complaint [4, 5].

Olfaction, gustation, trigeminal function, and nasal airflow are all anatomically bound to the oral-nasal region and are functionally interrelated. The flow of air through the nose facilitates odorants to reach the area of the olfactory mucosa. Orthonasal and retronasal olfaction depend on airflow, with the former being anteroposterior in direction and primarily for sensation of smells in the environment, while the latter being posteroanterior and primarily for sensation of vapors from the back of the mouth when eating or drinking [6–8]. In this way, retronasal olfaction and trigeminal inputs (temperature, texture, pungency) influence the perception of flavor and are associated with the sense of taste [6, 9, 10]. At the same time, most

✉ Anna Kristina Hernandez
akmhernandezmd@gmail.com

1 Department of Otorhinolaryngology, Smell and Taste Clinic, TU Dresden, Haus 5, Fetscherstrasse 74, 01307 Dresden, Germany

2 Department of Otolaryngology – Head and Neck Surgery, Philippine General Hospital, University of the Philippines - Manila, Manila, Philippines

3 Department of Otolaryngology – Head and Neck Surgery, Asian Hospital and Medical Center, Muntinlupa, Philippines

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odors also elicit both olfactory and trigeminal sensations, especially when presented at higher concentrations [6, 11–14]. The trigeminal nerve also signals sensations of pain, temperature and touch in the nose and mouth, while also influencing olfaction and perception of nasal patency [10, 15–17].

This study aimed to determine the relationship of olfaction, gustation, trigeminal function, and nasal airflow with each other in individuals without chemosensory complaints. Due to the large sample we aimed to test, we decided to use peak nasal inspiratory flow (PNIF, nasal airflow) and various chemosensory screening tests (q-sticks (orthonasal olfaction) [18], q-powders (retronasal olfaction) [19], trigeminal lateralization (trigeminal function) [20], and taste sprays (whole mouth gustation) [21]) to measure function. In addition, the study aimed to determine whether self-ratings (measured using visual analogue scales, VAS) for smell ability, taste ability, and nasal airflow, composite sinusitis symptom scores, significance of olfaction questionnaire scores, or other patient-related factors are related to the outcomes of these screening tests.

Materials and methods

The cross-sectional study design was approved by the Institutional Review Board at the University Clinic of the TU Dresden (application number BO-EK-201052020) and was conducted according to the principles expressed in the Declaration of Helsinki. Possible risks and benefits related to participation in the study were explained to participants during the initial consultation. All participants provided their written informed consent.

Participants

The study included individuals of at least 18 years of age without any chemosensory complaints who presented for testing at a private dental clinic. A standardized structured history was taken [22] including the following: age, sex, height, weight, history of smoking/alcohol consumption/chemical exposure/head injury/headaches, rhinologic symptoms (episodes of frequent sinusitis, allergic rhinitis, postnasal drip, frequent cold, nasal obstruction, runny nose, nasal polyps, and snoring), and presence of co-morbid conditions (nerve/brain disease, diabetes mellitus, hyper/hypothyroidism, hepatitis, kidney disease). VAS ratings, composite sinusitis symptoms, and significance of olfaction questionnaire scores were also determined. Participants with incomplete data were not included in selected analyses.

Five tests were investigated in this study, namely:

Screening Tests

Q-sticks (3-item orthonasal odor identification test)

In the q-sticks test [23], three odors (cloves, coffee, and rose) are presented in felt-tip pens similar to those used in the "Sniffin' Sticks" test [24]. These 3 odors were selected because they are widely known and their identification is not strongly dependent upon subjects' age [18]. The highest score is 3.

Trigeminal lateralization test

This test was conducted based on how it was done in a study by Frasnelli et al. [20], using 2 squeezable bottles pressed simultaneously to deliver an airstream into both nostrils, but only for a total of 10 times. Only one of the bottles contains 20 ml Eucalyptol (order number C80601; Sigma Aldrich, Taufkirchen, Germany) and participants must identify the which side of the nostril was presented with this substance. The highest score is 10.

Peak nasal inspiratory flow (PNIF)

PNIF is a measure of nasal airflow and was measured using the peak flow meter (Inspiratory flow meter, order number 3109750; Clement Clarke Int. Ltd., Harlow, UK). The test was done twice, with each participant asked to inhale deeply through both nostrils each time. The higher value of the two attempts was recorded.

Q-powders (3-item retronasal olfaction test)

The q-powders test [19] comprised three odors (cinnamon, banana, garlic; Givaudan Schweiz AG, Dubendorf, Switzerland). Participants were asked to choose which among the 6 descriptors, presented as flash cards, best describes the flavor of each of the powders. The odors were selected based on results from previous studies where the identification rates of the 3 selected odors were high (> 95%) [25]. The highest score is 3, a score of 0 may be interpreted as anosmia, while 1 or 2 would mean that further testing is required [19].

Taste spray total score (4 item whole mouth taste test)

Similar to Vennemann et al. [21], four basic tastes (sweet, sour, salty, and bitter) were tested using approximately 0.1 ml/spray, 1–2 sprays on the middle of the tongue. Participants were asked to identify the taste according to a list of 4 taste descriptors. After each sample, participants rinsed their mouth with water. Based on clinical experience, impaired taste function was assumed if the score was less than 3 [26].

Other measures of function:

Other Measures of Function

Visual analogue scale (VAS) rating for smelling ability, tasting ability, and nasal airflow

Participants were asked to rate their smelling ability, tasting ability, and nasal airflow from 0 to 10, with a score of 10 being the highest.

Composite sinusitis symptom score

This score is the combined score of the following (1 point each): Frequent sinusitis, allergic rhinitis, postnasal drip, frequent colds, nasal polyps, nasal obstruction, runny nose, and snoring; with a maximum score of 8.

Significance of olfaction questionnaire

Based on the work by Croy et al. [27], a modified 20-item questionnaire, in German, including items related to association, application, and consequence of sense of smell was administered to participants. A sum of the scores for each subtest (each item ranged from a score of 1–4) and the total score of all items and subtests were used in the analysis.

Data collection and statistical analysis

Patient records were assigned codes and anonymized. Data were encoded into a Microsoft Excel Office 365 version 2107 database (Microsoft Corp., Redmond, WA, USA) and checked for accuracy of encoding. Data analysis was done using SPSS software (Version 28.0; IBM Corp., Armonk, NY, USA). Pearson's r, spearman's rho, and t-tests were used in the analysis of the data, with a p value of < 0.05 considered significant.

Results

Results are summarized in Tables 1 and Fig. 1. Four hundred participants were included in the study, 156 men, 244 women, aged 18–82 years (mean: 46 years). Men (mean = 141.8, n = 153) had higher PNIF compared to women (mean = 118.5, n = 242, $t_{253.082} = 4.37$, $p < 0.001$). There were no significant differences between the genders for the chemosensory screening tests.

Age was negatively correlated with trigeminal lateralization ($r_{392} = -0.21$, $p < 0.001$) and PNIF ($r_{395} = -0.18$, $p < 0.001$), but not with the other tests. Differences of chemosensory test scores across the ages are summarized in Table 1 and in Fig. 2. Those aged 40 and older had lower trigeminal lateralization ($t_{390} = 2.58$, $p = 0.01$) and lower PNIF (40 and older: $t_{393} = 2.14$, $p = 0.033$). Those aged 60 and older had lower q-powders scores ($t_{391} = 2.03$, $p = 0.044$), while those aged 70 and older also had lower q-sticks scores ($t_{391} = 2.11$, $p = 0.035$).

Height ($r_{395} = 0.21$, $p < 0.001$) and weight ($r_{393} = 0.12$, $p = 0.022$) were also correlated with PNIF but not with any of the chemosensory screening tests.

Of the factors gathered from participants' personal history, we noted several significant findings. However, due to the low number of participants belonging to some groups, we decided to report results only from groups with $n \geq 20$. Q-powders scores were higher for those with exposure to chemicals (n = 69, $t_{364} = 3.03$, $p = 0.003$), while trigeminal lateralization (n = 80, $t_{106.088} = 2.80$, $p = 0.006$) and taste spray (n = 78, $t_{93.685} = 2.06$, $p = 0.043$) scores were lower for those with history of snoring. History of smoking, alcohol consumption, head injury, allergic rhinitis, postnasal drip, frequent colds, nasal obstruction, runny nose, and other comorbid conditions such as diabetes mellitus, hyperthyroidism, and hypothyroidism had no effect on chemosensory screening tests or PNIF. Variables other than those that have been mentioned had significant results but the group sizes were less than 20 for each.

Table 1 Differences of chemosensory tests among various age levels

Age range	Maximum n[a]	q-sticks	Trigeminal lateralization	PNIF	q-powders	Taste sprays
≥ 18	395					
≥ 30	347					
≥ 40	250		X	X		
≥ 50	164		X	X		
≥ 60	91		X	X	X	
≥ 70	19	X	X	X	X	

X Those with this age and older have significantly lower scores

[a]Maximum n: maximum number of participants analyzed for a particular age group

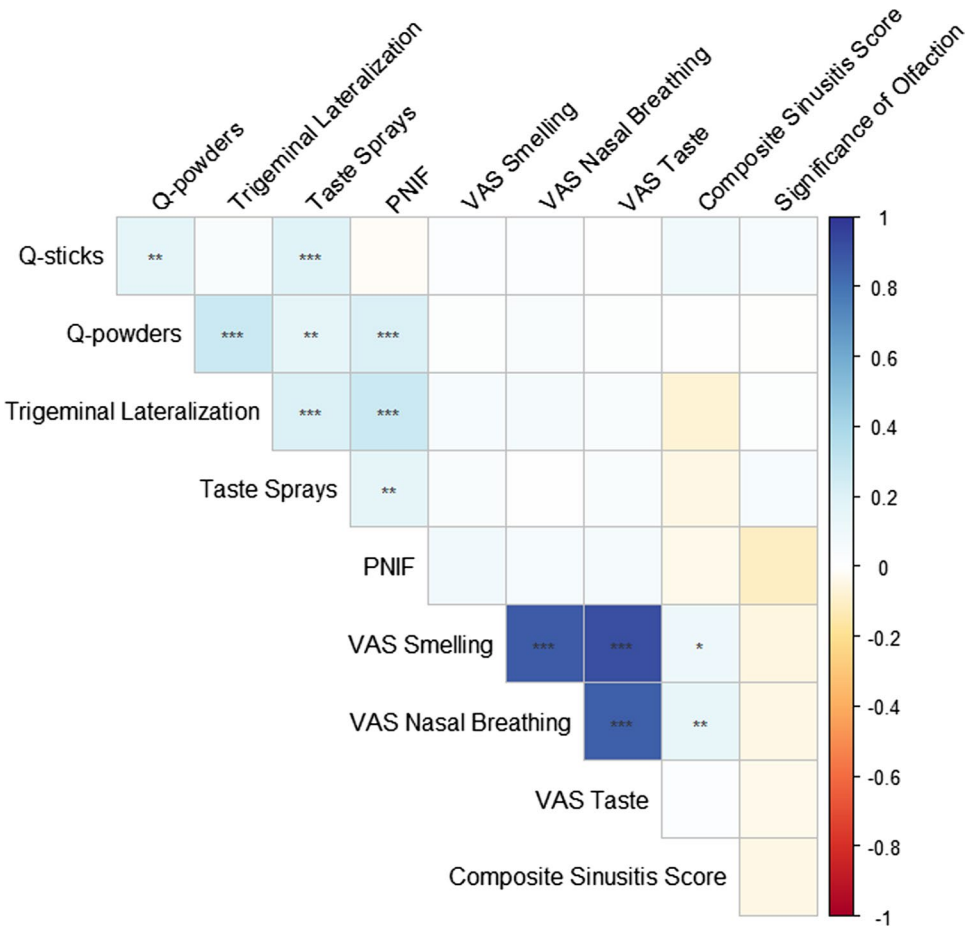

Fig. 1 Correlation between various chemosensory tests, PNIF, visual analogue scale (VAS) ratings, composite sinusitis symptom scores, and significance of olfaction questionnaire scores. Legend: box colors denote strength of correlation (blue: positive correlation, red: negative correlation), * $p < 0.05$, ** $p < 0.01$, ***$p < 0.001$

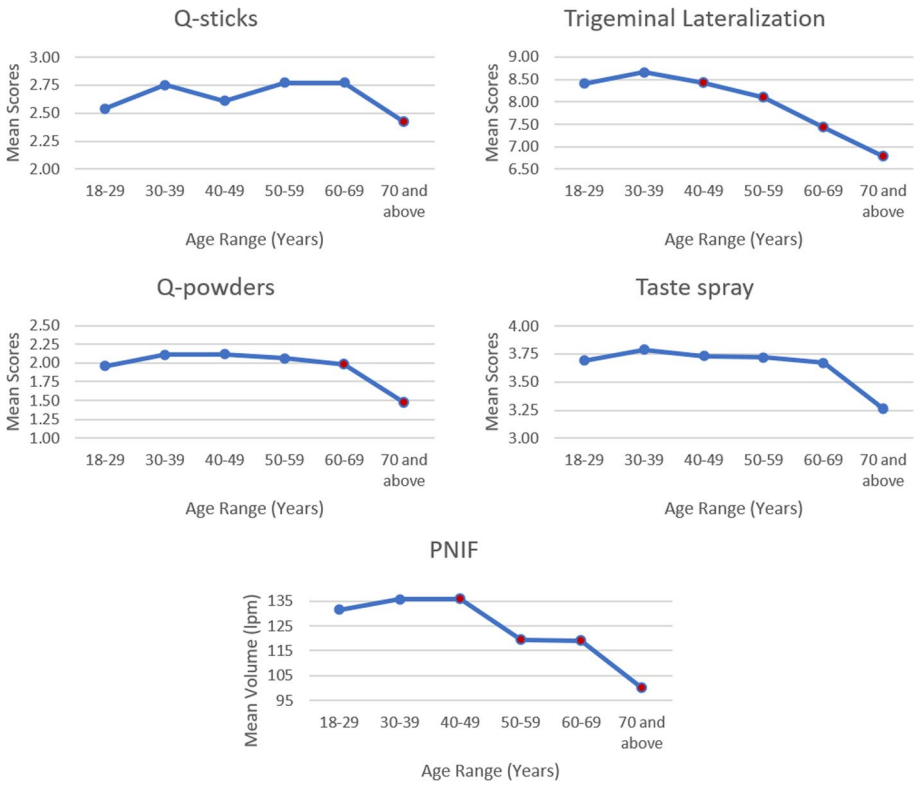

Fig. 2 Mean values for chemosensory screening and nasal airflow tests among different age groups. Significantly lower scores in this age group and older

The q-powders and taste spray scores were weakly positively correlated with all the other chemosensory tests and PNIF (Fig. 1). The Q-sticks and trigeminal lateralization tests were weakly positively correlated with q-powders and taste spray total scores, and with PNIF for the latter. PNIF was weakly positively correlated with trigeminal lateralization, q-powders, and taste spray total scores. Chemosensory test scores were not correlated with self-ratings (VAS), but a significantly higher taste spray total score was observed in individuals with VAS taste ability ratings ≥ 9 ($n = 13$, $t376 = 9.38$, $p < 0.001$), VAS smell ability ratings ≥ 8 ($n = 58$, $t101.138 = 2.06$, $p = 0.042$), and VAS nasal airflow ratings ≥ 6 ($t231.770 = 2.05$, $p = 0.042$).

Composite sinusitis symptom scores and significance of olfaction questionnaire scores (including subtests and total scores) were not correlated with chemosensory screening tests or PNIF (Fig. 1). There was a tendency, though, for those with a score of ≥ 1 on the composite sinusitis symptom score to have lower q-sticks scores ($t_{359.043} = 1.937$, $p = 0.53$). When exploring for possible relationship of significance of olfaction questionnaire scores to chemosensory test scores, only those with higher significance of olfaction (90th percentile, score of ≥ 71, $n = 41$) had a significantly higher q-sticks score ($t_{60.136} = 2.49$, $p = 0.016$).

Discussion

Several studies have investigated the relationship between the different chemical senses (orthonasal/retronasal olfaction, trigeminal function, gustation) and there have been some conflicting findings.

A study by Fonteyn et al. found that orthonasal and retronasal function are correlated among those with post-infectious, post-traumatic, idiopathic, toxic, and neurologic conditions [30], while Hummel et al. found higher intensities for retronasal versus orthonasal stimulus presentation in healthy individuals [31]. It has also been proposed that differing airflow patterns between orthonasal and retronasal flow may result in lower concentration of odors reaching the olfactory cleft [32]. Furthermore, it has also been proposed that orthonasal and retronasal stimuli are processed differently, given that odors may be presented at higher concentrations retronasally due to greater intraoral odor release from salivation, warming, and mastication [33, 34]. On the other hand, several studies have also documented individuals with poor orthonasal function in the presence of normal retronasal function [8, 29]. Conversely, evidence also exists in support of synergistic relationship between various chemical senses. For instance, orthonasal and trigeminal co-stimulation have been found to improve trigeminal localization [35]. Blankenship et al. also found that retronasal, but not orthonasal odors, share processing circuitry commonly associated with taste; and that orally-sourced (retronasal) olfactory input is processed by a brain region responsible for taste processing, whereas externally-sourced (orthonasal) olfactory input is not [36].

Interestingly, age was negatively correlated to trigeminal lateralization and PNIF, but not to the other tests. This may support the presence of a progressive age-related decline in intranasal trigeminal sensitivity and lung function [40–42]. Perhaps the few items present in orthonasal, retronasal, and whole mouth taste screening tests also precluded having enough variation in scores to determine a trend. Worth noting, however, was that the different chemical senses appear to begin deteriorating at specific ages. Trigeminal function and nasal airflow both appear to be the first to diminish, followed by retronasal, orthonasal, and lastly – gustation.

Our study has shown the presence of a weakly positive correlation of q-sticks (orthonasal test) and trigeminal lateralization (trigeminal function) to both q-powders (retronasal test) and taste spray total scores (whole mouth taste test), as well as PNIF (nasal airflow) for the latter, which seems to be in support of a relationship between these senses. This is partly consistent with a study by Migneault-Bouchard et al. [1] where they noted correlations between scores for olfaction, gustation, and trigeminal function. They found that olfactory loss leads to a decrease in taste and trigeminal sensation (compare with [2, 14]), instead of a compensation through hyperfunction of other chemical senses [1]. Another study by Han et al. found a similar interaction among the chemical senses, where patients with olfactory dysfunction showed increased electric taste thresholds and decreased scores for the umami taste strip [3].

In contrast, however, we did not find a correlation between q-sticks and trigeminal lateralization in our study. Although a complex interaction, both synergistic and antagonistic, has been found in previous studies between trigeminal and olfactory function [11, 37], screening tests and a cohort of only healthy individuals may not be the most ideal in confirming this relationship due to inherent limitations previously mentioned and further discussed later.

Retronasal and whole mouth taste tests were both weakly positively correlated to all other chemosensory tests and to PNIF. This reinforces the relationship of the various chemical senses, even airflow, in the appreciation of taste and flavor. The sensation of flavor is known to be a combined experience involving the sense of taste that is enhanced by retronasal olfaction. But it is also interesting that trigeminal sensation through somatosensation (temperature, texture, etc.) may also contribute in the appreciation of both taste and flavor [38] and our findings seem to be in support of this interaction (see also [39]).

Although we found significant findings depicting interactions between history of chemical exposure and q-powders,

as well as between snoring, trigeminal lateralization, and taste spray scores, some of these findings contradict what has previously been published in literature. For instance, chronic chemical exposure has been found to have adverse effects on human olfaction and is supported by findings in animal experiments [43]. However, we found that those with history of chemical exposure performed better in the q-sticks test in our study. We are unsure if previous chemical exposure leads to heightened retronasal sensation or if both the orthonasal and retronasal screening tests failed to discriminate well between varying levels of function when administered to healthy individuals, leading to these unusual findings. Snoring is one of the prominent symptoms of obstructive sleep apnea (OSA), with OSA having an incidence of 20–70% among snoring patients [44]. Previous studies also showed that snoring was associated with adverse effects on peripheral nerve function [45, 46]. However, a study by Heiser et al. [46] found no significant difference between taste strip scores and nasal trigeminal lateralization scores of those with and without OSA. Despite having more testing repetitions for trigeminal lateralization (40 compared to our 10), their sample size was smaller (n = 44). On the other hand, snoring may also be due to an altered balance of nasal and oral airflow from chronic rhinosinusitis (CRS) [47], as snoring also has increased prevalence among those with CRS [48]. Given both OSA and CRS are diseases associated with increased inflammation, this chronic state of inflammation, that can also be present in subclinical CRS, may result in increased production of inflammatory cytokines that may affect both the sense of smell and taste. Inflammation has been proposed to be toxic to olfactory neurons, causing potentially irreversible changes to the mucosa and resulting in the disturbance of olfactory mucus that may affect odor transduction [49–51]. Furthermore, inflammation has also been proposed to trigger apoptosis and abnormal cell turnover in taste buds, possibly leading to problems with taste transduction and ultimately causing taste dysfunction [52]. We are uncertain if our findings reflect true relationships or are simply an overestimation of the presence of relationships due to limitations of screening tests as a method for evaluation in healthy individuals. It appears to be prudent to reassess these factors using more comprehensive psychophysical tests and regard the present findings as a pilot in this direction which needs further confirmation despite the large sample size.

The relationship of sex and height to PNIF may be secondary to men and taller individuals being more likely to have larger lung capacity [53–55], leading to greater nasal inspiratory flow. The finding that nasal airflow is correlated with trigeminal lateralization is somewhat expected, given that trigeminal sensation serves as a means to protect the airway from potentially harmful substances which can then lead to shortening or cessation of inspiration reflexively [14, 15]. But the correlation of PNIF to q-powders and taste spray total scores may emphasize the role of nasal airflow in the perception of taste and flavor. Unexpectedly, there was no correlation between q-sticks and PNIF. The relationship between nasal airflow obstruction and olfaction has been frequently studied in literature [56–61], particularly in patients with sinunasal disease. However, our sample was comprised of healthy individuals and it is possible that this relationship between olfaction and airflow was not clearly depicted in this population. Also, although a relationship between olfaction and airflow through the olfactory cleft has been mentioned previously in literature [62, 63], PNIF measures airflow through the entire nasal cavity and not only to the olfactory cleft on maximal inspiration, and may also be confounded by the influence of lung function. For these reasons, we may not have observed a correlation between the two tests. We propose that these may be better explored using comprehensive orthonasal olfactory tests involving both healthy participants and those with olfactory loss.

Self-ratings of chemosensory function have been shown to be unreliable, at least in portions of the patients [28]. In the clinical setting, patients tend to classify an olfactory impairment with accompanying retronasal olfactory issues as a taste dysfunction [9, 29]. In the present study among healthy individuals, we found that VAS scores were also not correlated with any of the chemosensory screening tests or with PNIF. Although those with higher VAS ratings for smell / taste ability and nasal airflow had significantly higher taste spray scores, we attribute this finding to the limitation of screening tests to discriminate between varying degrees of function or dysfunction, given that the number of items are very few. Although self-ratings may be helpful in determining symptom burden in those with chemosensory dysfunction, the value of self-ratings in estimating olfactory function in healthy people is limited. This emphasizes the value of psychophysical testing, especially preceding any nasal surgical intervention, for a more accurate estimation of olfactory function.

We hypothesized that decreased chemosensory function may not simply be due to actual decrease in function but perceived importance of the lost function to an individual, such that similar deficits may be reported as varying in severity depending on value placed on the senses. However, there was no correlation between significance of olfaction subtest and total scores to any of the chemosensory screening tests. It was interesting, though, that those who had higher significance of olfaction scores also had higher q-sticks scores, which could also confirm that people who value their sense of smell also tend to perform better on psychophysical tests, particularly those that require attention and cognitive ability [24, 64].

Chemical senses are rarely experienced in isolation and various studies have shown activation of similar brain

regions when it comes to taste and oral somatosensory stimuli (anterior insula), as well as olfaction, oral texture of food, and perception of umami (orbitofrontal cortex) among others [38, 65, 66]. It remains uncertain how or where the integration of various chemical senses occurs exactly, but we propose that central nervous system processing may play a role in the integration of inputs from the different chemical senses.

Limitations

Smell and taste screening tests were created to facilitate more efficient assessment of olfactory and gustatory function, and these have been quite useful in clinical practice. However, there remain to be challenges when psychophysical chemosensory tests are shortened for ease and efficiency of testing. Shorter tests may not distinguish between varying degrees of function and dysfunction [67] and may have limited or overestimated some findings in our analyses. For example, the q-sticks test only has 3 items and there is no established distinction between what it means when scores vary from 0 to 3. It may be useful in screening for olfactory loss, especially if an individual scores 0 in the test. However, there is a possibility of false alarms, where individuals of normal olfactory function score less than 3. In addition, as much as one-third of those with a perfect score of 3 in the q-sticks test may still have abnormal orthonasal olfactory function [23]. Also, having fewer items may also influence how much chance performance affects outcomes [67]. Future studies may replicate our methodology but comparing more comprehensive orthonasal, retronasal, and taste psychophysical tests with trigeminal lateralization and nasal airflow measurements in patients both with and without olfactory loss.

