Published in final edited form as:
J Voice. 2023 March ; 37(2): 234–244. doi:10.1016/j.jvoice.2020.12.029.

Examining the Influence of Chemosensation on Laryngeal Health and Disorders

Carolyn K. Novaleski, Ph.D., CF-SLP[a,b,c], **Richard L. Doty, Ph.D.**[d], **Alissa A. Nolden, Ph.D.**[e], **Paul M. Wise, Ph.D.**[a], **Joel D. Mainland, Ph.D.**[a,f], **Pamela H. Dalton, Ph D., MPH**[a]

[a.]Monell Chemical Senses Center, 3500 Market Street, Philadelphia, PA 19104, USA

[b.]Department of Communicative Sciences and Disorders, Michigan State University, 1026 Red Cedar Road, East Lansing, MI 48824, USA

[c.]Department of Neurology, Mayo Clinic, 200 First Street SW, Rochester, MN, 55905, USA

[d.]Department of Otorhinolaryngology–Head and Neck Surgery, University of Pennsylvania Perelman School of Medicine, 3400 Spruce Street, Philadelphia, PA 19104, USA

[e.]Department of Food Science, University of Massachusetts-Amherst, 102 Holdsworth Way, Amherst, MA 01003, USA

[f.]Department of Neuroscience, University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104, USA

Abstract

Summary: Inhaled airborne stimuli are associated with laryngeal disorders affecting respiration. Clinically, several themes emerged from the literature that point to specific gaps in the understanding and management of these disorders. There is wide variation in the types of airborne stimuli that trigger symptoms, lack of standardization in provocation challenge testing using airborne stimuli, and vague reporting of laryngeal symptoms. Scientifically, evidence exists outside the field of voice science that could prove useful to implement among patients with impaired laryngeal-respiration. To expand this area of expertise, here we provide a thematic overview of relevant evidence and methodological tools from the discipline of chemosensory sciences. This review provides distinctions across the three chemosensory systems of olfaction, trigeminal chemesthesis, and gustation, guidance on selecting and delivering common chemosensory stimuli for clinical testing, and methods of quantifying sensory experiences using principles of human psychophysics. Investigating the science of chemosensation reveals that laryngeal responses to inhaled airborne stimuli have explanations involving both physiological mechanisms as well as higher cognitive processing. Fortunately, these findings are consistent with

Address correspondence and reprint requests to Carolyn K. Novaleski, Department of Communicative Sciences and Disorders, Michigan State University, 1026 Red Cedar Road, East Lansing, MI 48824. cnova@msu.edu.

This work was presented as a poster at the Voice Foundation's 47th Annual Symposium: Care of the Professional Voice in Philadelphia, Pennsylvania, May 30-June 3, 2018.

current pharmacological and nonpharmacological interventions for impaired laryngeal-respiration. Based on the close relationships among inhaled airborne stimuli, respiration, and laryngeal function, we propose that new perspectives from chemosensory sciences offer opportunities to improve patient care and target areas of future research.

Keywords

chemical senses; chemosensory; chronic cough; larynx; paradoxical vocal fold motion; vocal cord dysfunction

1. Introduction

The management of laryngeal disorders evolved considerably over the past several decades. Otolaryngologists and speech-language pathologists historically focused on phonatory and communicative functions of the larynx.[1,2] Gradually, clinicians expanded their practices to serve patients with impaired swallowing[3] and as a result, added assessment tools such as liquid testing stimuli comprised of different consistencies and videofluoroscopic radiology procedures.[4,5] More recently, disordered respiration became recognized in the breadth of laryngeal disorders,[6-11] here defined broadly as uncoordinated opening and closing of the vocal folds and/or disrupted airway sensory processing. In fact, dyspnea or shortness of breath accounted for up to 22% of patient referrals in one interdisciplinary voice and swallowing clinic.[12] However, clinicians currently face major challenges spanning the diagnosis and treatment of various laryngeal disorders affecting respiration. Unlike the implementation of new techniques to understand swallowing disorders, an overarching obstacle is the absence of relevant quantitative and qualitative outcome measures to characterize respiratory coordination at the level of the larynx.[8,13] Furthermore, clinicians report vastly different training, familiarity, and practice patterns.[14,15] These gaps contribute to the tendency to rely predominantly on anecdotal evidence to guide clinical decision making.[16]