Conclusion

Chemosensory screening tests and self-rated chemosensory function showed little or no correlation in participants without chemosensory complaints. In addition, gustatory function appeared to be correlated with olfactory and trigeminal function, and nasal airflow was related not only to olfactory but also to trigeminal function. Overall, the results suggest that chemosensory functions (orthonasal olfactory, trigeminal, retronasal olfactory, gustatory) and nasal airflow are correlated with each other, which we propose may be possibly mediated, at least in part, through central nervous system interactions.

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Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors have no competing interests to declare that are relevant to the content of this article.

Ethical approval The cross-sectional study design was approved by the Institutional Review Board at the University Clinic of the TU Dresden (application number BO-EK-201052020) and was conducted according to the principles expressed in the Declaration of Helsinki.

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Publication Discussion

How is intranasal trigeminal function related to olfaction and nasal airflow in healthy individuals?

The presence of a positive correlation of TLT scores (trigeminal function) with Q-Powders scores (retronasal olfaction) and PNIF (nasal airflow) is in support of a relationship between these senses. A study by Migneault-Bouchard et al. (Migneault-Bouchard et al., 2020) noted correlations between scores for olfaction and trigeminal function, instead of a compensation through the hyperfunction of trigeminal function. This also shows that trigeminal sensation may also contribute in the appreciation of flavor through retronasal airflow (Frasnelli et al., 2005; Lundstrom et al., 2011). In addition, the finding that nasal airflow is correlated with trigeminal function is somewhat expected, given that trigeminal sensation serves as a means to protect the airway from potentially harmful substances which can then lead to shortening or cessation of inspiration reflexively (Hummel and Livermore, 2002; Oleszkiewicz et al., 2018).

However, there was no correlation between Q-Sticks (orthonasal olfaction) and TLT scores in this study. Although complex synergistic and antagonistic interactions between trigeminal and olfactory function have been previously reported (see (Livermore and Hummel, 2004; Hummel and Frasnelli, 2019)), screening tests and a cohort of only healthy individuals may not be the most ideal setting to confirm this relationship. Smell and taste screening tests were used in this study for efficient assessment of trigeminal function, olfaction and nasal airflow and are useful in clinical practice. However, when these tests are shortened for ease and efficiency of testing, they may not distinguish between varying degrees of function and dysfunction so well (Doty, 2019) and may have limited or overestimated some findings in our analyses. For example, the Q-Sticks test only has three items and the interpretation of these scores when they vary from 0 to 3 has not been established. It may be useful in screening for olfactory loss, especially if an individual scores 0 in the test. However, there is a possibility of false alarms, where individuals of normal olfactory function score less than 3. In addition, as much as one-third of those with a perfect score of 3 in the Q-Sticks test may still have abnormal orthonasal olfactory function (Sorokowska et al., 2019). Having fewer items also influences how chance performance affects outcomes (Doty, 2019) and increasing the number of items in a test improves the reliability of the test (Doty et al., 1995; Doty, 2015).

Self-ratings of chemosensory function have been shown to be unreliable, at least in a proportion of the patients (Hummel et al., 2017b). In the clinical setting, patients tend to classify retronasal olfactory impairment as a taste dysfunction (Rozin, 1982; Nørgaard and

Fjaeldstad, 2021). In the present study among healthy individuals, we also found that VAS ratings were not correlated with any of the chemosensory screening tests or with PNIF. Although self-ratings may be helpful in determining symptom burden in those with chemosensory dysfunction, the value of self-ratings in estimating olfactory function in healthy people is limited. This emphasizes the value of psychophysical testing, especially preceding any nasal surgical intervention, for a more accurate estimation of function.

Given that there were limitations related to the use of screening tests and the inclusion of only healthy individuals in this study; we, then, aimed to determine next what is known about the interaction of these three systems in individuals who experience both OD and nasal obstruction.

Publication 2: Intranasal Trigeminal Function in Chronic Rhinosinusitis: A Review

Hernandez AK, Hummel T.

Expert Rev Clin Immunol. 2023;19(8):921-938. doi:10.1080/1744666X.2023.2231149

Abstract

Introduction: Chronic rhinosinusitis (CRS) affects 5–12% of the general population with significant effects on quality of life. Chronic inflammation also seems to affect intranasal trigeminal sensitivity.

Areas covered: A systematic literature search was done in Scopus, Web of Science, and PubMed in February 2023. The review addressed intranasal trigeminal function in patients with CRS and summarized current knowledge on trigeminal function as it relates to the symptoms, assessment, and treatment of CRS.

Expert opinion: Olfaction and trigeminal function are synergistic and this interaction may contribute to trigeminal dysfunction in CRS. Aside from anatomic blockage through polypoid mucosal changes, trigeminal dysfunction may affect the perception of nasal obstruction in CRS. Upregulated immune defense mechanisms leading to damage of nerve endings, changes in nerve growth factor release or other mechanisms may be responsible for trigeminal dysfunction in CRS. Since the pathophysiology of trigeminal dysfunction in CRS is poorly understood, current treatment recommendations are directed toward the therapy of CRS as an underlying cause, although the effect of surgery and corticosteroids on trigeminal function remains unclear. A standardized and validated trigeminal test that is accessible and easy to use in clinical settings would be beneficial for future studies.

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REVIEW

Intranasal trigeminal function in chronic rhinosinusitis: a review

Anna Kristina Hernandez [a,b,c] and Thomas Hummel [a]

[a]Smell and Taste Clinic, Department of Otorhinolaryngology, Faculty of Medicine Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany; [b]Department of Otolaryngology - Head and Neck Surgery, Philippine General Hospital, University of the Philippines, Manila, Philippines; [c]Department of Otolaryngology - Head and Neck Surgery, Asian Hospital and Medical Center, Muntinlupa, Philippines

ABSTRACT

Introduction: Chronic rhinosinusitis (CRS) affects 5–12% of the general population with significant effects on quality of life. Chronic inflammation also seems to affect intranasal trigeminal sensitivity.

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chemesthesis; chronic rhinosinusitis; nasal polyps; nose; olfaction; trigeminal; chemosensory

1. Introduction

Nasal chemosensation relies on the complex interaction of both the olfactory and trigeminal systems. The intranasal chemosensory trigeminal system is involved in the perception of odors, tactile sensation, temperature (heat, warmth, burning, cold, coolness, or freshness), respiration, and pain/tingling/stinging/irritation/pungency [1,2–6]. The trigeminal system plays a role as the sentinel of the respiratory system. It functions to protect the upper and lower airways from potentially harmful substances through physiologic reactions, such as: reflexive cessation of inhalation, subsequent expulsion or sneezing, and alteration of nasal congestion and secretions [4,7–10] (for extensive discussions on the anatomy and physiology of the trigeminal system, please see [8,11,12]).

Chronic rhinosinusitis (CRS) affects 5–12% of the general population [13] with significant effects on an individual's quality of life. The European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2020 defines CRS in adults as the presence of 2 or more of the following symptoms, where one must be nasal blockage/obstruction/congestion or nasal discharge, and the others: facial pain/pressure, reduction, or loss of sense of smell for at least 12 weeks [13]. The relationship of trigeminal function to olfaction has been extensively studied [3,7,8,14–17]. However, despite the importance of nasal blockage/obstruction/congestion as a key symptom in CRS, there have been relatively few studies that investigated how trigeminal function relates to this disease (Table 1).

This review summarizes published literature on trigeminal function among patients with CRS, including the challenges, limitations, and biases of previously published studies. Hopefully with a better understanding of what is currently known, knowledge gaps and suggestions for the direction of future studies can be identified.

2. Methodology

2.1. Literature search

A comprehensive literature search of three databases (PubMed, Web of Science, and Scopus) was performed on 2 February 2023 (Figure 1). Search terms included ('trigeminal' [All Fields] or 'trigeminal function' [All Fields]) AND ('chronic rhinosinusitis' [All Fields] or 'chronic sinusitis' [All Fields; Title-Abstract-Keywords for Scopus] or 'nasal polyp' [All Fields; Title-Abstract-Keywords for Scopus] or 'nasal polyposis' [All Fields; Title-Abstract-Keywords for Scopus]). However, it was noted that fewer studies were found using the term 'trigeminal function' so the term 'trigeminal' was retained. There were also some studies missed when only using 'chronic rhinosinusitis,' hence the addition of other keywords (i.e. chronic sinusitis, nasal polyp, nasal polyposis).

CONTACT Anna Kristina Hernandez akmhernandezmd@gmail.com Smell & Taste Clinic, Department of Otorhinolaryngology, Faculty of Medicine Carl Gustav Carus, Technische Universität Dresden, Fetscherstraße 74, Dresden 01307, Germany

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Article highlights

- Decreased trigeminal function has been documented in chronic rhinosinusitis (CRS) but results of studies depended on the stimulus, method of testing, and other factors.
- Trigeminal event-related potentials and trigeminal lateralization tests were the most commonly used tests to assess trigeminal function.
- The lack of standardized and validated measures for trigeminal function makes comparing results of different studies difficult.
- Subsequent studies would benefit from having control groups, larger sample sizes, and standardized and validated methods of trigeminal function measurement.
- Olfaction and trigeminal functions are synergistic, with both olfactory and trigeminal functions related to odor perception. Trigeminal dysfunction in CRS may likewise have contributions from this olfactory–trigeminal interaction.
- Aside from anatomic blockage through polypoid changes of the mucosa, trigeminal dysfunction may affect the perception of nasal obstruction in CRS.
- Several mechanisms may be responsible for trigeminal dysfunction in CRS including inflammatory responses related to upregulated defense mechanisms leading to damage of trigeminal nerve endings, or changes in nerve growth factor release. Discovery of exact mechanisms may have profound implications for diagnosis and management, as it may be more geared toward the different types of inflammation (Types I, II, or III) observed in CRS.
- We hypothesize a framework for trigeminal dysfunction in CRS, but further studies are required to determine the exact mechanisms of trigeminal function changes in CRS, and the influence of various treatment modalities, including biologicals, on intranasal trigeminal function.

2.2. Inclusion and exclusion criteria

All original articles with human participants, published in English, without date restriction were included. Other types of study designs (i.e. reviews, case reports, case series), formats (editorials, letters, conference papers, expert opinions, guidelines), those with patient populations not including CRS, and studies published in non-English language were excluded.

2.3. Data extraction and collection

The initial electronic search was done by the primary author and duplicates were removed. References were entered into a database (Excel; Microsoft Corp., Redmond, WA, USA) and the titles and abstracts were screened independently for relevance by the two authors of this review. Articles were considered relevant if one of the two authors rated them accordingly. Relevant articles were then evaluated based on the full-text version, by the two authors independently. Again, articles were considered relevant and subsequently included in the review if one of the two authors rated them accordingly based on the full-text version.

The following data were extracted from the articles: author, year, location, design, groups, basis of CRS diagnosis, sample size, intervention, outcome measures (other than trigeminal testing), trigeminal test used, and findings of trigeminal function in relation to (a) CRS, (b) olfaction, (c) nasal obstruction, (d) demographics (age, sex), (e) treatment modalities, and (f) others.

Table 1. Number of results on PubMed search [Title/Abstract].

Keywords	Number of records
'Trigeminal' + 'Chronic Rhinosinusitis/Chronic Sinusitis'	24
'Olfaction/Olfactory/Smell' + 'Chronic Rhinosinusitis/Chronic Sinusitis'	796

3. Overview of included articles

The initial database search resulted in a total of 281 manuscripts (Figure 2). After the removal of duplicates and screening of the titles and abstracts, 16 studies underwent full-text review and were subsequently evaluated for eligibility. Nine studies were included with a total of 659 participants, 208 of which were CRS patients, 223 were controls, and the remainder had other conditions related to olfactory dysfunction (OD) (i.e. post-traumatic, post-infectious, unspecified OD).

A summary of the included studies is found on Table 2. The included articles were published between 2006 and 2022, with authors based in Germany, Belgium, Canada, China, Turkey, Sweden, Greece, Switzerland, and Japan. Most studies included patients with nasal polyps. Eight studies explicitly stated the basis of diagnosis, which included clinical findings with nasal endoscopy, imaging, or clinical practice guidelines (European Position Paper on Rhinosinusitis and Nasal Polyps 2020 [13], Canadian guidelines for acute and chronic rhinosinusitis [26]). Although Huart et al. did not explicitly state the basis for CRS diagnosis in their study, this was later confirmed by the authors to have been based on clinical assessment [23]. There were no randomized controlled trials in the included studies. Most were prospective cohorts or cross-sectional studies. Only six studies had clearly defined control groups. Minovi et al. designated a 'control group' of individuals with little or no polyps, but it was unknown if these individuals had symptoms that still satisfied the criteria of CRS [19]. Most of the studies had small sample sizes for CRS patients (range: 10 to 45, mean = 23).

Trigeminal outcomes were measured using various methods (Table 3). The studies included varied methods of chemosensory measurement and CRS assessment: psychophysical ('Sniffin' Sticks" (Burghart Messtechnik, Holm, Germany, see also [27,28]) test battery [14,18,23–25], odor identification testing [19], n-butanol or phenyl ethyl alcohol threshold tests [20], retronasal odor identification test [18]) and electrophysiological (EEG-based (olfactory event-related potentials, OERPs [18,24,25]), olfactory tests; gustatory test ('taste strips' [14]); imaging modalities (magnetic resonance imaging (MRI) [18], and positron emission tomography (PET) [20]); nasal polyp grading (Lund Mackay [19,21], Lund Kennedy [22,24,25], and Lildholdt [25]); subjective ratings for olfaction [21,22] and other nasal symptoms (sneezing, nasal obstruction, rhinorrhea, facial pressure/pain, smell loss [24]; nasal patency [21]); and markers for inflammation (tissue eosinophil count [24]).

4. Trigeminal function in patients with chronic rhinosinusitis

There is evidence to support decreased trigeminal function in patients with CRS. The presence of inconsistent results in various studies included in this review greatly depended on the methodology and the specific tests used (see Tables 3 and 4).

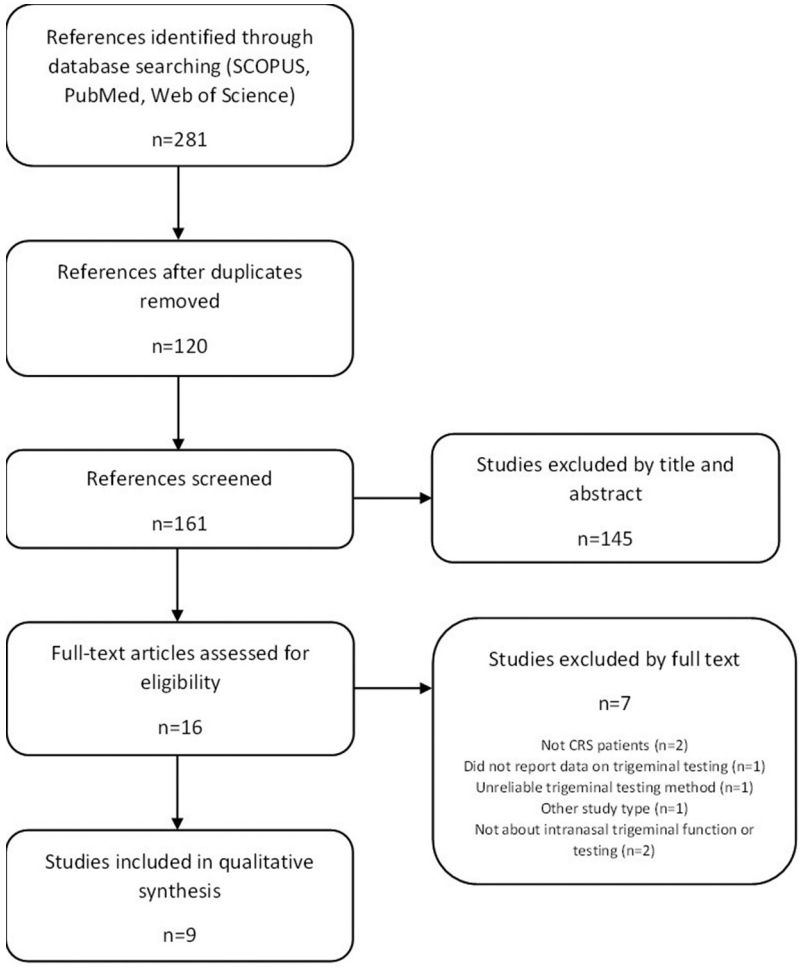

Figure 1. Literature search diagram.

Studies that used trigeminal event-related potentials (tERP) found decreased N1, P2, and N1P2 amplitudes [18] and prolonged N1 and P2 latencies [24,25], and also P1 latencies [25] in patients with CRS. Changes in relatively early components of tERPs (N1, P1) are believed to reflect exogeneous cortical activity related to chemosensory inputs, while later components (P2) are thought to relate more to the cognitive processing of the stimulus [29]. A lower tERP amplitude or longer tERP latency is typically observed with lower stimulus intensity, advanced age, or stimulation at less sensitive sites of the respiratory mucosa (i.e. posterior nasal cavity) [29]. Although modulated by numerous cognitive factors, like

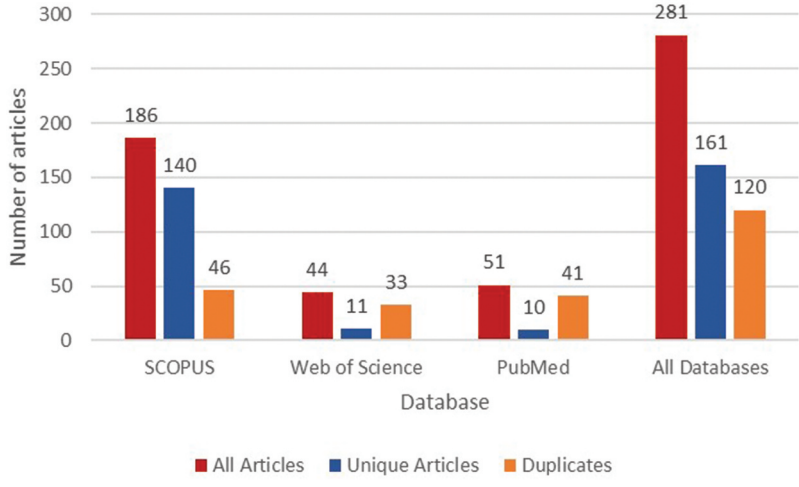

Figure 2. Summary of the number of articles found during database search.

Table 2. Summary of included articles.

Author	Study design	Participants (n)		
		CRS	Control	Total
Rombaux et al. (2006) [18]	Prospective comparative cohort	11	11	44
Minovi et al. (2008) [19]	Prospective comparative cohort	25	39	64
Savic et al. (2009) [20]	Cross-sectional study	12	12	24
Saliba et al. (2016) [21]	Prospective case-control	14	14	28
Poletti et al. (2017) [22]	Prospective	45	30	75
Huart et al. (2019) [23]	Cross-sectional study	20	86	131
Zhang et al. (2019) [24]	Cross-sectional study	40	0	40
Migneault-Bouchard et al. (2020) [14]	Cross-sectional study	31	0	178
Burghardt et al. (2022) [25]	Cross-sectional study	10	31	41

attention or vigilance, these electrophysiological results provide a less biased estimate of trigeminal sensitivity, e.g. less dependent on changes of nasal patency. While tERP shows relatively similar findings across studies, findings from other methods of measurement are less consistent.

Results from studies using trigeminal lateralization (sometimes also referred to as the odor localization task [8]) among patients with CRS have been mixed. While a couple of studies found significantly lower scores for CRSwNP [21,23] and CRSsNP [23], other studies also found no difference in CRS patients compared to controls [20] or to OD patients with other underlying causes [14].

Humans have great difficulty in identifying which nostril is stimulated when a selective olfactory stimulant is administered to one nostril [8,33,34]. However, when a stimulus activates the trigeminal system, individuals perform better in this task [35] and this performance even increases when the trigeminal stimulus is accompanied by olfactory stimulation [36]. Although within the context of this review, four studies used trigeminal lateralization, variations in the stimuli (differing volumes and concentrations of stimuli), the choice of using a solvent or otherwise (propylene glycol or air as a control), the ways the stimuli were presented (squeeze bottles or syringes), the number of trials (between 10 and 40), and interstimulus intervals (from 20 to 60 s) used made direct comparisons of results between these studies difficult (see Table 3). This same problem also applied when it came to interpreting and comparing the results with other testing methods used. Currently, there are no established parameters that define the difference between normal and impaired trigeminal function and how much difference may be observed in individuals with certain conditions in this test. Still, overall, the present results suggest that CRS patients have lower scores in the lateralization task than healthy controls.

Studies that used other measurement methods for trigeminal function also had mixed results. The trigeminal threshold test (see also Table 3) was done in three studies using three different stimuli with varying results: decreased trigeminal function for electrical stimulation [22] and mixed olfactory-trigeminal stimuli [23], and no significant difference for carbon dioxide (CO_2) [25]. Other studies using mixed olfactory-trigeminal stimuli [19,23] for non-threshold tests, and one that used self-ratings for intensity and pleasantness [25] also found decreased trigeminal function in CRS patients. On the other hand, those that used trigeminal negative mucosal potentials (NMP) [25] and an air puff test [22] found no significant difference between the trigeminal function of CRS patients compared to controls. Inconsistent results within published literature are likely affected by factors like the type of trigeminal test, the trigeminal stimulus used, or the low sample sizes.

5. Trigeminal function and olfaction

To fully experience chemosensations from the environment, both the olfactory and trigeminal systems must be intact [37]. At low concentrations, odorants primarily stimulate the olfactory system, but at higher concentrations, almost all odors elicit a trigeminal sensation [7,38,39]. Decreased trigeminal function has been observed in patients with acquired OD [15,38,40,41], while those with congenital anosmia were found to have trigeminal function comparable to healthy controls [2].

A study by Livermore et al. observed a complex relationship between both systems when olfactory or trigeminal stimuli were presented alone or in mixtures. Trigeminal sensation was found to dominate over olfactory sensation, olfactory inputs enhanced the responses to olfactory and trigeminal mixtures, and mixed stimuli dominated over olfactory or trigeminal stimuli in isolation [42]. Although the exact mechanisms remain uncertain, Frasnelli et al. proposed a model for olfactory and trigeminal interaction factoring in the roles of peripheral and central processing [40]. They hypothesized that a working olfactory system leads to inhibition of the trigeminal system peripherally. Specifically, it was proposed that, in healthy individuals, decreased peripheral activation occurs possibly due to the activation of intrabulbar trigeminal collaterals. At the same time, on a cortical level, olfactory activity augments the trigeminal activation [43]. In patients with acquired OD, however, peripheral activation is no longer decreased secondary to top-down regulation from trigeminal collaterals in the olfactory bulb, leading to increased peripheral trigeminal activation [40]. However, the decreased overall response to trigeminal stimuli may be the result of the decreased amplification of the trigeminal percept at the central nervous system level due to lack of olfactory input [40].

Only seven studies of this investigation analyzed the relationship of olfaction with trigeminal function (Table 5). Four studies used 'Sniffin' Sticks" [14,18,23,25,30,31] while the others used odor identification tests [19,21] and PET scan [20]. However, despite the difference in the olfactory and trigeminal tests used, six studies supported the presence of a relationship between the two systems. Rombaux et al. found a significant correlation between orthonasal, but not retronasal, olfaction and tERP (N1P2 peak-to-peak) amplitude. However, the sample size in this study was low ($n = 44$, of which only 11 had nasal polyps) and may have affected this outcome [18]. A correlation between trigeminal lateralization scores and olfactory scores was found by Migneault-Bouchard et al. ($r = 0.25$, $p = 0.006$) and Saliba et al. ($r_{28} = 0.48$, $p = 0.01$) [14,21]. Huart et

Table 3. Trigeminal assessment methods.

Study	Methodology	Description	Indicators of poor function	Stimulus Details	
Rombaux et al., 2006 [18]	tERP	ERPs from electrodes placed over the surface of the scalp and other parts of the head are recorded after controlled intranasal presentation of a stimulus (CO2 or ethyl alcohol) using an olfactometer. The stimulus evokes stinging sensations due to stimulation of the trigeminal nerve. (see also [27,28])	Low amplitude, increased latency	8 lpm, 36°C, 80% humidity, 200 ms stimulus duration, CO_2 50% v/v, 20 repetitions, ISI 30s	
Zhang et al., 2019 [24]	tERP			8 lpm, 36°C, 80% humidity, 200 ms stimulus duration, ethyl alcohol 30% v/v, 32 repetitions, ISI 15s	
Burghardt et al., 2022 [25]	tERP			6 lpm, 36°C, 80% humidity, 200 ms stimulus duration, CO2 40% v/v, 40 repetitions, ISI 18-20s	
Savic et al, 2009 [20]	Trigeminal Lateralization	Using a mixed olfactory-trigeminal stimulus (eucalyptol or menthol), participants are presented with 2 bottles (glass or squeezable plastic), 1 on each nostril which contains either the stimulus or non-stimulus (air or solvent). They are tasked to identify which side of the nose is stimulated. The sum of correct responses correspond to the score and higher scores indicate better function.	Low score	10 ml volume, 99% eucalyptol, odorless air, using a glass jar, 10 repetitions, ISI 60s	
Saliba et al., 2016 [21]	Trigeminal Lateralization			15 ml volume, 50% eucalyptol (dissolved in propylene glycol), propylene glycol only, using a handheld squeezing device and polyethylene bottles, 40 repetitions, ISI 30s	
Huart et al., 2019 [23]	Trigeminal Lateralization			20 ml volume, 50% menthol (dissolved in propylene glycol), propylene glycol only, using joint pistons of syringes, 26 repetitions, no data on ISI	
Migneault-Bouchard et al., 2020 [14]	Trigeminal Lateralization			30 ml volume, 99% eucalyptol, propylene glycol only, using squeeze bottles pressed simultaneously, 40 repetitions, ISI 30-40s	
Burghardt et al., 2022 [25]	Trigeminal NMP	NMPs from AgAgCl-electrodes placed on the anterior nasal septal mucosa are recorded after controlled intranasal presentation of a stimulus (CO2) using an olfactometer. The stimulus evokes stinging sensations due to stimulation of the trigeminal nerve.	Low amplitude, increased latency	6 lpm, 36°C, 80% humidity, 200 ms stimulus duration, CO_2 40% v/v, 40 repetitions, ISI 18-20s	
Burghardt et al., 2022 [25]	CO_2 detection threshold	Participants receive the stimulus (CO2) in both nostrils using a nasal cannula. Participants were tasked to press a button to indicate stimulus perception. Similar to odor thresholds, a 'CO2-threshold' was determined using a staircase procedure with 7 turning points, with the average of three measurements corresponding to the threshold. The longer the stimulus duration (increased threshold), the lower the sensitivity.	Increased threshold	100% CO_2, starting from 100 ms increasing by 50 ms steps until perception	
Poletti et al., 2017 [22]	Electrical detection threshold	Electrical stimuli were applied to the anterior nasal septum, anterior lateral nasal wall, and middle turbinate using a spherical electrode placed on a spectacle frame worn by the participant. Electrical threshold was determined by a staircase procedure. Higher electrical stimulus intensity correspond to worse trigeminal function.		50 µs, starting from 0.05 mA increasing by 0.05 mA then decreasing by 0.05 mA, then increasing by 0.01 mA until threshold is reached	
Poletti et al., 2017 [22]	Air puff test	Using a handheld device that fits two 250 ml squeeze bottles with a spout (see Supplementary 1), a similar volume of air puff is presented to both nostrils at the same time. Intensity was rated from 0 (no sensation) to 10 (very intense)	Low intensity rating	similar but unknown volume of air puff	
Huart et al., 2019 [23]	Trigeminal Threshold	Felt tip-like pens were presented to participants in triplets as a staircase method, 3-alternative forced choice task. Correct responses resulted in reversals and the mean of the last 4 reversals comprised the threshold score. A lower score corresponds to worse function.	Lower threshold score	menthol (dissolved in propylene glycol)	Similar to "Sniffin' Sticks" but: highest was 50% concentration, 10 dilutions (1:2), 10s stimulus duration for 3 sticks, ISI between triplets 30s
Huart et al., 2019 [23]	Trigeminal Discrimination	Felt tip-like pens were presented to participants in triplets, where one pen had a trigeminal stimulus, 2 other pens had olfactory stimuli. Participants should determine which pen contained the trigeminal stimulus. The sum of correct responses comprised the discrimination score. A lower score corresponds to worse function.	Low score	6 stimuli used: menthol, eucalyptol, propanol, ethanol, camphor, diallylsulfide	Similar to "Sniffin' Sticks" but: ISI between triplets 30s, order randomized
Huart et al., 2019 [23]	Trigeminal Identification	Felt tip-like pens with trigeminal stimuli and 5 cards were presented with verbal descriptors (pungent/astringent; burning/warm; scratching/tickling/sneezing; prickling; and cold/fresh. Participants should choose the appropriate descriptor for each stimulus. The sum of correct responses comprised the identification score. A lower score corresponds to worse function.			Similar to "Sniffin' Sticks" but: 5 verbal descriptors to choose from, ISI 30s, order randomized

(*Continued*)

Table 3. (Continued).

Study	Methodology	Description	Indicators of poor function	Stimulus Details
Minovi et al., 2008 [19]	7-item olfactory-trigeminal test	Participants were tasked to identify from a list of verbal descriptors the appropriate descriptor for the stimulus. The sum of correct responses was the score, left and right nostrils were tested separately and comprised the birhinal trigeminal score	Low score	7 stimuli used: menthol, formic acid, acetic acid, ammonium chloride, chloroform, pyridine, ether
Savic et al., 2009 [20]	PET	PET is an imaging modality using radiotracers that show changes in metabolism, blood flow, and regional chemical composition. Areas with higher activity show higher uptake and brighter spots on images [29].		99% acetone, in glass bottles with a cotton wand, 10 mm distance from the nostrils, 15s stimulus duration, 4 repetitions with 5s interval of breathing air, passive breathing
Savic et al., 2009 [20]	Respiratory index	Respiratory frequency (breaths per minute) and respiratory amplitude were recorded during scan using a strain gauge around the lower thorax; the product of frequency and amplitude is the score		
Poletti et al., 2017 [22]	Self-rating: Nasal breathing	1 (good) to 7 (no function)	Higher rating	
Burghardt et al., 2022 [25]	Self-rating: CO_2 intensity	0 (not intense) to 10 (extremely intense)	Lower rating	
Burghardt et al., 2022 [25]	Self-rating: CO_2 pleasantness	0 (very unpleasant) to 10 (very pleasant)		

Note: *tERP: trigeminal event-related potentials; lpm: liters per minute; °C: degrees Celsius; ms: milliseconds; CO_2: Carbon dioxide; v/v: volume per volume; ISI: interstimulus interval; s: seconds; ml: milliliter; NMP: negative mucosal potential; µs: microsecond; mA: milliampere; mm: millimeter; PET: positron emission tomography.

al. also found that trigeminal threshold scores were significantly correlated with olfactory threshold ($r = 0.50$, $p = 0.012$), discrimination ($r = 0.66$, $p < 0.001$), and identification ($r = 0.70$, $p < 0.001$) scores [23]. Although Burghardt et al. alluded to a possible interaction of olfaction and gustation, they also suggested that results should be re-investigated in a larger sample given that they only included 10 CRSwNP patients in their study [25]. Minovi et al. found that severe nasal polyposis was associated with both olfactory (r_{64}=-0.62, $p < 0.001$) and trigeminal (r_{64}=-0.41, $p = 0.001$) loss, although a direct correlation between olfactory and trigeminal scores was not explicitly stated [19]. In this review, only Savic et al. investigated which brain regions were activated by olfactory and trigeminal stimuli [20]. Healthy controls had activations for olfactory stimuli (vanillin or androstenone) in the amygdala, piriform cortex, agranular insular cortex, and fusiform gyrus. Furthermore, when acetone (a bimodal olfactory-trigeminal stimulus) was presented to the controls, additional areas, namely: the anterior cingulate, brainstem (trigeminal nucleus), thalamus (ventromedial nucleus and the pulvinar), sensorimotor cortex, and cerebellum, were also activated. Conversely, in anosmic patients, no activations for olfactory stimuli were observed. Only acetone elicited activations in similar areas as in controls (i.e. the anterior cingulate, brainstem, thalamus, and sensorimotor cortex), but not in the cerebellum. Areas deactivated by trigeminal stimuli in both anosmic patients and controls included the temporal and parieto-occipital cortex, with more deactivations in the frontopolar and dorsolateral prefrontal cortex in controls. When contrasting anosmic patients and controls, significant clusters (areas of differing activations between groups) appeared only for acetone–air as stimulus in the prefrontal cortex covering portions of the orbitofrontal cortex, and the parietal cortex (which overlapped with acetone-related deactivation in controls) [20]. Although Savic et al. found brain regions that were activated by both olfactory and trigeminal stimuli in healthy individuals, there were other areas that have been found in several studies to be especially activated by trigeminal stimuli, namely: the anterior cingulate gyrus, brainstem, thalamus, somatosensory cortices, cerebellum [8,20,45]. Interestingly, however, the difference in areas activated in healthy individuals and anosmic patients in the study by Savic et al. (which included CRS patients) is in support of a similar finding by Iannilli et al. that central trigeminal processing may be functionally reorganized in patients with impaired olfaction [20,46].

Previous studies proposed a synergistic relationship between olfaction and trigeminal sensation, where decreased olfaction can lead to reduced trigeminal sensitivity [22,25,41,47,48], although other studies found that one can also inhibit the other [20,42,49,50]. On the level of receptors, a recent study in mice found that ion channels related to trigeminal function (transient receptor potential channels vanilloid 1 (TRPV1) and 4 (TRPV4)) stimulated olfactory receptor neuron (ORN) progenitor cell proliferation and modulated cell maturation [51]. Although olfactory loss is part of the diagnostic criteria of CRS [13,52], with a prevalence of up to 90% depending on age [53], an interaction between the olfactory and trigeminal systems (see [54]) leading to lower trigeminal sensitivity in CRS patients appears to be present. However, it is difficult to separate the effects of olfaction on trigeminal sensation [38]. Nevertheless, there is agreement that olfactory activation affects trigeminal function and in turn that olfactory loss modulates trigeminal sensitivity [8].

Two studies that investigated trigeminal function also included individuals with other causes of olfactory loss. Although Huart et al. found that trigeminal function was affected in patients with CRS, post-traumatic olfactory dysfunction (PTOD), post-infectious olfactory dysfunction (PIOD), and Idiopathic OD [23], Migneault-Bouchard et al. did not [14]. Both studies had a low sample size of CRS patients (20 for the former and 31 for the latter) and used mixed olfactory-trigeminal stimuli, making the conflicting results inconclusive. Migneault-Bouchard et al. also found a significant correlation between the lateralization scores for the left and right nostrils among these patients ($p = 0.001$). However, they did not find the same correlation when comparing odor threshold scores and lateralization scores for a given nostril [14].

Huart et al. explored the possibility of a clinical trigeminal test, similar to 'Sniffin' Sticks" [23]. However, as previously mentioned, results were difficult to isolate from the effects of olfaction as they used mixed olfactory-trigeminal stimuli. Moreover, the scores from their clinical trigeminal test were not correlated with the trigeminal lateralization test, which they attributed to differences in methodology and the low sample size ($n = 59$, of which only 20 were CRS patients). But then, this casts some doubt whether the tests both effectively measure trigeminal function or not. Although the authors emphasized their attempt to decrease the influence of olfaction by specifically telling patients to focus on trigeminal sensations, this cannot be ascertained unless, perhaps, a purely trigeminal stimulus like gaseous CO_2 is used [23].

6. Trigeminal function and nasal airflow

Nasal obstruction is among the key symptoms of chronic rhinosinusitis [13,52]. Although the symptom is often attributed to a mechanical obstruction due to nasal polyps, other factors including trigeminal dysfunction have been proposed to contribute to the perception of impaired nasal airflow in CRS [20,21]. Interestingly, the perception of decreased nasal airflow has also been reported in patients with 'empty nose syndrome' suggesting that perceived nasal airflow is independent of nasal patency but related to mucosal sensitivity [55].

Two studies compared objective measurements of nasal airflow/breathing with trigeminal function measures. Savic et al. found that brain activations on PET scan, with acetone as the trigeminal stimulus, were slightly less pronounced in anosmic patients (including CRS patients) compared to controls. However, they also measured respiratory patterns [using a strain gauge, based on recorded respiratory frequency (in breaths per minute) and amplitude during each scan] which did not differ significantly between the 2 groups [20]. A couple of studies found that CRS patients rated their nasal patency as worse than controls [21,22]. However, a study by Saliba et al., also found normal peak nasal inspiratory flow (PNIF) measurements among CRS patients, despite having worse self-ratings for nasal patency [21]. This finding supports the presence of

Table 4. Summary of trigeminal findings in chronic rhinosinusitis.

Study	Methodology	Trigeminal Function	Details
Rombaux et al., 2006 [18]	tERP	Decreased	Lower N1 amplitude, P2 amplitude and N1P2 amplitude in nasal polyp patients, but other ERP parameters were not significantly different between groups
Zhang et al., 2019 [24]	tERP	Decreased (with more severe inflammation)	N1/P2 peak latencies were strongly correlated with tissue eosinophils
Burghardt et al., 2022 [25]	tERP	Decreased (only for latencies)	tERP amplitudes: There were no significant differences between averaged amplitudes |P1-N1| and |N1-P2| in CRSwNP patients and controls; tERP latencies: P1, N1, and P2 latencies were all significantly longer in CRSwNP patients
Savic et al, 2009 [20]	Trigeminal Lateralization	No effect	No significant difference between lateralization scores in anosmic patients (including CRS patients) compared to controls; all patients sensed the trigeminal stimulus and subsequently had clear cerebral activations
Saliba et al., 2016 [21]	Trigeminal Lateralization	Decreased	CRS patients had significantly lower trigeminal lateralization scores than controls (CRS, 22.1 ± 5.9; controls, 30.5 ± 4.3; $t = 4.3$, $P < 0.001$); CRS patients also had higher failure rates on the trigeminal lateralization task (failures: CRS, 9/14; controls, 2/14; $\chi 2 = 7.34$, $P = 0.007$)
Huart et al., 2019 [23]	Trigeminal Lateralization	Decreased	Patients with CRSwNP and CRSsNP had significantly lower scores compared to controls ($p < 0.001$ and $p = 0.005$, respectively)
Migneault-Bouchard et al., 2020 [14]	Trigeminal Lateralization	No effect	There was no significant difference between lateralization scores in CRS patients compared to OD patients with other underlying causes (i.e. PTOD, Idiopathic, PIOD)
Burghardt et al., 2022 [25]	Trigeminal NMP	No effect	NMP amplitudes: There were no significant differences between averaged amplitudes |P1-N1| and |N1-P2| in CRSwNP patients and controls; NMP latencies: Although latencies were prolonged in CRSwNP, the difference with controls was not significant
Burghardt et al., 2022 [25]	CO_2 detection threshold	No effect	No significant difference between CRSwNP and controls on the CO_2 threshold test ($t_{24} = 0.73$; $p = 0.47$).
Poletti et al., 2017 [22]	Trigeminal detection threshold	Decreased	CRSwNP had higher trigeminal perception threshold at the anterior nasal septum, anterior lateral nasal wall, and the middle turbinate pre-operatively
Poletti et al., 2017 [22]	Air puff test	No effect	No significant difference in air puff ratings between healthy subjects and patients (subjects: 1.05 ± 0.48 SD; patients: 1.0 ± 1.22 SD, $p = 0.64$) or between pre- and post-operative patients (pre: 1.0 ± 1.47 SD; post: 2.0 ± 1.75 SD, $p = 0.12$)
Huart et al., 2019 [23]	Trigeminal Threshold	Decreased	Patients with CRSwNP, CRSsNP and OD had significantly lower threshold scores compared to healthy controls ($p < 0.001$, $p = 0,024$ and $p < 0.001$, respectively)
Huart et al., 2019 [23]	Trigeminal Discrimination	Decreased	Discrimination scores were significantly different between groups ($p < 0.001$) (Control>CRSsNP>AR>CRSwNP>OD)
Huart et al., 2019 [23]	Trigeminal Identification	Decreased	Mean identification scores were significantly different between groups ($p = 0.001$) (Control>AR>CRSsNP>CRSwNP>OD, but AR and Control values seem to be comparable)
Minovi et al., 2008 [19]	7-item olfactory-trigeminal test	Decreased (especially in those with severe nasal polyps)	Chemosensory function was decreased in patients with severe nasal polyps ($F_{1,62} = 4.15$, $p = 0.46$)
Savic et al., 2009 [20]	PET Scan	Different sites activated and deactivated	Anosmic patients (including CRS patients) had significant activation only for acetone (but not for olfactory stimuli vanillin and androstenone) in the anterior cingulate, thalamus (ventromedial nucleus and the pulvinar), brainstem (trigeminal nucleus) and sensorimotor cortex, no activations in the hypothalamus, amygdala, piriform, insula, or cerebellum; healthy controls had activations in similar areas for olfactory and trigeminal stimuli, but additional sites in cerebellum, amygdala piriform, agranular insular cortex, and portions of the fusiform gyrus were activated with the trigeminal stimulus
Burghardt et al., 2022 [25]	Self-rating: CO2 intensity and pleasantness	Decreased	CRSwNP rated the CO_2 stimuli as less intense and less unpleasant compared to controls ($t_{24} = 2.50$; $p < 0.05$, and $t_{24} = 2.50$; $p < 0.05$)

Note: *tERP: trigeminal event-related potentials; ERP: event-related potentials; CRSwNP: chronic rhinosinusitis with nasal polyps; CRS: chronic rhinosinusitis; CRSsNP: CRS without nasal polyps; OD: olfactory dysfunction; PTOD: post-traumatic olfactory dysfunction; PIOD: post-infectious olfactory dysfunction; NMP: negative mucosal potential; CO_2: carbon dioxide; SD: standard deviation; AR: allergic rhinitis; PET: positron emission tomography.

another factor, perhaps trigeminal dysfunction, that contributes to the subjective impression of nasal obstruction in CRS patients [21].

Various theories have been suggested to explain nasal obstruction in CRS. One factor proposed was mucosal cooling, which involves an interaction between the temperature and humidity of inspired air and the structures inside the nasal cavity [56,57]. In CRS patients, the presence of mucosal edema can lead to limited surface area available for heat exchange. The combination of both impaired trigeminal function and morphologic changes in the nasal cavity leading to altered mucosal cooling [57] has been proposed to explain the perception of nasal obstruction in CRS [21]. Another factor identified was the transient receptor potential subfamily M member 8 (TRPM8), a cation channel that is activated by cold temperatures and sensitized, for example, by menthol (a mixed olfactory-trigeminal stimulus) [58]. Activation of TRP channels has been proposed to cause substance P (SP), nerve growth factor (NGF), neurokinins A and B (NKA/B), vasoactive intestinal peptide (VIP), calcitonin gene-related peptide (CGRP), and acetylcholine release in the nasal mucosa, leading to vasodilation and mucus secretion that can subsequently lead to a perception of nasal congestion [59–61]. It was also proposed that a reduction in TRPM8's sensitivity to cold temperatures may lead to impaired airflow detection [21,22].

The gradient of mucosal heat loss, which is important for the sensation of nasal patency, was found to not be uniform throughout the nasal cavity. It was reported to be concentrated anteriorly in the nasal vestibule and the anterior nasal valve [57,62]. This aligns with findings of Poletti et al. that the greatest trigeminal sensitivity is located in the anterior nasal cavity. Increased sensitivity to trigeminal stimuli in this area is critical for the protective function of the trigeminal system against potentially dangerous inhaled substances [22]. However, a later study found greater expression of TRPV1 receptors, which are the most common TRP receptors in the nasal cavity, at the posterior nasal cavity [63]. This suggests that the contribution of the posterior nasal cavity is possibly underestimated when it comes to airway safety. Postoperative improvement in trigeminal sensitivity was also found anteriorly at the nasal septum 3 months after surgery [22]. This finding demonstrates the possibility of recovery although further studies are required. However, it remains unclear whether the trigeminal function improvement after surgery was due to decreased inflammation, increased neuronal density, or other factors. Still, the importance of a functional trigeminal system cannot be overemphasized, especially in patients with weaker respiratory systems as in aspirin exacerbated respiratory disease (AERD).

The difficult part with some studies included in this review is the biases that go along with the method of testing chosen. For instance, Minovi et al. used olfactory and trigeminal tests with unknown validation and normative values. They also proposed that both olfactory and trigeminal scores obtained in their study were related to nasal patency, as their method required participants to inhale, introducing what they termed as a 'respiration-bound bias.' Thus, they attributed decreased trigeminal scores to decreased airflow, with less irritative molecules reaching the area of the respiratory epithelium [19]. But other studies also concluded that apart from anatomic obstruction, impaired trigeminal sensation contributed to the perception of nasal obstruction in CRS patients [21,22].

7. Trigeminal function in relation to age and gender

Only two studies of the present review investigated the relationship of age with trigeminal function, with contradicting results. A study by Migneault-Bouchard et al., found that age had a significant effect on trigeminal scores ($F_{1,172} = 16.94$; $p < 0.001$) [14]; however, Saliba et al., found no correlation between age and trigeminal function (r_{28}=-0.28, $p = 0.14$) [21]. When it comes to gender, only 2 studies investigated its relationship with trigeminal function, also with contradicting results. Minovi et al. found that women had a greater trigeminal score improvement after surgery ($p < 0.03$) [19], while Saliba et al. found that trigeminal function was not associated with gender ($t = -1.7$, $p = 0.11$) [21]. Previous studies with healthy controls and other patient groups found negative correlations between age and trigeminal function (healthy

Table 5. Trigeminal function related to olfaction.

Study	Trigeminal Test	Olfactory Test	Relationship of Olfaction to Trigeminal Function	Details
Rombaux et al., 2006 [18]	tERP	"Sniffin' Sticks" [27,28], 20-item Retronasal Powders Test [44]	Correlated	Significant correlation between orthonasal testing ($r = 0.21$, $p = 0.002$), but not retronasal testing ($r = 0.09$, $p = 0.05$), and N1P2 peak-to-peak amplitude after presentation with a trigeminal stimulus ($r = 0.21$, $p = 0.002$); normal trigeminal function may indicate good prognosis for recovery of olfaction
Minovi et al., 2008 [19]	7-item olfactory-trigeminal test	6-item odor identification test	Both decreased	Both olfaction and trigeminal function was decreased in patients with severe nasal polyps
Saliba et al., 2016 [21]	Trigeminal Lateralization	8-item odor identification test	Correlated	Trigeminal and olfactory functions were correlated ($r = 0.48$, $n = 28$, $p = 0.01$)
Huart et al., 2019 [23]	Mixed Olfactory-Trigeminal Threshold	"Sniffin' Sticks" [27,28]	Correlated	Trigeminal threshold scores significantly correlated with olfactory threshold ($r = 0.50$, $p = 0.012$), discrimination ($r = 0.660$, $p < 0.001$), and identification scores ($r = 0.70$, $p < 0.001$).
Migneault-Bouchard et al., 2020 [14]	Trigeminal Lateralization	"Sniffin' Sticks" [27,28]	Correlated	Olfactory and trigeminal scores were correlated, with age as covariate ($r = 0.25$, $p = 0.006$)

controls [38,64]; olfactory dysfunction [15,39]; empty nose syndrome [55]) but no effect for gender [15,55]. Although these findings may be prevalent in olfaction and trigeminal function in general, there seem to be less clear results on the effect of age and gender on trigeminal function among CRS patients.

8. Trigeminal function and inflammation

Only one study in our review directly investigated the relationship of inflammation with trigeminal function. Zhang et al. found that tissue eosinophil count was correlated with tERP N1 and P2 peak latencies, but not amplitudes, for ethyl alcohol as a stimulus [24]. Also, in the same study, they found a correlation between tERP latency and sneezing visual analogue scale (VAS) ratings, where worse ratings corresponded to longer latencies (Kendall's tau-b=−0.40, $p = 0.005$). However, since Kendall's tau was the analysis used, the quantitative effect this corresponds to is uncertain, as this analysis only gives an ordinal association between the two variables. Sneezing was found to be mediated by TRPV1 in mice [65]. TRPV1+ nasal neurons were found to selectively express neuromedin B, a peptide that activates neuromedin B receptor + (NMBR+) neurons in the area of the brainstem related to sneezing. These NMBR+ neurons were found to synapse with the caudal ventral respiratory group to induce sneezing when prompted by chemical irritants or allergens [65]. Interestingly, however, trigeminal function appears to be preserved, or even better, in allergic rhinitis (AR) patients [23,25,66]. Trigeminal CO_2 thresholds ($t_{63} = 2.69$; $p < 0.05$) were lower. Responses to a nasal mucosal signal (negative mucosal potential, NMP) had shorter latencies (N1: $t_{57} = 2.20$, $p < 0.05$; P2: $t_{57} = 2.30$, $p < 0.05$) and tERP P1 ($t_{26} = 2.12$, $p < 0.05$), N1 ($t_{26} = 2.12$, $p < 0.05$), and P2 ($t_{26} = 2.08$, $p < 0.05$) peak latencies were also significantly shorter in patients with AR [25]. Trigeminal lateralization was also found to be significantly better in patients with AR compared to CRS ($p = 0.002$), but the difference between scores of AR patients and healthy controls remained non-significant [23]. On the other hand, patients with asthma were found to have lower pre-operative scores on chemosensory function tests than patients without asthma ($p < 0.005$), but having asthma did not influence the effect of surgery on post-operative chemosensory function [19].