Despite the commitment to help this emergent patient population suffering from laryngeal-based respiratory symptoms, it can be tempting for clinicians to adopt the same principles of disordered phonation to understand disordered respiration. Here, we maintain that wielding phonatory expertise alone limits growth in this subspecialty. Rather, deliberately evaluating features of the patient’s history is necessary to identify specific clinical gaps unique to these disorders. Investigating outside fields for additional answers is a valuable approach to enhance the current knowledge about laryngeal disorders affecting respiration. Among some patients, exposures to various airborne odorant and irritant chemical stimuli are associated with the onset and exacerbation of abnormal laryngeal and respiratory function.[17-24] Moreover, odorant and chemical irritant stimuli are increasingly used during provocation challenge tests to evaluate laryngeal responses during flexible nasolaryngoscopy and spirometry.[25-30] In the following sections of this paper, we will synthesize clinical cases from the extant literature to uncover three important themes related to laryngeal disorders and inhaled airborne stimuli. Next, these themes will be divided accordingly by introducing the discipline of chemosensation, or the ability to sense chemical stimuli in the immediate environment. Finally, we will argue how more precise approaches, both conceptual and technical, are readily available from the field of chemosensory sciences to apply to clinical practices related to laryngeal disorders impacting respiratory function.

2. Clinical Evidence

The human larynx continuously modifies respiratory airflow and participates both actively and passively during multiple physiological functions.[31,32] When regarded as a respiratory organ, a vital role of the larynx is to protect the lower airway by engaging in a continuum of complex sensorimotor behaviors that can be reflexive as well as under volitional control.[33] Essential respiratory movements of the larynx during airway protection include airflow cessation during laryngeal closure (e.g., breath-hold maneuver),[34-36] increased intrathoracic pressure against a closed glottis (e.g., Valsalva maneuver),[37] and airflow expulsion during abrupt laryngeal abduction (e.g., expiratory reflex, cough reflex).[38,39] Despite the biological necessity for constant and rapid laryngeal adjustments, a heterogeneous group of non-pulmonary conditions has emerged[40] that reflects numerous patterns of disordered coordination of the laryngeal and respiratory systems. While it is beyond the scope of this review to describe all disorders, common conditions include paradoxical vocal fold motion and refractory chronic cough[41,42] (see reviews by Hull et al.[43] and Vertigan et al.[44]). The exact number of patients with these disorders remains unknown,[8] though it is estimated, as one example, that up to 7 million individuals have refractory chronic cough in the United States each year.[45] As summarized by Shembel and colleagues,[16] laryngeal-based respiratory disorders are characterized by intermittent dyspnea that accompanies imprecise laryngeal closure, which is linked to a variety of triggering stimuli.

Along the spectrum of laryngeal disorders affecting respiration, a major classification of triggers includes airborne stimuli. For instance, inhaled odorants were reported to trigger symptoms in more than half of patients diagnosed with irritable larynx syndrome.[22] Further, fragranced products were identified to exacerbate symptoms in up to 15% of patients with episodic paroxysmal laryngospasm.[17] Across studies, temporal relationships were observed between inhalation exposures of airborne stimuli and the subsequent development of disordered laryngeal breathing.[46-60] Table 1 summarizes the current body of evidence according to study design, patient number, patient description, triggering stimulus, exposure description, and diagnosis. For all included cases, airborne inhalation exposures were the antecedents to symptom onset. Diagnoses were confirmed with visual observation of complete or partial vocal fold adduction during respiration using flexible nasolaryngoscopy or bronchoscopy. Cases were excluded when precipitating exposure events were not described or probable diagnoses were based on symptoms alone.

While the current literature is only a series of case reports, these retrospective studies reveal important preliminary observations. As reported previously,[16] patients were diagnosed with multiple labels including vocal cord dysfunction, [46,48-50,54,56,58,60] paradoxical vocal cord dysfunction,[47] irritant-associated vocal cord dysfunction,[52,57] occupational irritant-induced vocal cord dysfunction,[59] irritant-induced paradoxical vocal fold motion disorder,[55] work-associated irritable larynx syndrome,[53] and laryngeal hypersensivity.[51] Consistent with previous literature,[8] diagnoses were observed in both children and adults (age range 15-73 years) and in 3.5 times more females than males. Occupational inhalation exposures were prevalent, accounting for 87% of the studies, particularly among nurses[50,54,57,59] and first responders.[46,49] In 60% of the studies, patients required hospitalization or emergency treatment.[46,50,53,54,56-60] In addition to the aforementioned challenges with laryngeal disorders affecting respiration, we identified specific gaps among patients whose symptoms are related to airborne inhalation exposures. We next provide a qualitative description of three prominent themes that appeared in the literature.