When it comes to the effect of inflammation on intranasal trigeminal function, the exact mechanism is unclear, but several theories have been proposed. Trigeminal sensitivity seems to depend on the duration of inflammation, with acute inflammation leading to increased trigeminal sensitivity and chronic inflammation leading to decreased sensitivity [67]. Similarly, patients with AR [25] and increased sneezing VAS ratings [24] were observed to have heightened trigeminal function similar to that which is observed in acute inflammation, while those with CRS were found to have decreased sensitivity. A previous study by Doerfler et al. proposed that allergen-related sensitization of trigeminal nerve endings occurs in AR, explaining this increased sensitivity [66]. Another study, however, also proposed theories related to nerve hypersensitivity in the context of cutaneous neuropathic pain; where 'dynamic denervation' secondary to inflammation may cause pro-inflammatory cytokines or other mediators to produce axonal excitation. Inflammatory processes may also cause increased production of nerve growth factor (NGF), which may also lead to the upregulation of TRPV1 and a subsequent increase in nerve excitation [68]. Although their study was done in the context of pain sensation, perhaps a similar mechanism applies for intranasal trigeminal sensation.

Local inflammatory processes were also found to influence the sensitivity of the TRPV1 receptor (mediating temperature sensation above 42°C and chemical stimulation (i.e. capsaicin)) and TRP ankyrin 1 (TRPA1) (mediating dull, burning, painful sensation; i.e. associated with mustard or wasabi consumption; also a sensor of pungent chemicals and oxidative stress). Activation of these TRP cation channels leads to the release of neuropeptides from nerve endings, cascading to the release of pro-inflammatory cytokines, resulting in nerve sensitization or activation [60]. Solitary chemosensory cells (SCC) in the inferior turbinate of healthy individuals were found to be associated with calcitonin gene-related peptide (CGRP)-reactive nerve endings. However, CGRP-positive nerve endings were not found in eosinophilic nasal polyp tissue [69] and this observed lack of innervation was attributed to downregulation of proteins associated with neuronal growth (i.e. ciliary neurotrophic factor receptor subunit alpha, neuronal growth regulator 1, neuronal cell adhesion molecule, neural cell adhesion molecule L1, platelet-derived growth factor subunit A, and netrin-4) and the axonal guidance signaling pathway (i.e. beta-nerve growth factor, semaphorin 3A, Ras-related C3 botulinum substrate 1, Bcl-2, protein kinase C delta type, and Fyn), as well as the upregulation of the Nogo receptor pathway related to axon growth inhibition that has been previously observed in CRSwNP [70].

In olfaction, chronic inflammation has been found to deactivate olfactory sensory neuron regeneration and instead, promote epithelial immune defense leading to impaired sensation in mice [71]. Whether a similar pathophysiology related to upregulated defense mechanisms leading to permanent damage of trigeminal nerve endings [22], changes in nerve growth factor release [72], or another mechanism is responsible for the trigeminal dysfunction observed, requires further investigation.

In addition, there exists a subtype of CRS with increased eosinophilia and nasal polyps. Eosinophils can release granule proteins which are neurotoxic [73–75] and may damage olfactory [24] and possibly trigeminal neurons as well. However, it appears that the effects are not unidirectional as the lack of innervation (possibly including trigeminal), observed in the study by Deng et al., was proposed to generate a pro-inflammatory state that causes SCC proliferation and increased interleukin 25 (IL-25) production which further drives type-2 inflammation [69].

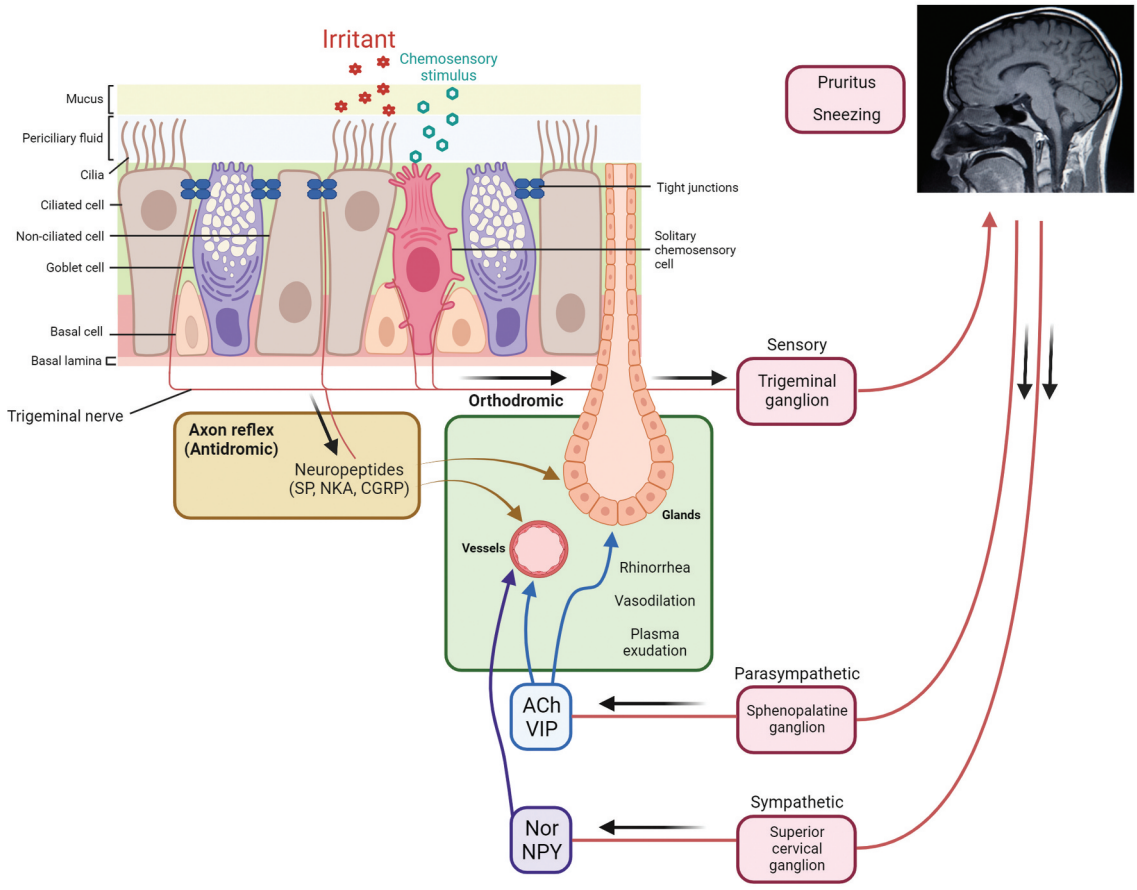

Figure 3. Histology and pathophysiologic mechanisms of the intranasal trigeminal system [based on [12]].

The trigeminal nerve is involved in chemosensory and somatosensory perception and is also connected with various intranasal pathophysiologic mechanisms involving both afferent (sensory) and efferent (parasympathetic, sympathetic, and axon reflex) pathways. Trigeminal nerve fibers are in close contact with solitary chemosensory cells, while trigeminal nerve free endings are also distributed in the respiratory epithelium. Signals may be orthodromic (to the spinal cord [32]) or antidromic (away from the spinal cord [32]), but effects may be centrally- or peripherally mediated through the brain and autonomic nervous system (sympathetic and parasympathetic). SP: substance P, NKA: neurokinin A, CGRP: calcitonin gene-related peptide, ACh: acetylcholine, VIP: vasoactive intestinal peptide, Nor: norepinephrine, NPY: neuropeptide Y. Figure created with Biorender.com.

8.1. Trigeminal function and nasal polyp grading

Three different nasal polyp grading methods were used in the included studies: Lund Mackay (endoscopic, anatomic, radiologic, surgical) [76], Lund Kennedy (radiologic, surgical, symptomatic, endoscopic) [77], and Lildholdt (endoscopic) [78]. Lund Mackay scores indicate disease severity and also the outcome of surgery in CRS [76,79]. A couple of studies found a moderate (r_{64}=-0.41, $p = 0.001$ [19]) to strong (r_{28}=-0.62, $p < 0.001$ [21]) negative correlation between Lund Mackay scores and trigeminal function. Furthermore, a study by Saliba et al. noted that Lund Mackay scores contributed a significant amount of variance to trigeminal lateralization scores on linear regression analysis, after controlling for age and gender ($F = 5.93$, $p = 0.004$, $R^2 = 0.43$), supporting the relationship between inflammation and trigeminal function [21]. In another study, preoperative Lund Mackay scores were correlated with both olfactory (r_{64}=-0.62, $p < 0.001$) and trigeminal scores (r_{64}=-0.41, $p = 0.001$). A higher degree of polyposis, or more severe disease, was correlated to decreased olfactory and trigeminal function [19]. A study by Poletti et al. found no significant correlation between Lund Kennedy scores and trigeminal perception threshold in all three sites they tested [22]. Although one study collected data on Lund Kennedy scores and Lildholdt scores, they did not analyze the correlation of these variables to trigeminal function and only concluded that participants included in their study had mild to moderate nasal polyposis and moderate inflammatory response [25].

The presence of nasal polyps also signals the severity of inflammatory disease. However, it has been speculated that compression of trigeminal nerve from the presence of massive nasal polyps may also contribute to trigeminal dysfunction. Vascular pressure on the trigeminal nerve in patients with idiopathic trigeminal neuralgia was considered to result in nerve injury leading to impaired olfactory function and to lower trigeminal sensitivity especially when the V1 and V2 branches are involved [80]. It remains uncertain if a similar compressive effect is possible in more peripheral branches of the trigeminal nerve.

8.2. CRS treatment and trigeminal function

Although olfactory function has been shown to improve with treatment (including corticosteroids and/or surgery), there seems to be a late-onset decline associated with CRSwNP patients after initial post-operative improvement [81,82]. One possible explanation proposed was that nasal mucosal

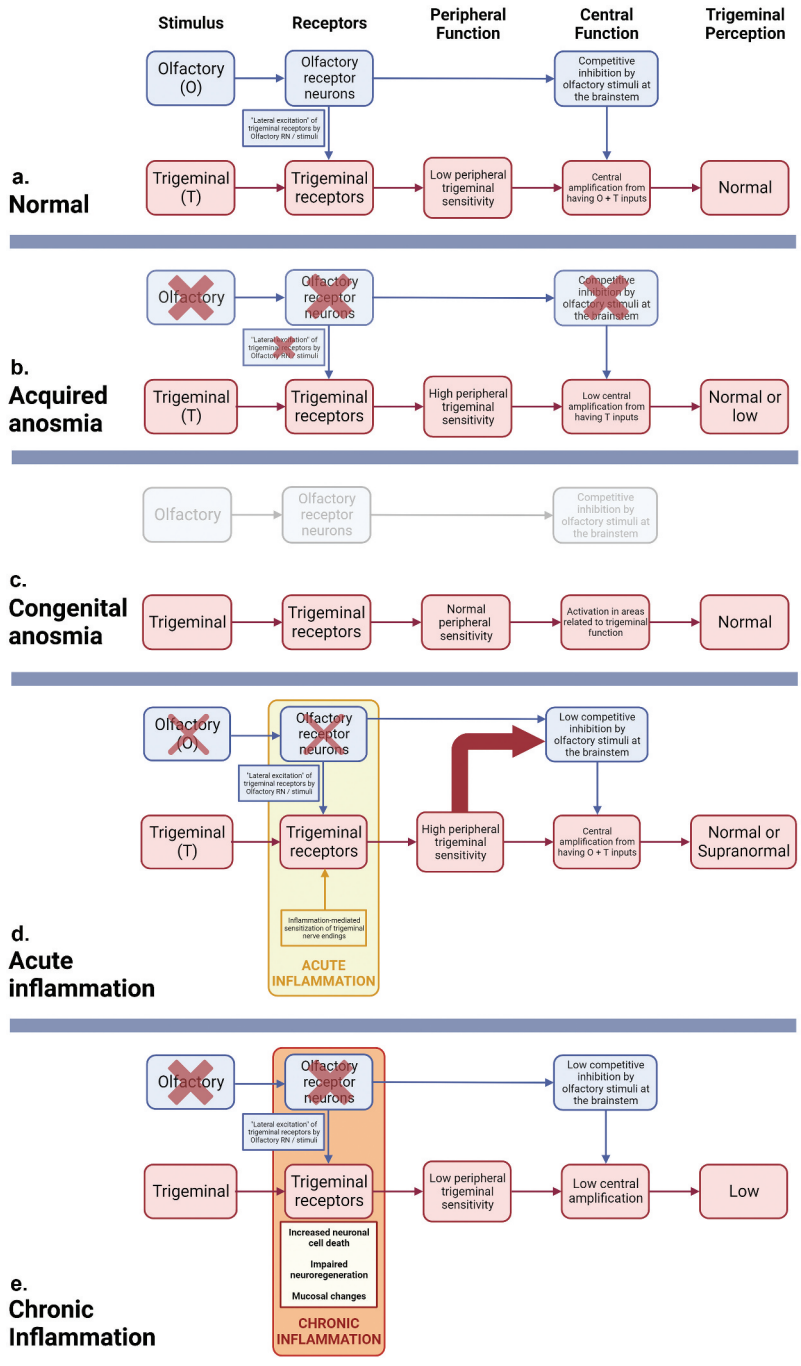

Figure 4. Theories on olfactory and trigeminal interaction.

A. Normal olfactory and trigeminal function: In normal olfactory and trigeminal function, there would be lateral excitation from olfactory stimulation and competitive inhibition at the level of the brain stem. This leads to low peripheral trigeminal sensitivity and increased central amplification due to the presence of olfactory and trigeminal signals, resulting in normal trigeminal perception.

B. Acquired Anosmia: Acquired anosmia would not have lateral excitation and competitive inhibition from olfactory stimuli, therefore, increased peripheral activation may occur in the setting of decreased central amplification due to the lack of olfactory inputs. This may result in normal or low trigeminal perception.

C. Congenital Anosmia: Individuals with congenital anosmia may be wired differently, in that their trigeminal system is not integrated with the olfactory system; thus, their trigeminal function is similar to that of healthy individuals.

D. Acute Inflammation: Inflammation (an unknown mechanism) may lead to increased nerve excitability and subsequently increased peripheral sensitivity (as is observed in allergic rhinitis). Some decrease in olfactory function may occur, but not to a similar severity as in acquired anosmia. This may still result in increased central activation from the presence of both olfactory and trigeminal stimuli, resulting in normal or hypersensitive trigeminal perception.

E. Chronic Inflammation: Chronic inflammation, as in CRS, may lead to a functional switch from neuroregeneration to immune defense in terms of olfaction and ORNs. Thus, a decrease in neuroregeneration of ORNs could lead to decreased olfactory function and absence of olfactory inputs as is seen in acquired anosmia. Inflammation may also lead to a similar failure of regeneration or increased neuronal cell death in trigeminal neurons, leading to fewer functioning trigeminal nerves and receptors. Furthermore, mucosal changes (i.e. diseased mucosa or nasal polyps) may occur in CRS that can alter the mucosal surface area with functional trigeminal receptor neurons, as well as decrease the viable surface area for effective mucosal heat exchange, leading to the perception of nasal obstruction. It is also possible that functional reorganization of central nervous system processing of both olfactory and trigeminal inputs occurs in CRS Figure created with Biorender.com.

eosinophilic inflammation may develop again, months after surgery [24].

8.2.1. Surgery

Surgery is usually advised for CRS patients whose disease fails to respond to medical therapy, to remove nasal polyps and diseased tissue, to relieve obstruction in the ostiomeatal complex, leading to improved drainage and ventilation in the sinuses [83]. However, there is limited evidence to support the benefit of surgery for trigeminal function in CRS patients.

Only 2 studies in our review investigated the effect of surgery on trigeminal function in CRS patients. A study by Minovi et al. found that only patients with severe nasal polyps, compared to those with little or no polyps, had a more pronounced increase in trigeminal scores after surgery, despite olfaction improving in all participants ($F_{1,62} = 26.2$; p=<0.001). Furthermore, other factors such as age, asthma, or number of previous surgical interventions had no significant impact on the effect of surgery on post-operative chemosensory function. Also, the presence of aspirin intolerance had no effect on trigeminal scores but predicted greater post-operative improvement in olfactory scores compared to patients without aspirin intolerance [19]. Poletti et al. explored whether trigeminal sensitivity varied in different areas of the nasal cavity among CRS patients before and after surgery [22]. Using electrical stimulation, the anterior lateral nasal wall was the most sensitive area for trigeminal stimuli among CRSwNP patients pre-operatively, while it was at the anterior nasal septum for healthy participants. Furthermore, there was improvement of trigeminal sensitivity at the area of the nasal septum, but not at the lateral nasal wall or the middle turbinate, in CRSwNP patients after surgery [22]. The exact mechanism of improvement from surgery on trigeminal function is unclear, but it may be related to the decreased inflammation from removal of nasal polyps, diseased mucosa, and increased accessibility of intranasal corticosteroids to previously obstructed areas after surgery.

8.2.2. Corticosteroids (systemic/topical)

Only one study explored the effect of systemic or topical steroids in CRS patients. Poletti et al., found no significant difference in endonasal trigeminal detection threshold between systemic or topical steroid treated and non-steroid treated patients post-operatively at all 3 tested locations [22].

9. Theories on the pathophysiology of trigeminal dysfunction in CRS

In this review, none of the included studies hypothesized about the exact pathophysiology of trigeminal function in CRS. Although there are several published reviews on intranasal trigeminal function (see also [8,12,37] and Figure 3), we found only one proposed model on trigeminal dysfunction in CRS [60] and another model that speculated about the interaction of the olfactory and trigeminal systems in relation to trigeminal perception [40]. Similar to this paper, several studies proposed peripheral interaction of both systems [36,40,84–86], while others showed central interaction [10,20,87], or both [42,88].

Several key factors were proposed to affect trigeminal perception, including the type of stimuli (solubility [3,89,90], concentration [7,38,39], bimodal activation of the olfactory and trigeminal systems [42]), receptors or ion channels activated [9,37,56,60,63], with uncertain mechanisms of signal augmentation [36,91] and inhibition [20,42,49,50] by olfactory stimuli, among others.

In light of the existing literature, we propose a framework to illustrate the possible olfactory and trigeminal interactions related to trigeminal perception in various conditions including CRS (Figure 4). We aim that this framework serves as a starting point for discussion, possibly as a guide for the direction of future studies about the trigeminal system. The framework remains to be a theory that awaits to be confirmed or disproven by scientific evidence.

Functioning olfactory and trigeminal systems, with both peripheral and central processing, are required for trigeminal perception and chemosensation, in general. In mice, trigeminal receptors (TRPV1 and TRPV4) were found to be expressed in the olfactory epithelium, with TRPV1 located near ORN axons [51]. It could be possible that trigeminal and olfactory systems interact peripherally through lateral excitation of the trigeminal receptors by olfactory stimuli [91], however the magnitude expected from this interaction may not be as great as initially thought [50]. A common central integrative area has been proposed, which involves the inferior parietal lobule, and the middle and superior temporal gyrus [10], the pre- and post-central gyrus, the cerebellum, the ventrolateral thalamus, the piriform cortex [87], the orbitofrontal cortex, and the insula [10,87]. However, in a mouse model, it was shown that olfactory stimulation activates the hypothalamus and results in descending inhibition of trigeminal activity in the brainstem, leading to modulation of trigeminal perception [92].

We hypothesize that in healthy individuals, olfactory stimuli activate ORNs, which may also lead to lateral excitation of trigeminal receptors. This would then produce decreased trigeminal sensitivity peripherally because of the constant activation of intrabulbar trigeminal collaterals [93] and consequent functional downregulation in the periphery of the trigeminal system. However, the presence of olfactory stimuli may also lead to activation in the hypothalamus, leading to descending inhibition of trigeminal signals at the level of the brainstem, resulting in decreased trigeminal activation centrally [42]. However, the presence of combined olfactory and trigeminal stimulation may lead to a greater central amplification, resulting in normal trigeminal perception, regardless of the presence of some degree of inhibition through the olfactory pathway.

Chronic inflammation, as in CRS, may lead to a functional switch from neuroregeneration to immune defense in terms of olfaction and ORNs [71]. Thus, a decrease in neuroregeneration of ORNs could lead to decreased olfactory function and the absence of olfactory inputs as is seen in acquired anosmia. Other inflammatory changes such as the anatomic obstruction

of the olfactory cleft and mucosal surface or mucus changes that would impair odorant binding, may also lead to decreased peripheral lateral, possibly also central, inhibition by olfactory stimuli.

Aside from its effects on olfaction, we hypothesize that chronic inflammation may also lead to persistent local effects similar to what has been observed in capsaicin for pain management. Capsaicin may invoke an initial excitation followed by a long-lasting refractory period in TRPV1 receptors, leading to the inability of previously excitable neurons to respond to trigeminal stimuli. This was referred to as 'defunctionalization' [68,94,95]. The possible mechanisms of defunctionalization include loss of membrane potential, depletion of neuropeptides, reversible retraction of nerve fiber terminals, calcium overload resulting in loss of mitochondrial function, plasma membrane disruption, and eventual collapse of nerve endings [68,94]. Defunctionalization is postulated to be accompanied by suboptimal nerve regeneration or increased neuronal cell death in trigeminal neurons [96,97], leading to fewer functioning nerves, downregulation of receptors [85], or dysfunction in ion channels (TRPV1, TRPM8, TRPV3, TRPA1, acid-sensitive ion channels, purinergic receptors [9]). Furthermore, mucosal changes (i.e. diseased mucosa or severe nasal polyposis) may occur in CRS leading to a reduction in functional trigeminal receptor neurons and decreased surface area for effective mucosal heat exchange. Massive nasal polyposis has also been hypothesized to compress nerve endings which may be detrimental for trigeminal function [80]. All of these may lead to impaired peripheral trigeminal processing and contribute to the perception of nasal obstruction. Trigeminal neuronal damage may result in low peripheral trigeminal sensitivity, while diminished olfactory inputs may lead to low central trigeminal activation, leading to a decrease in trigeminal perception overall [40].

It has been previously mentioned that functional reorganization of central nervous system processing of trigeminal inputs may occur in patients with olfactory loss [46] and we propose that this may also occur in CRS. When all of these are considered, this complex interaction of conditions related to chronic inflammation may help explain the context of impaired olfaction and nasal obstruction in relation to impaired trigeminal perception in CRS.

10. Conclusion

Trigeminal dysfunction is observed in chronic rhinosinusitis. However, the variations in the study methodologies preclude direct comparison of findings. Future studies would greatly benefit from a standardized and validated trigeminal test that is accessible and easy to use in clinical settings, possibly factoring in the different subtypes of CRS. Although a framework for trigeminal dysfunction in CRS is proposed in this review, there is more to learn from future investigations having control groups, larger sample sizes, standardized methods of trigeminal function measurement, and various treatment modalities (including biologics and other therapies).

11. Expert opinion

Although olfaction has been extensively studied in relation to CRS, there are fewer published studies investigating intranasal trigeminal function in this subset of patients. It is still unclear how much influence trigeminal function has on olfactory loss and nasal obstruction in the setting of CRS. However, more studies to investigate the exact mechanisms of trigeminal dysfunction in CRS may help provide better targeted therapies in the future that may impact not only trigeminal perception but also improve olfaction, nasal obstruction, and, as a consequence, patients' overall quality of life.

Most studies included in this review were only published in the last 20 years, and the prevalence and exact clinical significance of the differences in trigeminal function in CRS patients is unclear. We attributed this to the lack of a universal and clinically appropriate testing method for trigeminal function. Future studies may further develop the various methods currently in use (Devices that are currently used for clinical trigeminal testing may be reviewed here [35,38], also in Supplementary 1). Hopefully, a standardized and validated testing method for trigeminal function becomes available in the near future.

There have been studies that investigated the morphology of the olfactory epithelium in CRS, showing increased presence of lymphocytes, macrophages, and eosinophils [98], but no similar studies have been done to evaluate the morphology of the nasal mucosa or the intranasal trigeminal nerves in these patients. CRS is an inflammatory disease, but we did not find studies that investigated the relationship of inflammatory biomarkers in mucus, nasal polyps, or nasal mucosa in relation to trigeminal function. There are several important pathways that were determined to be related to CRS: for example, the coagulation pathway [99,100] in relation to fibrinolysis and excessive fibrin deposition in nasal polyps; and the NF-kB pathway that was found to promote olfactory sensory neuron regeneration in early olfactory inflammation, but in chronic inflammation was found to cause this pathway to functionally switch to immune defense [71]. However, we were unable to find studies that investigated any immune-related pathways in the context of trigeminal function in CRS. There were also few studies that compared intranasal trigeminal function among CRS patients in relation to those with other nasal diseases (i.e. allergic rhinitis, acute rhinosinusitis).