2.1. Variability in Triggering Airborne Stimuli

First, the types of reported airborne stimuli were highly variable across studies. The most frequently reported chemical and/or particulate stimuli included disinfectants,[46,47,50,52,58,59] dust from ceiling tiles, wood, the 9/11 World Trade Center disaster,[49,53,56,57] fumes from paint, gasoline, solder,[51,53,57] and household cleaning products.[53,57] Few studies reported stimuli concentrations of inhalation exposures. Although some studies described a specific odorant such as eucalyptus[54] or category of an odor mixture such as perfume,[53] the remaining cases focused on the odor sources (e.g., mold, cornfield)[48,60] or were unspecified.[53,57] Similarly, some authors labeled the exact chemical irritant such as glutaraldehyde,[50] while other authors relied on vague descriptions such as bleaching agents.[52] Of note, a patient reported that the odor of a particular food (i.e., corn) provoked her symptoms.[61] This finding is consistent with previous reports that specific tastants and food ingestion led to symptoms in 22-31% of patients with irritable larynx syndrome.[17,22]

In terms of inhalation exposure types, studies revealed that single incidents [46,50,51,53,55,57,58,60] in addition to repeated, ongoing exposures[47-49,52-54,56,59] preceded symptom onset. The range was quite wide in the reported durations of exposures. Acute symptom onset occurred in some studies,[46,49,59] even as quickly as 20-30 minutes after an exposure event.[50] In contrast, a chronic exposure was described in which symptoms presented up to 23 weeks following an incident.[49] In a few cases, there was evidence that subsequent symptoms generalized from an initial airborne stimulus to different stimuli[59,60] or other physical locations (i.e., buildings with mold from water damage).[48] Based on the available information, it remains difficult to pinpoint a single class of triggering airborne stimuli and concentration ranges that contribute to abnormal laryngeal function affecting respiration.

2.2. Inconsistency in Provocation Challenge Procedures

Next, there was considerable disagreement in the literature regarding the use of clinical procedures to elicit observable signs of uncoordinated laryngeal movements during respiration. Laryngeal provocation challenge testing involves presenting stimuli to patients with the intention of causing signs of laryngeal closure patterns in the clinic, typically while visualizing the vocal folds using flexible nasolaryngoscopy.[62,63] Indeed, several studies described the use of inhaled airborne stimuli as primary provocation challenges. Patients were instructed to inhale odorant or chemical irritant stimuli that were identified as specific triggers of their symptoms.[47,51,52,54,56] Otherwise, patients inhaled nonspecific stimuli such as methacholine, cayenne pepper, cleaning product, and perfume.[49,51,53,55] The methods of delivering airborne stimuli were variable and included gauze pads,[47,54] alcohol wipes,[48] and vials.[51] Stimulus preparations, concentrations, and durations of provocation tasks were rarely detailed, making it challenging to repeat the clinical procedures. Control stimuli (e.g., water, ammonia) were occasionally described to mask the target airborne stimulus.[51,54] While clinicians typically provided the stimuli, in one instance a patient prepared alkaline persulphate for her nasolaryngoscopy procedure.[52]

In contrast, a number of studies reported no provocation challenge testing as part of the clinical evaluation.[46,50,58-60] There are wider issues related to provocation challenges that we believe are worth mentioning. Beyond indicating the presence of complete or partial vocal fold adduction, there was a lack of further detail illustrating the characteristics of laryngeal physiology during respiration. Additionally, the authors did not report clinical procedures to measure other respiratory movements of the larynx, such as cough, during provocation. While used primarily for diagnostic purposes, studies did not indicate that laryngeal closure patterns were reassessed to compare changes resulting from treatment. Taken together, the absence of standardization in provocation tests using inhaled airborne stimuli is a barrier to replicating clinical procedures and comparing criteria used to support diagnoses.