The perceived inconsistency of results from various trigeminal tests may indicate the intricacy of interpretation of trigeminal assessment, since it remains unclear whether olfactory and trigeminal assessment may be regarded separately or whether to interpret one requires input from the other. It is possible that although we strive to find a single clinical test for trigeminal function, it may not be as simple as this. Furthermore, the effects of various CRS subtypes with different patterns of inflammation (Type I, II, III) remain

unaccounted for and may also influence varied effects on the trigeminal system, leading to different findings on testing.

Another challenge we identified in this review is that most studies investigating trigeminal function in CRS had low sample sizes, typically less than 50, and some studies did not have control groups. Subsequent studies may look at trigeminal function in a broader sample of participants, including factors such as: causes of olfactory loss, nasal diseases (i.e. AR, CRSsNP, CRSwNP, etc.), aging, and neurodegenerative diseases, among others. It also remains unclear to what degree the impairment of olfaction in CRS may be attributed to trigeminal dysfunction. It would be of interest to explore this and also the effects of existing CRS therapies, including biologics, on trigeminal function.

Based on the current literature, the authors postulate that olfaction and trigeminal functions are synergistic, with both olfactory and trigeminal functions related to odor perception. Trigeminal dysfunction in CRS may likewise have contributions from this proposed olfactory–trigeminal interaction. Furthermore, aside from anatomic obstruction of nasal polyps, trigeminal dysfunction may affect the perception of nasal obstruction in CRS.

Inflammatory responses related to upregulated defense mechanisms leading to permanent damage to trigeminal nerve endings [22], changes in nerve growth factor release [72], or other mechanisms may be responsible for trigeminal dysfunction in CRS, but this requires further investigation. The discovery of the exact mechanisms may have profound implications for diagnosis and management, as it may be more geared toward the different types of inflammation (Type I, II, or III) observed in CRS. Although the pathophysiology of trigeminal dysfunction in CRS is currently poorly understood, the current treatment recommendations are directed toward the treatment of CRS as an underlying cause, with hopes for subsequent trigeminal improvement with disease control.

The paucity of studies may be addressed by the increasing recognition that trigeminal perception goes hand-in-hand with several key symptoms of CRS. Also, a better framework for the pathophysiology of intranasal trigeminal function would also pave the way for improved study designs and testing methods in the future. Adoption of trigeminal function measurement into clinical practice is largely hindered by the limited options for testing, the lack of validated tests with normative values, and the inaccessibility of equipment commercially. The implications of improved trigeminal assessment are potentially far-reaching, hopefully leading to a better understanding of intranasal chemosensation (including both olfaction and trigeminal function) and intranasal peripheral nerve dysfunction, with therapeutic consequences. There is certainly room for collaboration between experts in various fields (Otorhinolaryngology, Immunology, Neurology, Pathology, and Genetics among others). Hopefully, more interest in this topic results in more studies with improved study designs and stronger evidence.

Declaration of interest

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ORCID

Anna Kristina Hernandez http://orcid.org/0000-0001-6711-7359
Thomas Hummel http://orcid.org/0000-0001-9713-0183

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Publication Discussion

What is the current understanding of intranasal trigeminal function in individuals experiencing both olfactory dysfunction and nasal obstruction, such as patients with chronic rhinosinusitis?

Patients with chronic rhinosinusitis were chosen as the sample for this review given that these patients have been reported to experience both OD and nasal obstruction. As such, it would be of interest to explore whether trigeminal dysfunction has been observed or investigated in CRS patients.

Not all studies examined the interaction between trigeminal function, olfaction, and nasal airflow. However, six out of the 16 included studies found a correlation between olfactory and trigeminal measures (range: r = 0.21 to 0.70, using tests such as tERP, TLT, trigeminal threshold test, 7-item olfactory-trigeminal test), as well as overlapping areas of activation on PET scans. A major challenge is that most studies used a bimodal stimulus, making it uncertain how much of the sensations were due to olfactory versus trigeminal stimulation (see Table 5 in Study 2). Furthermore, comparisons between the studies were restricted by the varying methods of testing used, and the generalizability of conclusions was limited by the low sample sizes of patients with CRS.

Although Savic et al. found brain regions that were activated by both olfactory and trigeminal stimuli in healthy individuals, specific areas were especially activated by trigeminal stimuli, namely: the anterior cingulate gyrus, brainstem, thalamus, somatosensory cortices, and the cerebellum (Savic et al., 2009; Albrecht et al., 2010; Hummel and Frasnelli, 2019). Interestingly, however, the difference in areas activated in healthy individuals and patients with anosmia in the study by Savic et al. (which included CRS patients) supports a similar finding by Iannilli et al. where controls had stronger activation after stimulation with CO_2 in the right prefrontal cortex, right somatosensory cortex, and left insula compared to those with anosmia (Iannilli et al., 2007; Savic et al., 2009). Conversely, those with anosmia had higher activations in the left supplementary motor area of the frontal lobe, right superior and middle temporal lobes, left parahippocampal gyrus, and the sub-lobar region of the left putamen and right insula. Common to both groups were activations in the cerebellum and right pre-motor frontal cortex (Iannilli et al., 2007). These studies, although showing activations in different brain areas (likely due to the differences in stimulus used), both show that central trigeminal processing may be functionally reorganized in patients with impaired olfaction.

Research on the relationship between trigeminal function and various causes of olfactory loss was limited, especially when also concerning studies that also included CRS patients. A recurrent challenge is the small number of CRS patients in these studies. For example, Huart et al. included 20 CRS patients and 25 patients with other types of ODs, while Migneault-Bouchard et al. included 31 CRS patients and 147 patients with other types of ODs. Furthermore, these studies used different stimuli for the TLT: Huart et al. used 50% menthol with propylene glycol in syringes, whereas Migneault-Bouchard et al., used 99% eucalyptol in squeeze bottles. These methodological differences complicate the interpretation of results across studies.

In addition, both studies used bimodal stimuli, making it difficult to isolate the effects of olfaction from trigeminal responses. Although Huart et al., stated their attempt at instructing patients to focus more on trigeminal sensations instead of the odors, using a purely trigeminal stimulus like gaseous CO_2 would be more definitive.

When it comes to nasal airflow, it is essential to differentiate between the actual volume of air entering the nose (*airflow*) and the degree of openness (*patency*) or blockage (*obstruction*) of the nose. In the study by Savic et al., no significant differences were found in respiration patterns between those with anosmia and controls, suggesting similar volumes of air inhaled and exhaled during presentation of different stimuli (acetone, vanillin, androstadienone, and estratetraenol). However, when it comes to the perception of nasal patency, the studies of Saliba et al., and Poletti et al., found that CRS patients rated their nasal patency as worse than how controls rated themselves (Saliba et al., 2016; Poletti et al., 2017).

Interestingly, Saliba et al. also measured nasal airflow in CRS patients using PNIF and found normal levels despite having reported worse nasal patency. In addition, CRS patients also had significantly lower scores on the TLT compared to controls (Saliba et al., 2016). This suggests that trigeminal dysfunction may contribute to the subjective perception of nasal obstruction in CRS patients. However, this finding requires confirmation from a larger sample, as the study only included 14 CRS patients.

The inconsistent and mixed results from various studies on the interaction of trigeminal function with olfaction and nasal airflow highlight the complexities of conducting and interpreting trigeminal assessments. It remains unclear whether olfactory and trigeminal assessment can be separated or if interpreting each requires considering the other. In addition, for CRS patients, it is still unknown how different CRS subtypes with varying

inflammatory patterns (Type I, II, III) affect the trigeminal system. This review demonstrates the challenges in consolidating findings on trigeminal function in CRS patients due to differences in methodology, low sample sizes, and the lack of control groups.

Hypothesis: Mechanism

It has been documented how chronic inflammation adversely affects the olfactory system at the periphery through increased neuronal cell death, impaired neurodegeneration, and mucosal changes (Chen et al., 2019). Since is unknown to what degree the trigeminal and olfactory systems interact, we propose that chronic inflammation might also result in a similar failure of regeneration or increased trigeminal neuronal cell death. Mucosal changes such as edema or nasal polyps may also alter the mucosal surface area having functional trigeminal nerves; which in turn, also decrease the viable surface area for effective mucosal heat exchange, resulting in the perception of nasal obstruction. Ultimately, the loss of amplification from lateral excitation of trigeminal nerves by olfactory stimulation at the periphery and the decreased competitive inhibition by olfactory stimuli at the brainstem may result in lower central amplification of already lower peripheral signals due to decreased trigeminal nerves at the periphery. This results to a net decrease of trigeminal function in CRS (Figure 7).

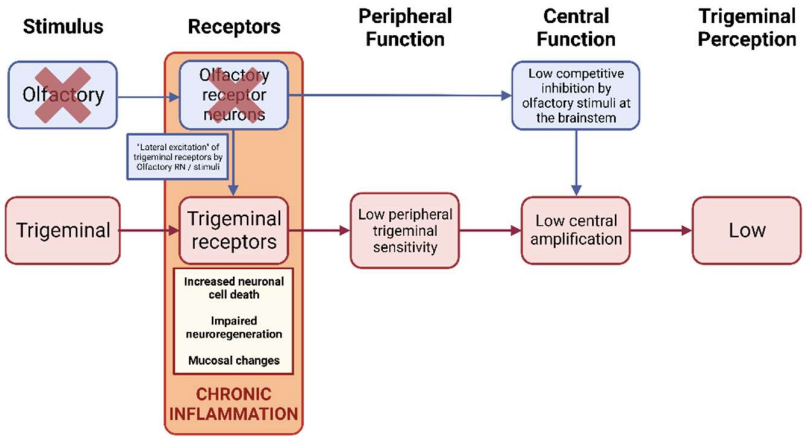

Figure 7. Theory on Olfactory and Trigeminal Interaction in Chronic Inflammation. (From Figure 4 in (Hernandez and Hummel, 2023)*).*

Based on what we already knew from these previously discussed studies, we proceeded to investigate how intranasal trigeminal function was related to perceptions of subjective nasal obstruction, objective measurements of nasal airflow, and olfactory function in a sample CRS patients and controls with non-nasal complaints.

Publication 3: Objective Nasal Airflow Measures in Relation to Subjective Nasal Obstruction, Trigeminal Function, and Olfaction in Patients with Chronic Rhinosinusitis

Hernandez AK, Uhl C, Haehner A, Cuevas M, Hummel T.

Rhinology. 2024; 62(4):394-402. doi:10.4193/Rhin23.270

Abstract

Background: This study aimed to determine how nasal airflow measures and trigeminal function vary among patients with chronic rhinosinusitis (CRS) versus healthy controls and whether these measures are correlated with subjective nasal obstruction (SNO), olfactory function, and CRS control.

Methodology: Participants included CRS patients and healthy controls. After a structured medical history, nasal airflow (peak nasal inspiratory flow [PNIF]; active anterior rhinomanometry [AAR]), trigeminal function (trigeminal lateralization test, CO_2 sensitivity), and olfactory ("Sniffin' Sticks" odor identification test) tests were performed. SNO ratings were also obtained.

Results: Sixty-nine participants were included (37 men, 32 women, mean age 51 years). There was no significant difference for objective nasal airflow between patients and controls, but CRS patients had worse SNO, trigeminal function, and olfaction compared to controls. SNO, but not objective nasal airflow tests, was negatively correlated with CO_2 sensitivity and odor identification.

Conclusion: The perception of nasal obstruction does not only depend on nasal airflow, but may also be modulated by trigeminal function and other factors. Thus, the role of objective nasal airflow measures as a sole method of functional nasal obstruction assessment in CRS remains limited.

Objective nasal airflow measures in relation to subjective nasal obstruction, trigeminal function, and olfaction in patients with chronic rhinosinusitis

Anna Kristina Hernandez[1,2,3], Caroline Uhl[1], Antje Haehner[1], Mandy Cuevas[1], Thomas Hummel[1]

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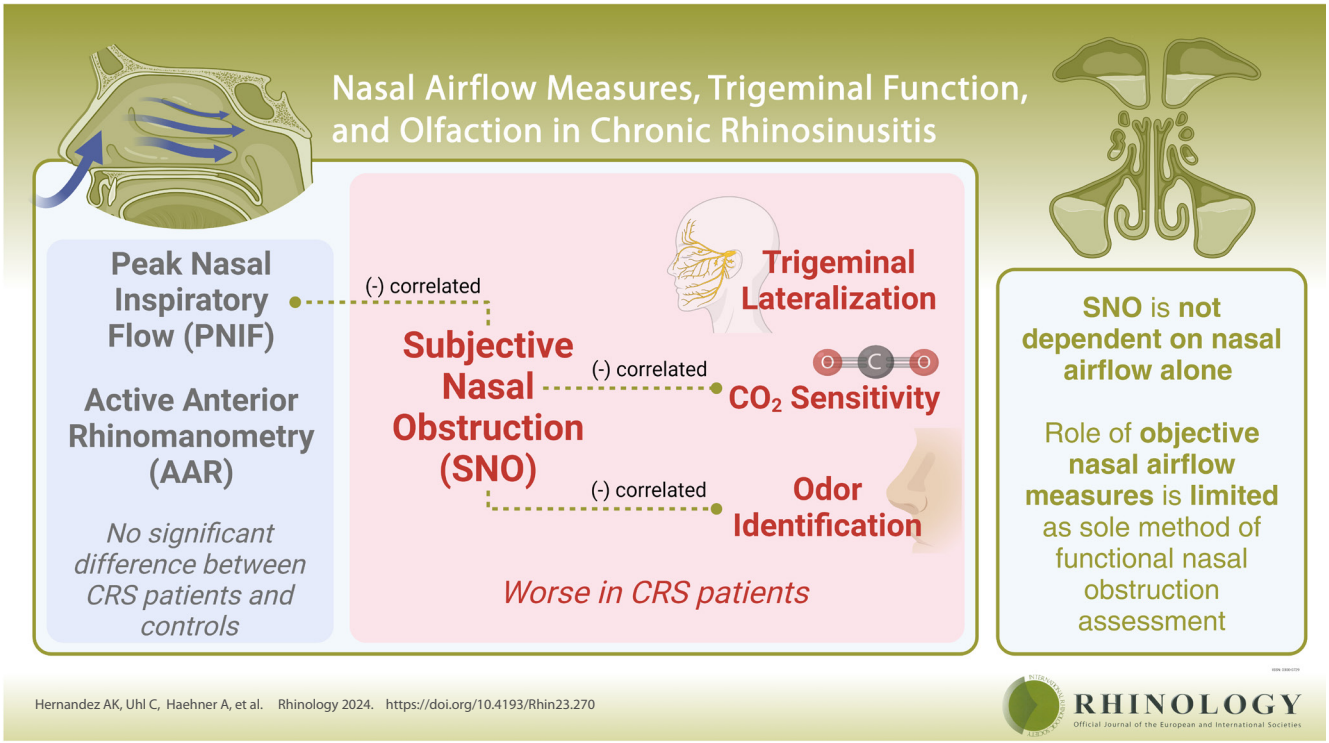

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Key words: nasal obstruction, sinusitis, nasal polyps, trigeminal nerve, rhinomanometry

Introduction

Chronic rhinosinusitis (CRS) affects 5-12% of the general population [1]. The presence of nasal obstruction and loss of smell are common symptoms that are associated with decreased quality of life (QoL) in patients [1–3]. Although fewer studies have focused on trigeminal function in CRS, there is evidence to support impairment in these patients [4–9].

Various studies have investigated nasal airflow [10–12], trigeminal function, and olfaction in CRS, but often only in isolation or in pairs. To our knowledge, only one study investigated these three parameters in CRS patients. Saliba et al. [7] performed nasal airflow, trigeminal, and olfactory tests in CRS patients without nasal polyps (CRSsNP). They found no significant differences in objective nasal airflow (measured using peak nasal inspiratory flow [PNIF]) and olfactory measures between patients and controls in their study. However, CRS patients reported worse subjective nasal obstruction and had decreased trigeminal sensation, and trigeminal sensation was proposed to modulate the sensation of nasal obstruction [7]. The sample size in their study was quite low, with only 14 CRS patients included.

Despite evidence showing a relationship between CRS and trigeminal function [5–9,13,14], as well as olfactory sensitivity and nasal airflow [1,15–17], complete psychophysical or objective tests for these parameters are more likely to be performed only during specialist consultations. Although anatomic nasal patency may be determined through nasal endoscopy, the European Position Paper on Rhinosinusitis and Nasal Polyps 2020 (EPOS 2020) guidelines made no explicit recommendations for objective nasal airflow testing (PNIF; active anterior rhinomanometry, AAR; or acoustic rhinometry) in CRS [1]. Moreover, the same guidelines did not elaborate on recommendations for trigeminal testing in CRS (1). Objective evaluation of nasal airflow may require instruments or equipment [18] that are not as easily accessible when compared to simply asking patients to give ratings or answer questionnaires. Furthermore, nasal obstruction in CRS has been hypothesized to be associated with decreased trigeminal function [7,9]. It is of interest to know the relationship between trigeminal function and nasal airflow and whether the former may be used to predict the latter among CRS patients.

Our study aimed to determine how nasal airflow and trigeminal function measurements vary between patients with chronic rhinosinusitis (CRS) and healthy controls and whether these measures correlate with subjective nasal obstruction (SNO), olfaction and disease severity.

Materials and methods

This cross-sectional study was approved by the Institutional Review Board of the University Hospital Dresden and was conducted according to the principles in the Declaration of Helsinki. All participants provided their written informed consent.

Participants

The study included adults (≥18 years), diagnosed with CRS based on the EPOS 2020 guidelines and admitted for surgery (CRS patients) and patients who consulted for non-nasal complaints (controls) at the University Hospital Dresden. Structured medical history was taken, including age, gender, previous nasal surgery (including the number and types of previous nasal surgeries), and rescue medications (intranasal corticosteroids ± biologics). CRS control (disease severity) and SNO ratings (see below) were also obtained.

CRS control score

To better understand the degree of disease severity among the CRS patients, we opted to estimate disease control using the following variables based on the EPOS 2020 guidelines on CRS control [1]: 1) Nasal symptom count (based on scores from items 1 [nasal obstruction], 3 [rhinorrhea], 10 [smell loss], 12 [facial pain/pressure], and 13 [sleep problems] of the Sinonasal Outcome Test-20 German Adapted Version [SNOT-20 GAV], where a score of ≥3 (moderate problem) would correspond to 1 point for each item; 2) Nasal polyp scores (Lildholdt or Lund Kennedy, taken bilaterally), where scores ≥2 would correspond to diseased mucosa, also corresponding to 1 point; 3) Rescue medications currently used, where one needed (at least) 1 course of rescue treatment (intranasal corticosteroids [mometasone or budesonide], biologics or both) corresponding also to 1 point. A sum of ≥3 out of the 7 variables was considered as uncontrolled CRS. Greater than 1 but <3 was considered as partly controlled CRS and 0 was controlled CRS.

Subjective nasal obstruction rating

Based on the work by Piccirillo et al. [19], a validated German translation of the 20-item Sinonasal Outcome Test [20] was administered to participants. This included items about rhinologic symptoms and overall QoL. Participants were instructed to rate each symptom from 0 (no problem) to 5 (problem as bad as it can be), to better illustrate the severity of the symptoms. Only the ratings for question 1 (SNO) were used in the analysis.

The following measures were also determined: PNIF and AAR (before and difference after decongestion; nasal airflow), trigeminal lateralization test and CO_2 sensitivity (trigeminal function), "Sniffin' Sticks" odor identification test (olfaction).

Peak Nasal Inspiratory Flow

Peak nasal inspiratory flow (PNIF) is a measure of nasal airflow (in l/min) using an inspiratory flow meter (Order number 3109750; Clement Clarke Int. Ltd., Harlow, UK). The test was done twice,

with each participant asked to inhale deeply through both nostrils with their mouths closed each time. The higher value of the two attempts was recorded.

Active Anterior Rhinomanometry

Active anterior rhinomanometry (AAR) measures nasal airway resistance from airflow and pressure readings. Using the Rhino-Sys system (Happersberger Otopront GmbH, Hohenstein, Germany), a probe was secured over one of the nostrils while the nose and mouth were covered with a mask attached to the device. Measurements (in ml/s) were done according to manufacturer recommendations and correspond to the total volume of air through the left and right nasal cavities during the inspiratory phase of the respiratory cycle at a trans-nasal pressure difference of 150 Pa) before decongestion (AAR B Before Decongestion with Xylometazoline hydrochloride), after decongestion (AAR B After Decongestion) and the difference between after and before decongestion (AAR B Change) were included in the analyses.

Nasal cycle

To control for the impact of the nasal cycle, all measurements of nasal airflow were noted as the sum of scores for both nostrils. A previous study by Gungor [21] found no correlation between VAS ratings for nasal patency and the nasal volumes or cross sectional areas during the nasal cycle and that the sum of the left and right volumes and areas were quite constant. Thus, the same method was applied in this study.

Trigeminal Lateralization Test

Using 2 squeezable polypropylene bottles pressed simultaneously using a device [22], puffs of air were delivered into both nostrils. One bottle contained 10 ml of 99% Eucalyptol (order number C80601; Sigma Aldrich, Taufkirchen, Germany) while the other bottle contained only air. Participants were asked to identify which side of the nose was presented with Eucalyptol (total of 20 presentations with randomized selection of stimulated nostril, interstimulus interval: 20 s). The sum of correct lateralizations comprised the score (highest: 20).

CO_2 sensitivity

Participants were presented with 100% CO_2 in both nostrils (airflow: 200 ml/min) using a nasal cannula and were asked to press a button when the stimulus was perceived. Until then, the stimulus duration increased by 100 ms steps at an interval of 8 s. Maximum stimulus duration was 2000 ms. A "CO_2 threshold" corresponded to the duration where participants were able to perceive the stimulus and was determined using a staircase method with seven turning points. For statistical analysis, the scores were multiplied by -1 for ease of interpretation and were subsequently referred to as "CO_2 Sensitivity", with a lower number corresponding to worse function.

"Sniffin' Sticks" 16-item Odor Identification Test

In the "Sniffin' Sticks" odor identification test (Burghart Messtechnik, Holm, Germany [23,24]), devices similar to felt tip pens filled with common odors were presented to participants at a distance of approximately 2 cm in front of both nostrils. They were asked to identify the odor from a selection of 4 verbal descriptors. The sum of correct answers comprised the score, ranging from 0 to 16 (highest).

Data collection and statistical analysis

Patient records were assigned codes and anonymized. Data were analyzed using SPSS software (Version 28.0; IBM Corp., Armonk, NY, USA). Independent sample t-test, Pearson's r correlation, chi-square test, and Fisher's exact test were used in the analysis of the data, with a p-value of <0.05 considered as significant.

Results

Sixty-nine participants were included (37 men, 32 women; age 28 to 76 years, mean 51 years). There were no significant differences in age, but there was a significant association between gender and group (patient/control group, $\chi_{(1,69)}=4.05$, $p=0.04$); and between previous surgery and group, with more patients having previous nasal surgery (Fisher's exact test, $p<0.001$); between asthma and group, with more controls not having asthma (Fisher's exact test, $p<0.001$). Means, medians, and frequencies are shown in Table 1.

Group differences for objective nasal airflow and trigeminal measures

There were no significant differences in PNIF and AAR measurements in CRS patients and controls. However, CRS patients had worse SNO ratings ($t_{64}=3.55$, $p<0.001$), lower trigeminal lateralization scores ($t_{67}=2.07$, $p=0.04$), decreased CO_2 sensitivity ($t_{56.96}=4.45$, $p<0.001$), and lower odor identification scores ($t_{48.46}=6.25$, $p<0.001$) compared to controls.

Correlation between the different objective nasal airflow measures and SNO

PNIF was positively correlated with AAR B After Decongestion ($r_{62}=0.28$, $p=0.03$), but not with AAR B Before Decongestion or AAR B Change. AAR B Before Decongestion was positively correlated with AAR B After ($r_{63}=0.77$, $p<0.001$) and negatively correlated with AAR B Change ($r_{63}=-0.47$, $p<0.001$). SNO ratings were negatively correlated with PNIF ($r_{65}=-0.26$, $p=0.04$) but were not correlated with AAR (Figure 1).

Correlation of nasal airflow measures with trigeminal function and olfaction

PNIF and AAR were not correlated with trigeminal and olfactory

Table 1. Means, medians, and frequencies of clinicodemographic variables.