2.3. Ambiguity in Laryngeal Symptoms

Finally, studies included vague descriptions of laryngeal symptoms and unquantifiable severity levels. Dyspnea was the most frequently reported symptom, which was reported in 93% of the studies. Other common laryngeal-based symptoms included cough (67%), dysphonia (67%), stridor or wheezing (67%), throat irritation, pain, or tightness (47%), chest tightness (33%), and dysphagia (7%). With the exception of the University of California, San Diego Shortness of Breath Questionnaire,[46] few studies included scores from formal questionnaires specific to laryngeal or respiratory symptoms. When patients were followed after the initial diagnosis, general statements indicated that patients' symptoms improved or resolved following treatment,[47,48,55,56] patients were able to resume previous activities,[60] and medication use for asthma decreased.[54,60]

Given that multiple disease etiologies can lead to overlapping laryngeal and/or respiratory symptoms, the ambiguity in patient reports of symptom severity remains an obstacle to differential diagnosis. Similarly, the lack of quantifiable, distinguishable laryngeal sensations makes it difficult to understand the extent that different treatment approaches change symptoms over time. Indeed, the literature is valuable in establishing an initial relationship between airborne triggering stimuli and the development of laryngeal disorders impacting respiration. However, the aforementioned themes reveal that there are opportunities to improve the understanding of these disorders. In the section that follows, we attempt to address these problems by dividing the discussion according to the three themes. We provide relevant scientific principles and methodologies established from chemosensory sciences that may assist with improving the clinical standardization of procedures using inhaled airborne stimuli and measuring laryngeal-respiratory symptomology.

3. Scientific Evidence

Humans regularly interact with chemicals, which are in a constant state of dispersion in inhaled air and ingested food. Chemosensation refers to the ability to sense chemicals, and it serves multiple important roles that include pleasure sensation, food enjoyment, and nutritional health.[64] The focus of this paper will be on chemosensation as a system of hazard detection, as it can act as a unique surveillance system that allows individuals to recognize whether external chemical stimuli entering the body contain toxins that could be harmful to one's health.[65] Not only does chemosensation permit individuals to make decisions about the safety of their immediate environment, but it also serves as a chemically sensitive protective mechanism via expulsive reflexes to protect the airway.[66] When chemicals cannot be avoided, there is increasing evidence that chemosensation is involved in regulating the immune response through neurogenic inflammation.[67,68]

Chemicals are detected via three primary routes of delivery that include inhalation, dermal absorption, and ingestion. These delivery routes correspond to the chemical sensory systems of olfaction, trigeminal chemesthesis, and gustation, respectively. All three chemosensory systems are neuroanatomically distinct. The reality, however, is that individuals have trouble separating these senses, frequently confusing them due to their close perceptual similarities.[69] Therefore, additional knowledge about chemically-mediated sensory and respiratory changes would benefit patients who experience laryngeal-based symptoms related to airborne triggering stimuli. Further, clinicians would benefit from increased awareness about the interplay of these sensory systems and established testing tools using chemosensory stimuli.

3.1. Differentiating the Chemosensory Systems

Different categories of airborne stimuli and their concentrations involve separate chemical sensory systems. During nasal respiration, the olfactory and trigeminal systems can be simultaneously activated. With each inspiration, air and other airborne stimuli (e.g., odorants, chemical irritants) flow through the anterior nares and nasal vestibule. While the nasal airway mucosa functions primarily to filter, warm, and humidify outside air,[70] the superior region of the nasal cavity is also lined with olfactory epithelium. As airborne chemicals travel across the olfactory epithelium, they bind to olfactory receptors and activate olfactory sensory neurons in the periphery. This sensory information is projected via the olfactory nerve (CN I) to the olfactory bulb and other brain regions where neural signals result in odor perception, or the sense of smell.[71] Olfactory function is useful to direct attention to odorant sources to warn of potential dangers such as spoiled food or toxic fumes.[72] Odor perception is influenced by factors such as past experiences, expectations, attention, and memory.[73] For instance, the pairing of natural gas (odorless) with a sulfur compound (odorous) results in an important learned association between the smell of a malodor, sulfur, and possible danger (gas leak), which subsequently leads to change in behavior (evacuating a building).

If olfaction, among its many functions, is the chemical sensing system intended to alert individuals to modify behaviors to prevent perceived harmful substances before entering the body, then trigeminal chemesthesis is an additional system meant to warn of environmental irritants that can initiate reflexes resulting in the body forcefully expelling foreign material.[66] Separate from olfactory function, the mucus membranes lining the nasal cavity, as well as the oral cavity and eyes, house afferent endings of the trigeminal nerve (CN V).[74] When activated by inhaled chemicals, the resulting sensation is referred to as chemesthesis, or sensory irritation. In contrast to clinical terminology, sensory irritation is not synonymous with tissue inflammation,[75] and instead refers to temporary sensations such as tingling, stinging, itching, pain, warming, and cooling in the upper airways.[76] Common examples of nasal chemesthesis include pungency or stinging sensation when cleaning with chemical disinfectants and cooking with chili peppers. Additionally, oral chemesthesis can be perceived as tingling when drinking carbonated beverages, and ocular chemesthesis is frequently experienced as burning of the eyes while chopping onions.[77]

Chemesthetic sensations can subsequently activate defense mechanisms to protect the upper airway against dangerous substances. For instance, chemically sensitive protective mechanisms include increased salivation, mucus secretion in the nasal cavity, and tearing of the eyes.[67,77] Similarly, nasal chemesthesis is involved in restricting entry into or expelling unwanted material from the body via airway defense mechanisms that frequently involve laryngeal adduction, likely through indirect vagal pathways.[78,79] These upper airway reflexes include respiratory depression, apnea, coughing, and sneezing.[74,80,81] Of note, respiratory physiology can be altered even in response to olfactory sensory feedback, with inhalation airflow rates decreasing with higher concentrations of odorants.[82] Even when the nasal passages may fail to prevent airborne stimuli from entering the airway, specialized solitary chemosensory cells are expressed throughout the remainder of the upper and lower airway epithelia, including the larynx.[81,83] In particular, the laryngeal chemosensory system is highly responsive to chemical stimuli[83] and well equipped to engage in protective responses via the glottic closure reflex.[83,84] For a recent comprehensive review about the laryngeal chemoreflex, please see Pathak et al.[85]

Finally, the third chemical sensory system, gustation or taste, refers to the perception of non-airborne chemicals dissolved in saliva from foods and beverages. Gustation is perceived through activation of specialized taste cells primarily in the lingual papillae and is innervated by the facial nerve (CN VII), glossopharyngeal nerve (CN IX), and vagus nerve (CN X).[71] The primary sensory taste qualities are sweet, salty, bitter, sour, and umami (savory). Volatile molecules in food are capable of activating olfactory receptors as air flows in the opposite direction during drinking and eating. This pathway, called retronasal olfaction, occurs during mastication as molecules in the oral cavity are transported upward to the nasopharynx.[86] Although the gustatory and retronasal olfactory systems are separate in the periphery, these senses work in parallel to contribute to flavor perception during food intake.[87]

It is unsurprising that such critical airway defense mechanisms are readily modifiable to help ensure airway clearance, as the capability to modify upper airway reflexes is highly advantageous to human survival. In addition to peripheral sensation and motor reflexes, higher-order brain circuits are involved in airway defenses. Specifically, cough can be volitionally regulated via prefrontal cortical control of motor pathways.[88] The degree of voluntary control of airway protective reflexes is helpful to assist with enhancing or suppressing the intensity of a cough response according to a given scenario.

Higher cognitive processes, such as attention, learning, health beliefs, and expectations, substantially influence airway sensory processing and upper airway reflexes, as these factors contribute to how individuals interpret situations involving airborne stimuli.[89] For instance, a person's sensation of the urge-to-cough while inhaling an airborne stimulus, citric acid, was significantly higher after an experimenter labeled the stimulus as harmful. Similarly, individuals were more likely to cough upon breathing citric acid when instructed to pay close attention to cough sensations.[90] Even an experimenter describing an inhaled odorant as unhealthy led to greater objective measures of airway inflammation among patients with asthma.[91] From a clinical perspective, it is admittedly difficult to dissociate the physiological versus cognitive effects of inhaled airborne stimuli.