	Frequency (n, %)			Mean (SD)			p-value
Variables	**With CRS**	**Without CRS**	**Total**	**With CRS**	**Without CRS**	**Total**	
Clinical-demographic							
Age				54.4 (13.1)	47.9 (14.0)	51.4 (13.8)	0.05
Gender							
Men	24 (34.8%)	13 (18.8%)	37 (53.6%)				0.04*
Women	13 (18.8%)	19 (27.5%)	32 (46.4%)				
Groups	37 (53.6%)	32 (46.4%)	69 (100%)				
Asthma							
Yes	19 (27.5%)	2 (2.9%)	21 (30.4%)				<0.001*
No	18 (26.1%)	30 (43.5%)	48 (69.6%)				
Previous Nasal Surgery							
Yes	37 (53.6%)	3 (4.3%)	40 (58.0%)				
Endoscopic Sinus Surgery (ESS)	17 (24.6%)	0 (0%)	17 (24.6%)				
Septoplasty	4 (5.8%)	3 (4.3%)	7 (10.1%)	1.8 (1.4)	0 (0)+	1.0 (1.3)	<0.001*
ESS and Septoplasty	5 (7.2%)	0 (0%)	5 (7.2%)				
Unknown or others	4 (5.8%)	0 (0%)	4 (5.8%)				
No	7 (10.1%)	29 (42.0%)	36 (52.2%)				
Rescue Medications							
INCS	20 (29.0%)	0 (0%)	20 (29.0%)				
Mometasone	19	0	19				
Budesonide	1	0	1				
INCS + Omalizumab	1 (1.4%)	0 (0%)	1 (1.4%)				<0.001*
None	16 (23.2%)	32 (46.4%)	48 (69.6%)				
CRS Control Score							
Uncontrolled	23 (62.2%)						
Partly Controlled	12 (32.4%)			3.53 (0.9)			
Controlled	0 (0%)						
Unknown	2 (5.4%)						
Nasal Airflow							
PNIF				124.7 (51.4)	125.6 (46.8)	125.1 (48.9)	0.94
AAR B Before Decongestion				832.4 (456.7)	801.4 (487.8)	817.1 (468.7)	0.80
AAR B After Decongestion				984.3 (443.1)	994.9 (404.5)	989.5 (421.1)	0.92
AAR B Change				151.9 (312.2)	193.6 (304.3)	172.4 (306.6)	0.59
Trigeminal							
Trigeminal Lateralization				15.7 (2.8)	17.2 (3.0)	16.4 (3.0)	0.04*
CO_2 Sensitivity				-1648.4 (448.0)	-1076.5 (596.3)	-1383.2 (592.4)	<0.001*
Olfactory							
Odor Identification				9.1 (3.5)	13.1 (1.4)	10.9 (3.4)	<0.001*
Quality of Life							
Subjective Nasal Obstruction Rating				2.0 (1.3)	1.0 (0.9)	1.5 (1.2)	<0.001*

INCS: Intranasal corticosteroids; PNIF: peak nasal inspiratory flow, AAR: rhinomanometry, B: bilateral, Change: difference between after and before decongestion; CO_2: Carbon dioxide; * statistically significant, $p<0.05$; + Variable was not normally distributed based on skewness and kurtosis [58], thus data was reported as Median (IQR: Interquartile Range).

function. However, SNO ratings were negatively correlated with CO_2 sensitivity (r_{66}=-0.34, p=0.01) but not with trigeminal lateralization (Figure 1). In addition, SNO was also negatively correlated with odor identification (r_{63}=-0.38, p=0.002), and positively correlated with CRS control (r_{34}=0.64, p<0.001) scores, as well as the number of previous surgeries (r_{66}=0.33, p=0.01).

Exploratory subgroup analyses (Figure 2)

Mild nasal obstruction versus severe nasal obstruction (SNO ratings)

When looking at participants who rated nasal obstruction as less problematic (0 to 1, n=36) versus very problematic (4 to 5, n=5), those who reported severe nasal obstruction had lower

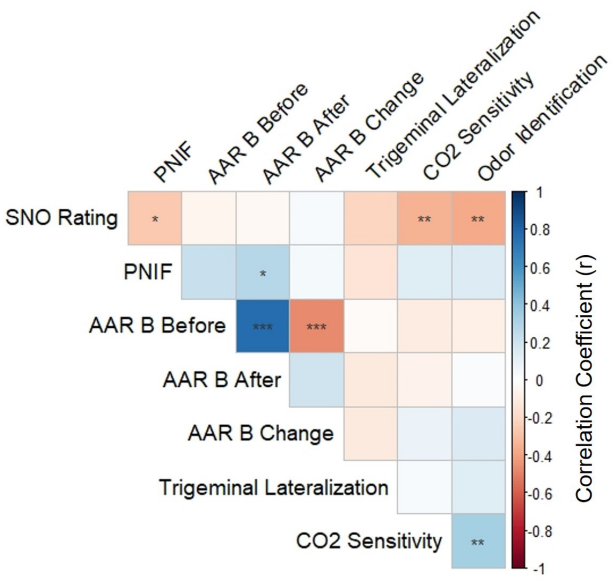

Figure 1. Correlations between subjective nasal obstruction ratings, objective nasal airflow, trigeminal function, and olfactory tests. Box colors correspond to direction and strength of correlation (blue: positive correlation, red: negative correlation, darker colors denote stronger correlation); * p < 0.05, ** p < 0.01, *** p < 0.001; SNO Rating: Sinonasal Outcome Test-20 German Adapted Version Question 1 [Nasal Obstruction] Rating, PNIF: peak nasal inspiratory flow, AAR: rhinomanometry, B: bilateral, Before: before decongestion, After: after decongestion, Change: difference between after and before decongestion; CO_2: Carbon dioxide.

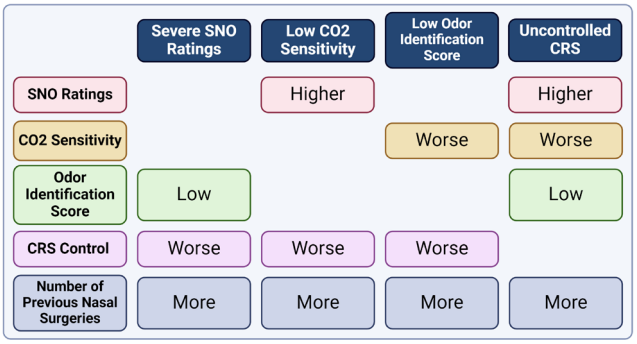

Figure 2. Exploratory subgroup analyses. SNO: subjective nasal obstruction; CO_2: Carbon dioxide; CRS: chronic rhinosinusitis; Severe SNO rating: ≥4; Low CO_2 sensitivity: <-1556ms, Low odor identification score: ≤10, Uncontrolled CRS: ≥3 points in the CRS control score; results of trigeminal lateralization subgroup analysis was not included in the figure due to non-statistically significant findings.

odor identification scores (t_{38}=2.86, p=0.01), worse CRS control (t_{36}=6.46, p<0.001) and more previous surgeries (t_{39}=2.35, p=0.02). There were no significant differences for any of the objective nasal airflow measures or trigeminal function tests between these groups.

Low vs. normal trigeminal lateralization scores

When comparing participants' trigeminal lateralization scores and dividing them based on the cut-off of <15 as low, ≥15 as normal [25], there were no significant differences for any of the objective nasal airflow measures, SNO ratings, CO_2 sensitivity, odor identification scores, CRS control scores, or number of previous surgeries.

Low vs. normal CO_2 sensitivity

Based on a previous publication [26], CO_2 threshold values greater than the 90th percentile (1556 ms, n=99) in their sample indicated poor CO_2 sensitivity and this was used to classify the participants into 2 groups (<-1556 as low, ≥-1556 as normal). There were no significant differences for any of the nasal airflow measures or for trigeminal lateralization between the groups. Those with low CO_2 sensitivity had higher SNO ratings (t_{64}=3.17, p=0.002), lower odor identification scores (t_{64}=2.62, p=0.01), and more previous surgeries (t_{67}=2.02, p=0.047).

Low vs. normal odor identification score

Odor identification scores are regarded to be low if ≤10 [24]. There were no significant differences for any of the nasal airflow measures or for trigeminal lateralization between the groups. However, those with low odor identification scores had worse CO_2 sensitivity ($t_{49.72}$=2.60, p=0.01), and more previous nasal surgeries ($t_{24.77}$=3.89, p<0.001).

Uncontrolled versus partly controlled CRS

Only 12 patients had partly controlled CRS, 23 had uncontrolled CRS, while 2 had unknown control status. Those with uncontrolled CRS had lower PNIF ($t_{13.24}$=2.42, p=0.03), higher SNO ratings ($t_{35.71}$=4.16, p<0.001), and lower odor identification ($t_{30.1}$=4.84, p<0.001) scores. However, there were no significant differences for AAR, trigeminal function measures, and number of previous nasal surgeries.

Severe nasal obstruction patients: described

Only 5 patients rated their nasal obstruction as 4. None of the patients rated their nasal obstruction as 5. Three patients had low PNIF (<120 [27]), 4 had low AAR Before (taking the mean of measurements for both sides of the nose, (normal: ≥700 [28,29]), 1 had a low trigeminal lateralization (<15 [25]) score, 4 had low CO_2 sensitivity (low: <-1556 [26]), 3 had low odor identification (low: ≤10 [24]), all had uncontrolled CRS, 4 were women, 4 had asthma, all had at least 1 previous surgery with 3 having had previous nasal polyp surgery.

Discussion

Nasal airflow, trigeminal function, and olfaction may all be af-

fected in CRS. However, this study supports the following key findings: 1) objective nasal airflow measurements were not different between CRS patients and controls, while trigeminal function was decreased in CRS patients; 2) objective nasal airflow measures were not correlated with trigeminal or olfactory tests, while SNO ratings were correlated with more variables, including PNIF, CO_2 sensitivity, odor identification, CRS control score, and number of previous nasal surgeries.

Nasal obstruction is a core symptom of CRS [1] and may be assessed using patient reported outcome measures (PROM, i.e. SNOT-22 [30], a more recent version of SNOT-20 GAV) and objective measures (PNIF, AAR, and acoustic rhinometry) in the clinical setting [31]. SNOT-22 has been routinely used in to assess CRS patients' quality of life and the outcome of surgical intervention. Although it has been regarded as the highest quality validated PROM in adult CRS patients [32], the definitive role of objective nasal airflow measures in CRS remains unclear [1], especially as these tests may inherently have limitations (see below) and are often reserved for use in research settings [31].

PNIF measures the maximum volume of nasal airflow during deep inspiration. AAR was used to measure the total volume of air through the left and right nasal cavities taken on 2 separate measurements and not as a measure of nasal resistance at 150 Pa, as what other published studies have done. According to a study by Vogt et al., the application of the parameter of 150 Pa in resistance computations is physically and mathematically incorrect when applied to an unsteady airstream that quickly changes velocity and direction due to the irregular nasal anatomy [33]. When AAR is performed with nasal decongestion, this allows the investigation of anatomic structures related to nasal resistance, but may dampen the influence of mucosal changes as is experienced in daily nasal breathing. Accurate measurement of both tests depends on an airtight seal around a mask placed over the nose and mouth, tight lip closure, avoidance of nasal vestibular collapse (PNIF) or alteration of nasal opening when pressure probe is secured (AAR), good pulmonary function, and patient cooperation for maximal inspiratory effort. PNIF measurements are highly reproducible and testing is quick and easy to perform using portable and inexpensive equipment [34]. However, the unnatural breathing pattern (deep and rapid inhalation) may not parallel physiologic breathing. On the other hand, conditions for AAR testing (humidity, temperature, comfortable seating, positioning, etc.) must be standardized [35] and a computer is required to operate the equipment, making transportation around a clinic or hospital impractical [34].

To the best of our knowledge, our study is the first to compare 2 objective nasal airflow measures in a sample of CRS patients and controls. Previous studies have found a negative correlation between SNO ratings and PNIF [11,27,36] but not AAR [28,37,38], but many of these studies did not include CRS patients [39]. The lack of correlation between these objective nasal airflow measures may indicate that the conduct of testing (PNIF: maximal inspiration in normal birhinal breathing; AAR: normal monorhinal breathing, also influenced by effort) may affect participants' test performance. Although measures to reduce nasal cycle influence were attempted, only after nasal decongestion do AAR measures correlate with PNIF. Decongestion typically results to a nasal airflow increase of approximately 20% [29,40], possibly explaining how AAR B After Decongestion could be correlated to PNIF performed at maximal inhalation. This shows that the influence of the nasal mucosa and the nasal cycle on objective nasal airflow measures should not be underestimated.

Although both PNIF and AAR measure nasal airflow volume, it is also likely that the volume of air going through the nose may not be the most significant factor, nor the best measure to approximate the perception of SNO. Similar to what was highlighted in a letter by Nivatvongs et al. [41], the relationship between subjective symptoms and physiological variables is complex and may help explain the lack of correlations with objective nasal airflow measures and more correlations with SNO. Physiologic abnormalities, as in objective tests of nasal airflow or psychophysical trigeminal function, help explain only one aspect of the complete understanding of symptom burden and quality of life, where patient factors such as previous experience, cultural expectations, age, socio-economic status, and co-morbidities may interact and contribute to the subjective perception of disease and its severity [41]. The multifactorial nature of an individual's perception of nasal obstruction is evident in our findings through the correlation of SNO ratings with measures of nasal airflow, trigeminal and olfactory function, and disease severity (CRS control and number of previous nasal surgeries).

We hypothesize that subjective nasal obstruction may be modulated by: 1) volume of nasal airflow; 2) trigeminal dysfunction; 3) location of obstruction; 4) mucosal heat exchange, and 5) increased work of breathing – among others.

Volume of nasal airflow

Physiologic breathing involves nasal airflow of up to 500 ml/s [42]. Increased physical activity may increase required airflow up to >1 liter, requiring supplementation with mouth breathing [42]. When the nose is obstructed in CRS due to mucosal changes (nasal polyps), or increased nasal secretions and the physiologic volume of nasal airflow is not achieved, this may contribute to the perception of nasal obstruction.

Trigeminal dysfunction

CRS patients have been found to have decreased trigeminal

function [5–9, 43–45] but the exact mechanism on how it relates to nasal obstruction is unknown. However, mucosal cooling [46,47], TRP channel activation leading to a cascade of proinflammatory cytokine release [48–50], and a reduction in TRPM8 sensitivity [7,9,51], as well as post-surgical dysfunction after functional nasal surgery [45] have been proposed to explain the perception of nasal obstruction in CRS.

Location of obstruction

The nasal valve is the narrowest area of the nasal airway [52] and any compromise to the structural support of the valve or the adjacent structures (nasal septum, upper lateral cartilages, inferior turbinate), or an anatomic obstruction in this area is likely to result in the perception of nasal obstruction [42,53].

Mucosal heat exchange

A study by Zhao et al. found that when air temperature was constant, humidity of inspired air modulates the perception of unilateral nasal patency. Instead of static air temperature, it was related to the interaction between an individual's nasal anatomy and the inspired airflow, where varying mucosal heat loss would result in different experiences of nasal patency [47]. Mucosal changes in CRS can lead to alterations in viable surface area for effective for heat exchange [22].

Increased work of breathing

It was proposed by Vogt et al., that the sensation of force required for the work of nasal breathing follows the logarithmic scale of Weber-Fechner, where subjective sensation is proportional to the logarithm of the original force required for nasal breathing [33]. The nasal cavity also has the ability to compensate to ensure adequate airflow is achieved. When resistance is higher despite the absence of physical activity, the required effort for nasal breathing increases until additional mouth breathing or total mouth breathing is required to achieve adequate airflow [42]. This provides additional signals that nasal obstruction is present.

Information related to trigeminal stimulation passes through the trigeminal nucleus, brainstem, and to cortical areas [54] that are shared with the olfactory system [55]. A previous study by Chao et al. showed that olfactory (phenyl ethyl alcohol, PEA) and mixed olfactory-trigeminal (menthol) stimuli mediated the perception of nasal patency and those with better olfaction reported greater nasal patency after PEA exposure [56]. Although it has been hypothesized that cognitive processes, specifically related to emotion, may contribute to the perception of nasal obstruction in empty nose syndrome [54], it is unknown to what degree central processing and integration of sensory information influences this perception. The correlations between SNO, trigeminal and olfactory function appear to be in support of some interaction between these senses. In CRS patients complaining of nasal obstruction but having unremarkable nasal endoscopic findings, it is important to include a trigeminal function test in the assessment of nasal obstruction.

The similarity in the qualities of the 5 patients with severe SNO ratings affirms that SNO is multifactorial and may be more distinct in severe disease. Trigeminal function or nasal airflow tests should not be used in isolation to evaluate nasal obstruction. Although PNIF may be more practical for routine clinical use; and CO_2 sensitivity, through the CO_2 threshold test, may be a more specific trigeminal test (compared to trigeminal lateralization that also has an olfactory component and has not been validated to account for adaptation [57]), our findings emphasize the importance of performing both subjective and objective measures and correlating the findings from each when assessing nasal obstruction.

Limitations of the study relate to sample composition, with most CRS patients having previous nasal surgery. Future studies may explore these interactions in a larger sample of patients with heterogeneous distribution of previous nasal surgery and severity of disease.

Conclusion

The perception of nasal obstruction does not appear to depend solely on nasal airflow. Trigeminal function, location of obstruction, mucosal heat exchange, as well as increased work of breathing, among other patient factors, may contribute to one's perception of nasal obstruction; thus, the role of objective nasal airflow measures as a sole method of assessment of nasal obstruction in CRS remains limited and would benefit from additional information from trigeminal function tests and SNO ratings.

Authorship contribution

AKH: data analysis, writing, review, and editing; CU: conceptualization, data collection, review, and editing. AH: conceptualization, supervision, review, and editing. MC: conceptualization, supervision, review, and editing. TH: conceptualization, supervision, review, and editing.

Conflict of interest

The authors do not have any conflict of interest to declare.

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Anna Kristina Hernandez
Smell & Taste Clinic
Department of Otorhinolaryngology
Faculty of Medicine Carl Gustav Carus
TU Dresden
Dresden
Germany

Tel: +49 351 458 4189
Fax: +49 351 458 4326
E-mail:
akmhernandezmd@gmail.com

Anna Kristina Hernandez[1,2,3], Caroline Uhl[1], Antje Haehner[1], Mandy Cuevas[1], Thomas Hummel[1]

[1] Smell and Taste Clinic, Department of Otorhinolaryngology, Faculty of Medicine Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany

[2] Department of Otorhinolaryngology – Head and Neck Surgery, Philippine General Hospital, University of the Philippines – Manila, Manila, Philippines

[3] Department of Otorhinolaryngology – Head and Neck Surgery, Asian Hospital and Medical Center, Muntinlupa, Philippines

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Basile Landis

Publication Discussion

Is intranasal trigeminal function related to the subjective perception of nasal obstruction, objective nasal airflow measurements, and olfactory function in patients with sinonasal olfactory loss? Moreover, can psychophysical trigeminal function tests estimate measured nasal airflow in these patients?

This study had used two distinct methods for assessing trigeminal function and nasal airflow, aiming to determine whether the findings could be replicated across different testing approaches. TLT scores were not correlated with any of the objective nasal airflow measures (PNIF and AAR), olfaction, or the number of previous nasal surgeries. However, CO_2 sensitivity was negatively correlated with SNO ratings and number of previous nasal surgeries ($r_{69} = -0.33$, $p = 0.01$), and positively correlated with odor identification scores.

The results indicate trigeminal dysfunction in CRS patients, demonstrated by decreased CO_2 sensitivity within this group. There was also no significant difference between CRS patients and controls for any of the objective nasal airflow measures. This shows us that, at least in CRS patients with mild to moderate disease, trigeminal dysfunction partly explains the sensation of SNO in the absence of a significant decrease in nasal airflow. Although SNO ratings were weakly negatively correlated with PNIF, our findings indicate that the total volume of nasal airflow may not be the sole factor that determines the perception of nasal obstruction. Instead, this perception of obstruction may be driven more by the dysfunction of other senses that rely on normal nasal airflow, such as the ability to smell or perceive trigeminal stimuli. Unfortunately, it appears that trigeminal function alone should not be used estimate objective nasal airflow because they each measure completely different things. However, trigeminal function (i.e., CO_2 sensitivity) may approximate subjective nasal obstruction and proves to be important to measure, especially in patients still complaining of nasal obstruction despite having a normal volume of nasal airflow.

However, the lack of correlation between the two trigeminal measures may be attributed to differences in the stimuli used and in the methods of conducting the tests. CO_2 is an odorless trigeminal stimulus that is also a TRPV1 agonist. Mean recognition thresholds for CO_2 are possible at 32% v/v (at an airflow of 8 L/min and stimulus duration of 200 milliseconds), while CO_2 could be distinguished from blanks at even lower concentrations (23% v/v) (Hummel and Livermore, 2002). In addition, CO_2 stimulation may result in pre-pain sensations due to low-level excitation of nociceptors (Handwerker and Kobal, 1993; Hummel and Livermore, 2002). On the other hand, the TLT involved the use of eucalyptol, a bimodal stimulus which is a TRPM8 agonist. Although the authors emphasized to participants that

the sensation being tested when using bimodal stimuli relates to trigeminal sensation (i.e., cooling, freshness) and not the odor itself, the effects of the interaction of peripheral and central processing of the bimodal stimulus on performance remains undetermined. Substance P and other peptides released from trigeminal fibers have been shown to modify olfactory receptor responses. In addition, trigeminally mediated nasal reflexes (i.e., nasal congestion, changes in mucus consistency, respiration) may also influence olfactory perception (Hummel and Livermore, 2002). Aside from these differences, the conduct of testing for the two trigeminal measures vary greatly. The TLT is more cognitively demanding as it involves the detection of a bimodal stimulus, discrimination of the stimulus from air, identification of the side of stimulation, and the proper communication of this laterality by raising the appropriate limb. In contrast, CO_2 sensitivity mainly relies on the detection of the trigeminal stimulus from a continuous airflow and pressing a button once it has been detected. It may be argued that the TLT, although more easily adaptable in the clinical setting, is a more cognitively demanding task, may approximate other competencies aside from trigeminal function, and may benefit from using a purely trigeminal stimulus. Furthermore, a recent study indicated that a 40-item TLT may be more appropriate for trigeminal testing as tests with fewer items resulted in a greater influence of chance on performance ((Mai et al.), In Press). Ultimately, the use of different stimuli that are agonists of different receptors, coupled with the activation of nociceptors for one stimulus and olfaction for the other, and the differences in the conduct of testing, may explain why results of these tests are not correlated. Essentially, these are 2 different tests that measure 2 different aspects of trigeminal function (pain, cooling + olfaction).

The number of previous nasal surgeries –taken here as a possible indicator of more severe inflammatory disease— indicate that the more surgeries a patient undergoes, the worse their perception of SNO, CO_2 sensitivity and olfaction becomes; and nasal airflow improves less after decongestion. Surgery is often recommended for CRS patients who do not respond adequately to medical treatment and surgical interventions in the anterior part of the nasal cavity are thought to potentially impact trigeminal and olfactory sensitivity by altering intranasal airflow (Masala et al., 2019). However, there is limited research on how intranasal surgery affects trigeminal function and existing studies have some conflicting results. A study by Minovi et al. found that those with severe nasal polyps had a greater improvement in trigeminal scores after surgery, when compared with those having little or no polyps (Minovi et al., 2008). Another study found that trigeminal sensitivity tended to be weaker in patients who had any type of functional nasal surgery, despite having similar olfactory scores, although the sample of this study was small (n = 32, 13 patients and 19 controls) (Migneault-Bouchard et al., 2022). In patients undergoing septoplasty for nasal obstruction,

decreased trigeminal sensitivity was present even before surgery and septal surgery had no effect on trigeminal sensitivity (Scheibe et al., 2014). Empty nose syndrome patients had lower TLT scores and lower “Sniffin’ Sticks” scores, but septoplasty had no significant role in addressing trigeminal or olfactory impairment in these patients (Konstantinidis et al., 2017). In another study, pre-operative TLT scores remained unchanged while mean nasal obstruction VAS ratings improved between baseline and 6 weeks after surgery (septoplasty OR septorhinoplasty ± turbinoplasty) (Bischoff et al., 2020). It seems possible that trigeminal dysfunction may occur in the setting of inflammation or even prior to surgery for nasal obstruction, however, to what degree this function is affected by surgery and the alteration of intranasal structures remains to be determined.

CRS control scores, which approximate symptom control –and also possibly the degree of persistent inflammation– of patients after treatment, indicate that patients who had poorer control after treatment: had lower PNIF; nasal airflow improved more after decongestion; and had worse perception of nasal obstruction. Chronic inflammation leads to the deactivation of olfactory sensory neuron regeneration and a shift to the promotion of epithelial immune defense in mice (Chen et al., 2019). However, it remains unclear whether a similar pathophysiologic mechanism applies to the trigeminal system, where upregulated immune defense mechanisms result in permanent damage of trigeminal nerve endings (Poletti et al., 2017) or changes in the release of nerve growth factors (Millqvist et al., 2005), among others. Taken together, it seems chronic inflammatory changes, as in CRS, play a significant role when it comes to trigeminal dysfunction, nasal obstruction, and OD.

Although only 23 patients had uncontrolled CRS, the preliminary information from this group showed that SNO ratings, CO_2 sensitivity, and odor identification scores were all worse compared to those with partly controlled CRS; and that SNO may be more distinct in severe disease. The perception of nasal airflow is believed to have an underlying neurosensory mechanism (Sozansky and Houser, 2015; Shen et al., 2017) but trigeminal function (or nasal airflow tests) should not be used in isolation to evaluate nasal obstruction. Although PNIF may be more practical for routine clinical use; and CO_2 sensitivity, through the CO_2 threshold test, may be a more specific trigeminal test (compared to TLT that uses a bimodal stimulus), our findings emphasize the importance of performing both subjective and objective measures and correlating the findings from each when assessing nasal obstruction.

Discussion and Outlook

In summary, the findings in the three studies in this thesis show the following:

1) **Interaction between intranasal trigeminal function, olfaction and nasal airflow / obstruction:** Based on psychophysical and objective nasal airflow tests, there is an interaction between intranasal trigeminal function, olfaction, and nasal airflow/obstruction in healthy individuals and CRS patients.
2) **Trigeminal dysfunction in CRS patients:** In patients that experience OD and nasal obstruction (CRS patients), trigeminal dysfunction was also observed. However, comparing results across different studies is challenging due to the lack of standardized and validated methods for assessing intranasal trigeminal function.
3) **Complex olfactory and trigeminal interaction:** A complex interaction exists between the olfactory and trigeminal systems, where the absence of olfactory input may lead to decreased intranasal trigeminal perception. In CRS, chronic inflammation may lead to epithelial or neuronal damage at the periphery, resulting in diminished central amplification of olfactory signals at the brainstem level.
4) **Trigeminal dysfunction and nasal obstruction:** While nasal obstruction in CRS patients is partly influenced by trigeminal dysfunction, this does not fully account for the perception of nasal obstruction. The TLT alone is insufficient for estimating nasal obstruction, as other factors like the location of the obstruction, mucosal heat exchange, increased work of breathing, and other patient-specific factors should also be considered.

Overview: Trigeminal Function, Olfaction, and Nasal Airflow Interactions

Olfactory and trigeminal stimuli differ, such that individuals are typically unable to lateralize selective olfactory stimuli. It is only when a trigeminal component is present, that individuals are able to successfully perform this task (Kobal et al., 1989). Most odors stimulate the trigeminal nerve at higher concentrations (Doty et al., 1978; Cometto-Muñiz et al., 2003; Wysocki et al., 2003; Hummel et al., 2016). Although ipsilateral simultaneous presentation of a pure odorant with a trigeminal stimulus improves localization (Tremblay and Frasnelli, 2018), the intensity of an olfactory stimulus (hydrogen sulfide, H_2S) reduces when co-presented with a selectively trigeminal (CO_2) or bimodal stimulus (carvone) (Livermore et al., 1992). Interestingly, however, the temporal relationship of stimuli appears to be important as the presentation of a trigeminal stimulus before an odor stimulus was also found to improve olfactory sensitivity (Jacquot et al., 2004). As air is inhaled through the nose, it shifts from laminar airflow outside the nasal cavity to more turbulent airflow intranasally. This turbulence

ensures that airflow comes into contact with the nasal mucosa and a portion of this airflow reaches superiorly to the area of the olfactory cleft (Zhao et al., 2004; Sozansky and Houser, 2014; Masala et al., 2019).

Given that several studies investigating trigeminal function had relatively lower sample sizes, we aimed to investigate the correlation of trigeminal function, olfaction and nasal airflow in a larger sample in Study 1. The correlation we found between trigeminal function, retronasal olfaction, and nasal airflow was weak, but these results still support an interaction between the chemical senses and nasal airflow in a larger group. Trigeminal function was not correlated with orthonasal olfaction, but we attribute this more on the nature of screening tests (see also Limitations). In a global study, trigeminal thresholds were correlated with odor thresholds for phenyl ethyl alcohol and to a lesser degree – subjective olfactory function (Oleszkiewicz et al., 2020). In Study 1, however, VAS ratings were not correlated with any of the chemosensory screening tests or with PNIF. Aside from subjective ratings being relatively less reliable, at least in some groups of patients (Landis et al., 2003), these ratings may not also be so useful in a sample of healthy individuals with minimal variability in scores.

Studies 2 and 3 provided evidence in support of a similar interaction between trigeminal function, olfaction, and nasal airflow, among CRS patients – individuals who already typically experience OD and nasal obstruction. However, the varying stimuli used and the differences in the manner of trigeminal function testing made it difficult to contrast results from the few studies present (see Study 2). There have been attempts at isolating only trigeminal function by using selective trigeminal stimuli (e.g., CO_2). However, the intranasal trigeminal system appears to have a complex interaction with olfaction, where one can potentiate and inhibit the other in certain situations. In rats, trigeminal nerve fibers have even been found not only in the respiratory epithelium but branches were also shown to extend to both the olfactory bulb (from V1, (Finger and Böttger, 1993)) and the spinal trigeminal complex in the brainstem (Schaefer et al., 2002). In addition, another study found that a selective trigeminal stimulus (CO_2) may be perceived as more intense when simultaneously presented with an olfactory stimulus (H_2S) compared to when it is co-presented with a bimodal stimulus (carvone) (Livermore et al., 1992). It seems sensible to assess trigeminal function and olfaction together as this configuration also closely resembles daily life (see also Central Integration of Sensory Inputs).

A study by Mainland and Sobel proposed that a sniff (which involves the movement of air into the nose) is not simply a means to bring stimuli into the nose, but is instead a part of the

olfactory (or the intranasal chemosensory, to include trigeminal also) percept (Mainland and Sobel, 2006). Changing various parameters related to sniffing (duration, airflow, volume, frequency) is expected to alter the perception of stimuli. In a pilot study, a shorter duration (200 milliseconds) of intranasal trigeminal stimulation in a TLT resulted in significantly lower scores compared to the averages at longer durations (500 and 600 milliseconds) (Jobin et al., 2021). Furthermore, the perception of airflow during a sniff can also be regarded as a trigeminal mechanosensory stimulation and could also likewise affect olfactory and intranasal chemosensory trigeminal perception. A study that investigated co-presentation of PEA and air puffs (weak: 2 L/min, and strong: 4 L/min) found improved localization for PEA + air puffs as co-presented stimuli compared to its individual components. However, a statistically significant improvement in localization was only observed for mixtures including weak air puffs (Karunanayaka et al., 2024). While the studies included in this thesis demonstrate some degree of interaction, the extent to which airflow and its perception affect chemosensation remains to be fully investigated.

Unstandardized Methods of Trigeminal Assessment

Although interactions between trigeminal function, olfaction, and nasal airflow / obstruction were evident in the three studies in this thesis, the use of different types of tests and stimuli made comparisons between results challenging. An easy-to-perform, practical, clinical intranasal trigeminal test has yet to be developed or validated. Although the TLT has been used extensively in literature as one of the common intranasal psychophysical trigeminal tests, the optimal manner of performing this test has yet to be determined, given that factors such as ISI, duration of stimulus presentation, stimulus concentration, and type of stimulus and choice of negative/neutral stimulus may affect test performance.

The TLT is performed with a bimodal stimulus (typically eucalyptol or menthol) that activates TRPM8 (but may also inhibit TRPA1, (Takaishi et al., 2012; Caceres et al., 2017)) and is considered safe and tolerable despite repeated presentations during testing. Admittedly, by measuring the response to an agonist of a specific TRP ion channel, we are unsure if this provides an accurate estimate of the function of the entire trigeminal system. A recent study by Chen et al. that included 50 participants (19 normosmic, 31 dysosmic) reported that none of the TLT scores for different trigeminal stimuli (eucalyptol, mustard oil, and vinegar) were correlated with each other (Chen et al., 2024). This may indicate that the degree of sensitivity in one type of TRP ion channel may not necessarily be similar to the sensitivity in other TRP ion channels. As mentioned earlier, the activation of different TRP ion channels result in different trigeminal sensations and it has been found that mixtures composed of agonists of different receptors result in more intense sensation and better lateralization

(Frasnelli et al., 2011a). However, presenting mixtures introduces a unique dilemma: when a bimodal stimulus (carvone) and a selective trigeminal stimulus (CO_2) were co-presented in a mixture, the intensity of CO_2 was perceived as lower, while the intensity of carvone was perceived as higher, compared to when each stimulus was presented alone (Livermore et al., 1992). Moreover, tERP latencies for mixtures with CO_2 as a component were shorter than the latencies of any of the individual components (CO_2, carvone and hydrogen sulfide) and that of the mixture of olfactory and bimodal stimuli (Livermore et al., 1992).

In addition, a couple of studies included in Study 2 used propylene glycol (PG, 1,2 propanediol) as a control. PG often serves as a solvent for the dilution of odors and has been regarded as a control for several psychophysical tests. However, a recent study found that PG is recognized at a threshold concentration of 42% ± 28% (n = 15) with reports of a slight cooling sensation (Sirous et al., 2019). ERPs were also performed in this study and a clear P2 component after presentation of PG was noted, which was subsequently localized to originate from the postcentral gyrus, insula, operculum, thalamus, and cerebellum. Based on their findings, the use of PG –especially at higher concentrations— as a neutral stimulus for TLT, warrants further investigation.

Furthermore, repeated stimulation of trigeminal stimuli at short ISIs can produce an increase in rated intensity, which was referred to as “sensitization”. In contrast, if the ISI is long, the perceived intensity can markedly decrease, which is referred to as “desensitization” (Hummel et al., 1994; Brand, 2006). Although initial studies investigating this concept were performed in relation to taste and the oral cavity, intensity ratings and tERP amplitudes for intranasal CO_2 stimulation were also found to be reduced by 30-50% at the shortest ISI (10 seconds) and were largest at an ISI of 90 seconds. This corresponds to what appears to be a “saturation” of trigeminal stimulation at ISIs of less than 10 seconds (Hummel and Kobal, 1999). On the other hand, a longer duration of stimulus presentation may also introduce a similar “saturation” phenomenon, as the trigeminal system has been shown to detect the total number of molecules in a given period, rather than the concentration of a stimulus (Cometto-Muñiz and Cain, 1984; Frasnelli et al., 2017). Individuals cannot consistently lateralize eucalyptol (undisclosed concentration) when it was presented for less than 500 milliseconds, but accuracy increased with longer stimulus duration (Frasnelli et al., 2017). In effect, it may be inferred that a reduced concentration of eucalyptol may be compensated by increasing the duration of stimulus presentation (Wise et al., 2009). In order to come up with a standardized and validated clinical test, the factors that have been mentioned earlier should be considered.

In this thesis, the number of presentations in the TLT varied between 10 and 40 as well. A recent investigation ((Mai et al.), In Press) found that the 10- and 20-item versions of this test had a mean score (in a sample of 194 participants and also including previously published data from 820 participants) that overlapped with scores that one could achieve by chance (based on a binomial distribution, see also (Croy et al., 2014b)). Admittedly, the TLT in both Studies 1 and 3 had presentations of less than 40 and perhaps it would be beneficial to re-investigate these using the 40-item version of the test (see also Limitations).

Trigeminal Function in Olfactory Loss

As it is difficult to separate olfaction from trigeminal function, the effect of olfaction on trigeminal function has been investigated more in patients with olfactory loss. It appears that the absence or reduction of olfactory inputs may contribute to the decrease in intranasal trigeminal perception. OD patients have been found to have lower TLT scores (Hummel et al., 2003; Frasnelli et al., 2007), lower intensity ratings (Frasnelli and Hummel, 2007), and decreased central trigeminal responses (tERP amplitudes) (Hummel et al., 1996; Frasnelli et al., 2007); however, trigeminal function appears to be preserved in those with neurodegenerative (Barz et al., 1997; Tremblay et al., 2019) and congenital OD (Laska et al., 1997). A study of 92 patients with olfactory loss also showed that nasal patency ratings increased more after chewing menthol (for 30 seconds) in individuals with better olfactory function (Schriever and Hummel, 2015). Menthol stimulates TRPM8 and nasal patency ratings could then be taken as an estimate for trigeminal perception. In one study measuring CO_2 sensitivity, trigeminal sensitivity was worse (longer stimulus duration required prior to perception) in patients with olfactory loss (Hummel et al., 2016), but there were no significant differences in trigeminal function due to the different causes of OD (Hummel et al., 2003, 2016). However, in another study measuring trigeminal detection threshold using formic acid, trigeminal thresholds were worse (higher in concentration), specifically greater in post-traumatic OD than in sinonasal OD (Gudziol et al., 2001). The mechanism as to why this impairment is observed in some groups with olfactory loss but not in others is unclear. Although we included a hypothesis to explain this in Study 2, this requires further studies.

Central Integration of Sensory Inputs

A functioning olfactory system seems to be required for normal trigeminal function and this is likewise indicated by significant overlaps in the corresponding brain areas involved in the processing of olfactory and trigeminal information. Specific areas in the brain such as: the left superior temporal, right intraparietal sulcus, left medial and lateral orbitofrontal cortex were activated by an artificial mixture composed of olfactory and trigeminal stimuli (Boyle et

al., 2007a), and that trigeminal stimulation resulted in activations in areas typically related to olfactory processing, namely: ventral insula, middle frontal gyrus, and the supplemental motor area (Hummel et al., 2005); as well as the piriform cortex, anterior orbitofrontal cortex, rostral insula, and superior temporal gyrus (Boyle et al., 2007b). A recent study highlighted that olfactory and trigeminal stimuli need not reach known multisensory-specific brain regions prior to being integrated into a coherent sensory experience. Instead, the primary olfactory cortex (piriform cortex, amygdala, entorhinal cortex) is a site for multisensory integration. The orbitofrontal cortex, superior temporal cortex, inferior parietal cortex, cingulate cortex, and the cerebellum were also involved in the network for multisensory integration (Karunanayaka et al., 2024).

Although most studies used bimodal stimuli and there has always been a desire to isolate trigeminal function assessment by using a selectively trigeminal stimulus such as CO_2 (Huart et al., 2019), an important question to ask is "is it really necessary to take these two systems separately?" Previous studies have shown overlapping cortical activation patterns for trigeminal and olfactory stimuli which are believed to result from the close interconnections involved in processing information from these chemosensory systems (Boyle et al., 2007b, 2007a; Savic et al., 2009). In addition, studies have also found that presentation with a mixture of olfactory and trigeminal stimuli leads to higher cortical activations than the sum of its components (Boyle et al., 2007a; Karunanayaka et al., 2024). From this perspective, it seems reasonable to assess olfactory and trigeminal functions concurrently, as isolating them by using olfactory-specific or trigeminal-specific stimuli would not adequately reflect the dynamic interaction between these two chemosensory systems and would not resemble how these stimuli are often encountered in daily life.

It has been hypothesized that cognitive processes, specifically related to emotion, may contribute to the perception of nasal obstruction in empty nose syndrome (Kanjanawasee et al., 2022). However, it is unknown to what degree central processing and integration of sensory information influences this perception.

Trigeminal Dysfunction Explains Only a Part of Nasal Obstruction

In order for the nose to function properly, it requires the passage of airflow through it. As mentioned earlier, *airflow* (actual volume of air entering the nose), *patency* (how open the nose is based on volume or cross-sectional areas of the nasal cavity), and *obstruction* (blockage) are terms often encountered in literature. However, these three terms differ and each one may not provide a holistic measure for the functional movement of air through the nose which matters the most to patients.

Study 1 showed that in healthy individuals, trigeminal function (10-item TLT) was correlated with PNIF, although relatively weak. This supports the idea that airflow enables trigeminal stimuli to enter the nose and be detected. In Study 2, we observed that in CRS, nasal obstruction may be due to two main factors: 1) mechanical blockage by nasal polyps, edematous mucosa, and thick nasal mucus, and 2) trigeminal dysfunction. Study 3 provided support that trigeminal function was worse in CRS patients despite objective nasal airflow measures being comparable to controls.

Evidence for impaired trigeminal function in groups of patients (i.e., chronic nasal obstruction (Migneault-Bouchard et al., 2021), COVID-19 (Juratli et al., 2024), empty nose syndrome patients (Konstantinidis et al., 2017)), despite having objective or subjective airflow measures being comparable with controls have been reported in the literature. Furthermore, despite attempts to measure functional nasal respiration (using a strain gauge (Savic et al., 2009), PNIF (Saliba et al., 2016), and nasal patency ratings (Saliba et al., 2016; Poletti et al., 2017)), objective measures (strain gauge and PNIF) were often not significantly different between CRS patients and controls, while nasal patency ratings were often worse in patients. This discordance between subjective and objective nasal airflow measurements, which has also been evident in several studies (Eccles and Jones, 1983; Jones et al., 1987; Sipila et al., 1994; Sozansky and Houser, 2014; Saliba et al., 2016; Shen et al., 2017), may be due to the fact that the sensation of nasal patency or obstruction both do not depend only on volume of nasal airflow or nasal resistance. Therefore, objective nasal airway measures, like AAR, AR, and PNIF, have limited usefulness in determining nasal patency or obstruction when used alone.

Although a mechanism to explain the role of trigeminal dysfunction in CRS patients has been proposed in Study 2, we hypothesize that SNO may be a more complex perception. Although ultimately, factors that affect the perception of SNO may primarily involve impaired nasal airflow and trigeminal dysfunction, but functional information from other factors such as viable mucosal area for heat exchange, the location of obstruction and increased work of breathing may also be relevant. Local or topical anesthesia in the nasal vestibule or nasal cavity results in a sensation of nasal obstruction without changes to objective nasal airflow measures (Jones et al., 1987; Durrant et al., 2023). Physiologic breathing involves nasal airflow volumes of up to 500 ml/s, which may increase to > 1 liter during exercise, subsequently leading to supplementation of respiration through the mouth (Beule et al., 2023). If the required nasal airflow volume at rest is not achieved and increased work of breathing is required, then this may lead to the perception of nasal obstruction. In addition,

any compromise to the nasal valve (the narrowest area of the nasal airway (Jones, 2001)) and the adjacent structures to it (nasal septum, upper lateral cartilages, inferior turbinate) may restrict the volume of air through the nose, likewise leading to the perception of nasal obstruction (Kridel and Sturm, 2021; Beule et al., 2023). Trigeminal dysfunction may be from immature TRPM8 ion channels (Migneault-Bouchard et al., 2024), failure of stimuli to reach the trigeminal nerves (airflow-related), or it may also be due to pathologic nasal mucosa that no longer functions as a viable surface for mucosal heat exchange (Zhao et al., 2011) and likely has damaged trigeminal nerve endings. Mucosal heat exchange, also known as mucosal cooling (Zhao et al., 2011, 2014), refers to the dynamic process where airflow loses heat as it comes into contact with the nasal mucosal wall. This occurs through a combination of conductive heat loss, driven by the temperature gradient, and evaporative heat loss, driven by the water vapor pressure gradient, within the nasal cavity. This process is influenced by the interaction between the nasal anatomy and the inhaled air. Variations in nasal structure and physical conditions can affect this process, resulting to differences in how individuals perceive nasal patency.

Total Nasal Airflow Volume: Limited Use in the Assessment of Nasal Obstruction

Most of the studies included in this thesis involved the use of objective nasal measures for total airflow volume. However, relying on this measure to estimate nasal patency or obstruction may be inadequate, as a significant decrease in total nasal airflow volume may only become evident in very severe cases of obstruction when compensatory respiratory mechanisms (i.e., greater inspiratory effort) are no longer effective. However, due to the lack of better alternatives, PNIF may be the most practical screening tool in clinical settings, though it is important to remain aware of its limitations.

In the development of a useful and practical clinical test for nasal obstruction, perhaps, focus may be directed towards the assessment of the anterior part of the nose. The respiratory mucosa is not a homogeneous tissue and it may have varying sensitivities to trigeminal stimulation depending on the stimulus quality and site of stimulation (Frasnelli et al., 2004; Poletti et al., 2017). The vestibule or anterior nasal cavity is the most sensitive and functionally relevant in warning us of potential respiratory dangers as it allows the body to activate reflexes (i.e., breathing cessation, sneezing, mucus production, mucosal congestion) in response to trigeminal signals from possible threats (Clarke and Jones, 1994; Frasnelli et al., 2004; Sozansky and Houser, 2014). Future efforts should explore the development of a portable device to measure mucosal cooling or heat loss, as this technology could become a valuable tool for evaluating nasal obstruction, should it become more accessible.

Limitations

Study 1 used screening tests to facilitate ease of testing in a larger sample. However, shorter tests may not be able to distinguish between varying degrees of function and dysfunction (Doty, 2019) and may have limited or overestimated some findings. Having fewer items may also influence how much chance performance affects outcomes. The same issue may also apply to the TLT. At the time when Studies 1 and 3 were conducted, we used the 10-item TLT for Study 1 and 20-item TLT for Study 3, consistent with their use in prior publications. More recent findings ((Mai et al.), In Press), however, show that a lower number of presentations is suboptimal and may benefit from replication. Study 3 had a relatively low sample size, with most patients having undergone at least 1 previous nasal surgery.

Outlook for Future Research

The studies included in this thesis answered several questions related to the trigeminal system as it relates to olfaction and nasal airflow / obstruction. However, more questions and issues remain that require systematic scientific investigation. Future studies should be directed towards addressing the following:

1) *From Study 1: using comprehensive orthonasal, retronasal, and trigeminal psychophysical tests, as well as airflow assessment methods that investigate intranasal airflow distribution and mucosal heat exchange*

   It would be interesting to revisit the same variables in Study 1 but using more comprehensive orthonasal, retronasal, and trigeminal (40-item TLT or other methods) psychophysical tests and an objective nasal airflow measure that determines intranasal airflow distribution as well as mucosal heat exchange (preferably in a portable device) among patients with and without olfactory loss.

2) *From Study 3: improving sample size, disease severities, history of surgery*

   Some limitations were identified in Study 3 and may be worth reinvestigating in a larger sample of patients, having a heterogeneous distribution of disease severities, and including those who have not yet undergone surgical treatment.

3) *Determining the histopathologic basis of trigeminal dysfunction in CRS and in various olfactory disorders*

   The pathophysiology of intranasal chemosensory trigeminal dysfunction remains poorly understood. There are limited methodologies available to investigate the potential causes of this dysfunction, which may include failure in various levels such as: TRP ion channels, neuronal damage and/or impaired regeneration, mucosal inflammation, and central processing. Understanding these mechanisms could help

explain why trigeminal dysfunction may be observed in CRS but not in other types of olfactory dysfunction (i.e., neurodegenerative, congenital OD).

4) *From Studies 2 and 3: Developing a standardized, validated, practical, clinical intranasal chemosensory trigeminal function test*

   Studies 2 and 3 already showed us the challenges related to the investigation of trigeminal function and emphasized the importance of a standardized manner of testing – preferably, one that excludes the effects of olfaction and is practical to perform in the clinical setting. The adoption of trigeminal function measurement in clinical practice faces significant barriers. These include limited testing options, the lack of validated tests with established normative values, and the inaccessibility of equipment commercially. Improving trigeminal assessment could have far-reaching implications, potentially leading to a better understanding of intranasal chemosensation (including both trigeminal function and olfaction) and intranasal peripheral nerve dysfunction, with therapeutic consequences.

Conclusion

Although initially thought perhaps to only be structurally related to each other by their proximity to each other in the head, intranasal trigeminal function, olfaction, and nasal airflow perception are functionally interrelated based on psychophysical chemosensory and objective nasal airflow tests. What is known about intranasal trigeminal function remains limited in comparison to the other chemical senses. However, dysfunction in the trigeminal system significantly contributes to olfaction and the perception of nasal airflow. The conduct of the three studies included in this thesis also exposed the pitfalls and challenges related to intranasal trigeminal and nasal airflow testing and comparison of existing findings in this field. A more practical method of assessment may hopefully be developed in the near future to aid in a more holistic diagnosis of trigeminal disorders in the context of olfaction and nasal obstruction.

In the first study, we explored the relationship between intranasal trigeminal function, olfaction, and nasal airflow using screening tests conducted on healthy participants. While there are limitations in how effectively screening tests with fewer items can categorize individuals based on performance, we found that trigeminal function (TLT) was positively correlated with retronasal olfaction (Q-Powders), and total nasal airflow volume (PNIF). However, we did not observe a similar correlation with orthonasal olfaction (Q-Sticks), likely due to the test's limited ability to stratify individuals as it only included three items. VAS ratings were also not correlated with any of the chemosensory screening tests or PNIF. While self-ratings may be useful for estimating symptom burden in patients, they may not be as applicable to healthy individuals. This highlights the importance of conducting psychophysical testing before any nasal surgical intervention to more accurately assess function, which can serve as a baseline for evaluating treatment outcomes.

In the second study, we reviewed what is currently known about trigeminal function in CRS patients, a group that already experiences olfactory dysfunction and nasal obstruction. Although the number of studies available was limited (n = 16), the evidence indicates that trigeminal function and olfaction are interrelated and that CRS patients do experience trigeminal dysfunction. This dysfunction may result from anatomic blockage due to nasal polyps, edematous mucosa, nasal congestion, or thick nasal mucus; or it may also be due to neurologic- or immune-related responses such as: upregulated immune defense mechanisms causing trigeminal nerve damage, changes in nerve growth factor release, or other factors (e.g., dysfunctional or immature TRPM8 receptors). Since the exact pathophysiology of trigeminal dysfunction remains unclear, we proposed a hypothesis on

how chronic inflammation leads to trigeminal dysfunction through both peripheral and central processes. Most studies did not elaborate on specific interventions for trigeminal dysfunction in CRS, as current recommendations are directed towards the therapy of CRS as an underlying cause. The effects of surgery or corticosteroids on trigeminal dysfunction in CRS remain uncertain. A major limitation in advancing research on intranasal trigeminal function is the lack of a standardized, validated test that is both appropriate and practical for clinical use. Future studies should address the differences in methodology, low sample sizes, and lack of control groups.

In the last study (Study 3), we investigated how trigeminal function compared with subjective nasal obstruction, objective nasal airflow tests, and olfaction among patients with CRS. In the process, we hoped to determine whether a trigeminal function test may be used to estimate nasal obstruction in these patients. Trigeminal function was measured using TLT and CO_2 sensitivity, objective nasal airflow was measured using AAR and PNIF, while olfaction was measured using the "Sniffin' Sticks" odor identification test; and SNO ratings were also obtained. SNO ratings, trigeminal function, and olfaction were all worse in CRS patients compared to healthy controls, while AAR and PNIF were both not significantly different between groups. In addition, CO_2 sensitivity and odor identification were both negatively correlated with SNO ratings, but not with any of the objective nasal airflow tests. This emphasizes that the perception of nasal obstruction does not simply depend on total nasal airflow volume as measured by objective nasal airflow tests, but it may also be modulated by trigeminal function, increased work of breathing, location of obstruction, and mucosal heat exchange, among others.

The three studies included in this thesis contribute to what is currently known about intranasal trigeminal function and suggest possible directions for future research. The first study is one of the few to examine both objective nasal airflow tests and psychophysical assessments of olfactory and trigeminal function, and is likely the first to use VAS ratings and screening tests in a large sample of healthy individuals. Here we elaborated on the interactions between trigeminal function, olfaction, and nasal airflow, and we discussed the limitations of VAS ratings and screening tests in this context. The second study is the first literature review focused on intranasal trigeminal function in CRS patients. While the findings confirm that trigeminal dysfunction is present in this group, current clinical guidelines do not emphasize its assessment, highlighting the pressing need for a standardized test to enable better comparison of results. The third study investigated how intranasal trigeminal function relates to SNO and objective nasal airflow tests, and explored whether trigeminal function tests may be used to estimate the nasal obstruction. Our study confirmed previous findings

of inconsistencies between subjective and objective nasal airflow measures. However, our preliminary data indicate that individuals with uncontrolled CRS have poorer SNO ratings, CO_2 sensitivity and odor identification scores, suggesting a more pronounced relationship between these factors in those with more severe disease. Furthermore, CO_2 sensitivity and odor identification, but not AAR and PNIF, were negatively correlated with SNO which shows that the perception of nasal obstruction may be influenced not only by nasal airflow volume, but by other factors, including trigeminal dysfunction, location of obstruction, increased work of breathing, and mucosal heat exchange, among others. Overall, these studies offer valuable insights and help shape ideas and the path for future research in this field.

Zusammenfassung

Einführung

Die Nase spielt eine wichtige Rolle bei der Sinneswahrnehmung und der Nasenatmung. Sie ist unerlässlich für die Geruchswahrnehmung (olfaktorische Funktion) sowie die Erwärmung, Befeuchtung und Filterung der Luft (respiratorische Funktion) und ermöglicht uns außerdem, Schmerz, Irritation und Temperatur zu empfinden - Reize, die vor potenziellen Bedrohungen der Atemwege warnen (trigeminale Funktion).

In dieser Dissertation wird untersucht, wie die Trigeminusfunktion, der Geruchssinn und der nasale Luftstrom bei Gesunden und bei Menschen mit sensorischen Einschränkungen zusammenwirken.

Hypothesen

In Studie 1 untersuchten wir die Beziehung zwischen der intranasalen Trigeminusfunktion, dem Geruchssinn und dem nasalen Luftstrom bei gesunden Personen. Wir stellten die Hypothese auf, dass die Ergebnisse der verschiedenen Tests miteinander korrelieren würden, was die Interaktion zwischen diesen chemosensorischen Systemen und dem nasalen Atemfluss unterstützt.

Studie 2 konzentrierte sich auf die Überprüfung der intranasalen Trigeminusfunktion bei Patienten mit chronischer Rhinosinusitis (CRS), die unter Geruchsstörungen und nasaler Obstruktion leiden. Unsere Hypothese war, dass CRS-Patienten eine trigeminale Dysfunktion aufweisen, was ihre empfundene nasale Obstruktion erklären könnte. Wir verwendeten verschiedene Ansätze zur Bewertung der trigeminalen Funktion in der Hoffnung, damit sinnvolle Aussagen zur klinischen Anwendbarkeit der entsprechenden Verfahren zu erhalten.

In Studie 3 wollten wir untersuchen, ob die intranasale Trigeminusfunktion den nasalen Luftstrom abschätzen kann (unter Berücksichtigung objektiver und subjektiver Bewertungen). Darüber hinaus untersuchten wir die Korrelationen zwischen subjektiver nasaler Obstruktion (SNO) und objektivierenden Messungen des nasalen Luftstroms, zwier psychophysischer trigeminaler Tests sowie Riechtests. Unsere Hypothese war, dass die trigeminale Dysfunktion mit der nasalen Obstruktion bei CRS-Patienten korreliert, was auf ihre Anwendbarkeit als klinisches Instrument zur psychophysischen Bewertung der nasalen Obstruktion hindeuten würde.

Methoden

In Studie 1 wurden verschiedene Screening-Tests (Q-Sticks [orthonasales Riechen], Q-Pulver [retronasales Riechen], TLT [Trigeminusfunktion] und maximaler nasaler inspiratorischer Luftfluss [PNIF, nasaler Luftstrom]) bei 400 Gesunden durchgeführt. Demografische und klinische Daten sowie Selbsteinschätzungen des Riechvermögens und des nasalen Luftstroms (Bewertungen auf visuellen Analogskalen [VAS]) wurden erfasst. Die Datenanalyse erfolgte mit Pearsons r, Spearmans rho und t-Tests.

Studie 2 beinhaltete eine umfassende Literaturrecherche in den Datenbanken PubMed, Web of Science und Scopus mit den Suchbegriffen: „trigeminal“ AND [„chronic rhinosinusitis“ (CRS) OR „chronic sinusitis“ OR „nasal polyp“ OR „nasal polyposis“]. Eingeschlossen wurden englischsprachige Originalartikel ohne Datumsbeschränkung, während andere Studientypen (z. B. Übersichtsarbeiten, Fallberichte/Serien, Leitartikel, Konferenzbeiträge usw.), solche, an denen keine CRS-Patienten beteiligt waren, und nicht englischsprachige Veröffentlichungen ausgeschlossen wurden. Nach dem Screening von 281 Manuskripten erfüllten 9 Artikel die Einschlusskriterien und wurden von den Autoren (im Volltext) geprüft. Die Daten wurden in Microsoft Excel unter Verwendung von Häufigkeiten, Mittelwerten und qualitativen Beschreibungen zusammengefasst.

In Studie 3 unterzogen sich die Teilnehmer einer Reihe von Tests zur intranasalen Trigeminusfunktion (TLT und CO2-Empfindlichkeit), zum nasalen Luftstrom (PNIF, aktive anteriore Rhinomanometrie [AAR]) und zum Geruchssinn (Geruchserkennungstest mit „Sniffin' Sticks“). Die Teilnehmer füllten auch den „Sinonasal Outcome Test-20 German Adapted Version“ (SNOT-20 GAV) aus, aus den SNO-Bewertungen (basierend auf Item 1) und CRS-Kontrollwerte (abgeleitet aus den Antworten auf die Items 1, 3, 10, 12 und 13) berechnet wurden. Die Datenanalyse umfasste t-Tests, Pearsons r, Chi-Quadrat-Tests und exakte Fisher-Tests, die mit dem Softwarepaket SPSS durchgeführt wurden.

Ergebnisse

In Studie 1 wurden 156 Männer und 244 Frauen (Mittelwert: 46 Jahre) einbezogen. Die TLT-Werte korrelierten positiv mit den PNIF- und Q-Pulver-Werten, nicht aber mit den Q-Stick-Werten. Die Ergebnisse der chemosensorischen Tests waren jedoch nicht mit den VAS-Bewertungen korreliert.

Die in Studie 2 eingeschlossenen Studien stützen den Befund einer trigeminalen Dysfunktion bei CRS-Patienten auf der Grundlage verschiedener Bewertungsmethoden (d.h. ERP, TLT, CO2-Erkennungsschwelle, elektrische Schwelle, Luftpuff-Test, Trigeminale

„Sniffin‘ Sticks“, 7-item olfaktorisch-trigeminaler Test und Positronen-Emissions-Tomographie [PET]). Direkte Vergleiche zwischen den Studien waren jedoch aufgrund von Unterschieden bei den Stimuli (oft bimodal, unterschiedliche Konzentrationen) und der Methodik (z. B. Verwendung verschiedener Interstimulusintervalle bzw. Kontrollreize [Luft vs. Lösungsmittel]) schwierig. Nur zwei Studien untersuchten den Zusammenhang zwischen der Trigeminusfunktion und dem nasalen Luftstrom oder den Atemmustern. In einer Studie wurden keine signifikanten Unterschiede in den Atemmustern zwischen Patienten und Kontrollpersonen festgestellt, während die andere Studie ergab, dass CRS-Patienten ihre nasale Durchgängigkeit trotz normaler PNIF-Messungen schlechter einschätzten als Kontrollpersonen. Trotz Vorliegens verschiedener Erklärungen zur Wechselwirkung zwischen Geruchs- und Trigeminusfunktion sind weitere Studien erforderlich.

In Studie 3 wurden 37 Männer und 32 Frauen (Altersmittel 51 Jahre), darunter 37 CRS-Patienten und 32 Gesunde, einbezogen. Bei den objektiven Messungen des nasalen Luftstroms (PNIF, AAR) wurden keine signifikanten Unterschiede zwischen Patienten und Kontrollen festgestellt; allerdings wiesen CRS-Patienten im Vergleich zu den Kontrollen schlechtere SNO-Bewertungen, eine schlechtere Trigeminusfunktion (CO2-Empfindlichkeit) und ein schlechteres Riechvermögen auf. Die SNO-Bewertungen waren negativ mit der CO2-Empfindlichkeit und der Geruchserkennung korreliert, während die objektiven Messungen des nasalen Luftstroms keine signifikanten Korrelationen aufwiesen.

Schlussfolgerungen

In Studie 1 korrelierte die Trigeminusfunktion bei Gesunden mit dem (retronasalen) Riechvermögen und dem nasalen Luftstrom. Chemosensorische Funktionen und nasaler Luftstrom sind miteinander verbunden und werden zumindest teilweise durch Interaktionen auf zentralnervöser Ebene vermittelt.

Studie 2 deutet darauf hin, dass die Interaktion zwischen Trigeminusfunktion und Geruchssinn zur trigeminalen Dysfunktion bei CRS beitragen kann. Neben mechanisch-anatomischen Verlegungen (d.h. Schleimhautveränderungen und hochvisköser Schleim) kann eine trigeminale Beeinträchtigung die Wahrnehmung einer nasalen Obstruktion bei CRS beeinflussen. Zu den möglichen Mechanismen gehören u.a. heraufregulierte Immunabwehrmechanismen, die zu einer Nervenschädigung führen, oder Veränderungen Nervenwachstumsfaktorfreisetzung. Angesichts des begrenzten Verständnisses der trigeminalen Dysfunktion bei CRS richten sich die Behandlungsempfehlungen auf die Therapie des CRS als zugrundeliegende Ursache, obwohl die definitiven Auswirkungen von Operationen und Kortikosteroiden auf die Trigeminusfunktion noch unklar sind. Es besteht

Bedarf für einen standardisierten, praktischen und validierten Trigeminustest, der in der klinischen Praxis leicht durchführbar ist, um die Patientenbeurteilung zu verbessern und die künftige Forschung zu vereinheitlichen.

In Studie 3 war die Wahrnehmung der nasalen Obstruktion nicht nur vom nasalen Luftstrom abhängig, sondern kann auch durch die Trigeminusfunktion und Faktoren wie die Lage der Obstruktion, die Atemarbeit und den Wärmeaustausch der Schleimhaut moduliert werden. Daher ist die Rolle objektiver Messungen des nasalen Luftstroms als alleiniger Methode zur Bewertung der funktionellen nasalen Obstruktion bei CRS nach wie vor begrenzt. Die Einbeziehung von trigeminalen Funktionstests und SNO-Bewertungen kann eine umfassendere Bewertung der nasalen Obstruktion ermöglichen.

Summary

Introduction

The nose plays an important role in sensory perception and nasal respiration. It is essential for odor perception (olfaction); warming, humidifying, and filtering air (respiratory); and also allows us to feel pain, irritation, and temperature –mechanisms that warn of potential respiratory threats (trigeminal).

As these systems involve structures that are anatomically proximal to each other in the head, this thesis examines how trigeminal function, olfaction, and nasal airflow interact in both healthy individuals and those with sensory impairments.

Hypotheses

In Study 1, we sought to examine the relationship between intranasal trigeminal function, olfaction, and nasal airflow in healthy individuals. We hypothesized that screening test scores would correlate with each other, supporting the interaction between these chemosensory systems and nasal airflow.

Study 2 focused on reviewing what is known about intranasal trigeminal function in CRS patients, who experience olfactory dysfunction and nasal obstruction. We hypothesized that CRS patients would exhibit trigeminal dysfunction, which can help explain their reported nasal obstruction. Additionally, we anticipated identifying various methods of trigeminal assessment and hoped to gather a sufficient number of studies to allow for meaningful comparisons and generalizable conclusions.

In Study 3, we aimed to explore whether intranasal trigeminal function could serve as a means to estimate nasal airflow (considering both objective and subjective assessments). In addition, we examined the possible correlations between Subjective Nasal Obstruction (SNO) ratings and objective nasal airflow measures; the two trigeminal psychophysical tests; and trigeminal tests and olfactory tests / SNO ratings / objective nasal airflow measures. We hypothesized that trigeminal dysfunction would correlate with nasal obstruction in CRS patients, suggesting its potential use as a clinical tool for psychophysical assessment of nasal obstruction.

Methodology

In Study 1, various screening tests (Q-Sticks [orthonasal olfaction], Q-Powders [retronasal olfaction], TLT [trigeminal function], and peak nasal inspiratory flow [PNIF, nasal airflow]) were performed on 400 healthy individuals. Demographic and clinical data, along with self-ratings for smelling ability and nasal airflow (visual analogue scale [VAS] ratings) were collected. Data analysis was done using Pearson's r, Spearman's rho, and t-tests in SPSS.

Study 2 involved a comprehensive literature search using the PubMed, Web of Science, and Scopus databases with the search terms: 'trigeminal' AND ['chronic rhinosinusitis' (CRS) OR 'chronic sinusitis' OR 'nasal polyp' OR 'nasal polyposis']. Articles from original studies, written in English, without date restrictions, were considered, while other study types (e.g., reviews, case reports/series, editorials, conference papers, etc.), those not involving CRS patients, and non-English publications were excluded. After screening 281 manuscripts, 9 articles met the inclusion criteria and were reviewed (full text) by the authors. Data were summarized in Microsoft Excel using frequencies, means, and qualitative descriptions.

In Study 3, participants underwent a series of tests for intranasal trigeminal function (TLT and CO_2 sensitivity), objective nasal airflow (PNIF, active anterior rhinomanometry [AAR])] and olfaction (Sniffin' Sticks odor identification). Participants also completed the Sinonasal Outcome Test-20 German Adapted Version (SNOT-20 GAV), from which SNO ratings (based on item 1) and CRS control scores (derived from responses to items 1, 3, 10, 12, and 13) were calculated. Data analysis involved t-tests, Pearson's r, chi-square tests and Fisher's exact tests, performed using SPSS.

Results

In Study 1, 156 men and 244 women (mean: 46 years), were included. TLT scores were positively correlated with PNIF and Q-Powders, but not with Q-Sticks scores. However, chemosensory test scores were not correlated with VAS ratings.

The studies included in Study 2 support the finding of trigeminal dysfunction in CRS patients based on various assessment methods (i.e., ERP, TLT, CO_2 detection threshold, Electrical threshold, air puff test, Trigeminal Sticks, 7-item Olfactory-Trigeminal Test, and positron emission tomography [PET]). However, direct comparisons between studies were challenging due to differences in stimuli (often bimodal, varying concentrations) and methodology (e.g., interstimulus interval, neutral stimuli used [air vs. solvent]). Only two studies explored the link between trigeminal function and nasal airflow or breathing patterns.

One study reported no significant differences in breathing patterns between patients and controls; while the other study found that CRS patients rated their nasal patency worse than controls despite having normal PNIF measurements. Although hypotheses have been proposed to explain the interaction between olfactory and trigeminal function, further research is needed.

In Study 3, 37 men and 32 women (mean: 51 years) comprising 37 CRS patients and 32 healthy controls were included. No significant differences were found in objective nasal airflow (PNIF, AAR) measurements between patients and controls; however, CRS patients exhibited poorer SNO ratings, trigeminal function (CO_2 sensitivity), and olfaction compared to controls. SNO ratings were negatively correlated with CO_2 sensitivity and odor identification, whereas objective nasal airflow measures showed no significant correlations.

Conclusions

In Study 1, trigeminal function was correlated with (retronasal) olfaction and nasal airflow in healthy individuals. Chemosensory functions and nasal airflow are interconnected, potentially mediated, at least in part, by interactions within the central nervous system.

Study 2 suggests that the interaction between trigeminal function and olfaction may contribute to trigeminal dysfunction in CRS. Beyond anatomic obstructions (i.e., mucosal changes and thick mucoid secretions), trigeminal impairment may influence the perception of nasal obstruction in CRS. Potential mechanisms include upregulated immune defense mechanisms leading to nerve damage or changes in nerve growth factor release, among others. Given the limited understanding about trigeminal dysfunction in CRS, treatment recommendations are directed toward the therapy of CRS as an underlying cause, although the definite effects of surgery and corticosteroids on trigeminal function are still unclear. There is a need for a standardized, practical, and validated trigeminal test that is easy to implement in clinical settings to enhance patient assessment and guide future research.

In Study 3, the perception of nasal obstruction does not only depend on nasal airflow, but may also be modulated by trigeminal function and factors such as: location of obstruction, work of breathing, and mucosal heat exchange. Thus, the role of objective nasal airflow measures as a sole method of functional nasal obstruction assessment in CRS remains limited. Incorporating trigeminal function tests and SNO ratings can provide a more comprehensive evaluation of nasal obstruction.

Publication Data

(according to Journal Citation Reports, as of July 2024, https://jcr.clarivate.com/jcr/home)

European Archives of Oto-Rhino-Laryngology

"European Archives of Oto-Rhino-Laryngology is an international scientific journal covering the broad variety of head and neck diseases with an inherent focus on clinical and translational research in all specialties of Oto-Rhino-Laryngology and Head & Neck."

2022 Journal Metrics
Journal Impact Factor: 2.6
5-year Impact Factor: 2.5
Immediacy Index: 0.4
Eigenfactor Score: 0.01485
Normalized Eigenfactor: 3.23276
Article Influence Score: 0.632
Rank (Otorhinolaryngology): 12 / 43

Expert Review of Clinical Immunology

"A MEDLINE-indexed, peer-reviewed journal providing the latest research on the performance of new therapeutic and diagnostic modalities in clinical immunology."

2022 Journal Metrics
Journal Impact Factor: 4.4
5-year Impact Factor: 4.8
Immediacy Index: 0.9
Eigenfactor Score: 0.00560
Normalized Eigenfactor: 1.21912
Article Influence Score: 1.240
Rank (Immunology): 77 / 161

Rhinology

"Rhinology is the official Journal of the International Rhinologic Society and one of the journals of the European Rhinologic Society…[and] provides a platform for the dissemination of rhinologic research and reviews, as well as position papers, task force reports and guidelines, amongst an international scientific audience."

2023 Journal Metrics
Journal Impact Factor: 4.8
5-year Impact Factor: 4.2

Immediacy Index: 1.7

Eigenfactor Score: 0.00246

Normalized Eigenfactor: 0.53952

Article Influence Score: 0.999

Rank (Otorhinolaryngology): 3 / 65

Contributions in the Publications

Study 1: Conceptualization; data organization and verification, data analysis, writing – original draft, review and editing

Study 2: Conceptualization, methodology, data collection, data analysis, writing – original draft, review and editing

Study 3: Conceptualization, data analysis, writing – original draft, review and editing

Other Publications

Journal Articles

Mai Y, **Hernandez AK**, Haehner A, Konstantinidis I, Hummel T. 2024. Normative data of odor lateralization task. Rhinology (In Press)

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Book Chapters

Whitcroft KL, **Hernandez AK**, Hummel T. Olfactory Function and Dysfunction. In Flint P. et al., editors. Cummings Otolaryngology 8th Edition. Philadelphia: Elsevier. (In Press, For Publication in 2025)

Hernandez AK, Zou L, Hummel T. Olfactory and Gustatory Sensation-Perception. In: Boyle GJ, Northoff G, Barbey AK, et al., eds. The Sage Handbook of Cognitive and Systems Neuroscience: Neuroscientific Principles Systems and Methods. SAGE Publications Inc.; 2023:398-413.

Conferences and Presentations

Part of the presented work was introduced at the following international meetings:

April 22, 2023 "Associations between gustatory, trigeminal and olfactory functions and nasal airflow"
Association of Chemoreception Sciences XLV Conference
Bonita Springs, Florida, United States of America

September 20, 2023 "Differences in trigeminal function, olfaction, and nasal airflow measurements in patients with and without chronic rhinosinusitis"
European Chemoreception Research Organization XXXIII Conference
Nijmegen, Netherlands

December 1, 2023 "Intranasal trigeminal dysfunction in chronic rhinosinusitis"
German ENT Society Meeting
University of Geneva, Geneva, Switzerland

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Appendix

Sinonasal Outcome Test – 20 German Adapted Version

Items in bold typeface were included as basis for the CRS Control Score, Question 1 was also referred to as the subjective nasal obstruction (SNO) rating in Study 3

Datum:…… PbdID……..

SINO-NASAL OUTCOME TEST 20 (SNOT-20 GAV)

Sehr geehrte Teilnehmer,

Wir bitten Sie den vorliegenden Fragebogen vollständig zu beantworten.

Um beurteilen zu können, wie stark die einzelnen Symptome ausgeprägt sind, kreuzen Sie bitte bei jeder einzelnen Frage die entsprechende Ziffer an.		Kein Problem	Sehr geringes Problem	Kleines Problem	Mittelgradiges Problem	Hochgradiges Problem	Schlechter kann es nicht mehr werden
Einzelfragen							
1	**Nasenatmungsbehinderung**	0	1	2	3	4	5
2	Niesreiz	0	1	2	3	4	5
3	**Ständiges Naselaufen**	0	1	2	3	4	5
4	Sekretfluss in den Rachen	0	1	2	3	4	5
5	Dickes, schleimiges Nasensekret	0	1	2	3	4	5
6	Räusperzwang, trockener Hals	0	1	2	3	4	5
7	Husten	0	1	2	3	4	5
8	Druckgefühl auf den Ohren	0	1	2	3	4	5
9	Ohrenschmerz	0	1	2	3	4	5
10	**Riechminderung**	0	1	2	3	4	5
11	Schwindelgefühl	0	1	2	3	4	5
12	**Gesichtsschmerz, Druckgefühl im Gesicht**	0	1	2	3	4	5
13	**Probleme beim Einschlafen**	0	1	2	3	4	5
14	Nächtliches Aufwachen	0	1	2	3	4	5
15	Tagesmüdigkeit	0	1	2	3	4	5
16	Verminderte Leistungsfähigkeit	0	1	2	3	4	5
17	Konzentrationsschwäche	0	1	2	3	4	5
18	Frustrationen / Rastlosigkeit / Reizbarkeit	0	1	2	3	4	5
19	Traurigkeit	0	1	2	3	4	5
20	Nebenhöhlenbeschwerden sind mir peinlich	0	1	2	3	4	5

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