3.2. Selection and Reliable Delivery of Chemosensory Stimuli

Despite the abstract nature of odorant and chemical irritants, there are tools to both quantify stimuli concentrations and deliver them reliably. A common application of chemosensory testing is the clinical evaluation of chemical sensory losses such as anosmia, or smell loss.[92] Fortunately, adjustments to the concentrations of standardized chemosensory stimuli have been performed to test specific patient populations such as multiple chemical sensitivity.[93,94] An added benefit of using such stimuli is that chemical safety data have already been determined, with years of established normative data on chemosensory function among various patient populations.[95]

Selecting appropriate chemosensory stimuli remains an important consideration. Indeed, airborne molecules are capable of concurrently stimulating two distinct sensory systems in the nasal cavity, which are innervated by separate sensory receptors and cranial nerves. As a result, the perceptions of olfaction and chemesthesis are often confused in daily life.[96] Even in well controlled research experiments, differentiating olfaction from chemesthesis is a major challenge because at high enough concentrations, most odorants transition to being perceived as sensory irritants by activating the trigeminal nerve.[78] Because the majority of inhaled environmental exposures actually represent complex mixtures of multiple chemicals, the exact perceptual boundaries are unclear between odorant versus sensory irritant percepts. Responses to inhaled airborne stimuli might better represent a continuum of learned associations between both chemical senses.[82]

Generally, it is accepted that vanillin (sweet) and phenylethyl alcohol (rose-like) are pure odorants that activate only the olfactory system.[91,97] Thus, these two compounds are recommended when the goal is to measure the sense of smell while carefully controlling for potential interactions with the trigeminal system. In contrast, carbon dioxide is a sensory irritant that activates the trigeminal system with little or no detectable odor perception.[98,99] Other examples of commonly used chemosensory stimuli include isoamyl acetate (banana), limonene (lemon), carvone (spearmint), acetaldehyde (green apples), acetone (nail polish remover), butanol, menthol, and eucalyptol.[100] If the goal is to elicit reflex cough, capsaicin and citric acid are frequently used chemicals.[101] For clinicians and researchers who are capable of preparing their own stimuli, liquid solutions of compounds can be diluted to the desired concentrations using solvents such as mineral oil. When stimuli preparations are not possible, a reasonable alternative is to purchase pre-diluted chemicals, which will be discussed in more detail below.

A primary delivery system for chemosensory stimuli is olfactometry. Sophisticated instrumentation is necessary only when seeking high accuracy in stimuli presentation, such as the use of computer-controlled, air-dilution olfactometers in research laboratories.[102] For clinical applications, however, such detailed levels of precision are often unnecessary. In contrast to precision, reliability is a more important issue when delivering stimuli for clinical chemosensory testing.[103,104] Clinical assessment procedures should generally be repeatable, or performed the same way, to allow for meaningful interpretations of results between and within patients. Examples of reliable, low technology delivery systems include glass sniff bottles, plastic squeeze bottles, felt-tipped pens, perfumer's strips, 'scratch and sniff odorized strips, and alcohol pads.[103] Several commercially available products can be purchased to save time. In particular, clinically practical olfactory tests with normative data include the University of Pennsylvania Smell Identification Test,[105] Sniffin' Sticks Test,[106] and Snap and Sniff Threshold Test.[104] In addition, the NIH Toolbox Odor Identification Test is a less expensive alternative.[107] Although these products offer the benefit of easy application in the clinic, the disadvantage is that these delivery options might require more expense.

There are several caveats to testing with chemosensory stimuli. First, olfactory adaptation is the phenomenon of temporary desensitization of a chemosensory stimulus after initial exposure to it.[108] Therefore, inhaling high concentrations of a stimulus will typically lead to subsequent difficulty detecting, or perhaps the complete inability to detect, the same stimulus at a reduced concentration. To minimize the confounding effects of olfactory adaptation, brief recovery periods with no chemosensory exposures are necessary before presenting the next trials. Second, chemosensory testing frequently involves the addition of control stimuli, or blanks, between trials (e.g., odorless solvent). Controls are especially useful to determine whether inhaling a target stimulus causes a sensory experience or motor response in comparison to inhaling clean air alone. Controls can also be used to help ensure that individuals remain blinded to the stimulus that they will next be exposed to, thereby reducing cognitive influences that could lead to biased responses.

3.3. Sensory Testing using Psychophysical Measurements

After chemosensory stimuli and delivery systems have been chosen, a final step is to assess individuals' responses to stimuli to infer how the chemosensory systems are functioning. To achieve this, researchers and clinicians rely on psychophysical testing measures. Human psychophysics is the study of understanding the relationships between different sensory perceptions and quantitative stimuli.[109] In chemosensation, psychophysics aims to examine how individuals perceive odorants, sensory irritants, and tastants. A clinical parallel of eliciting responses to chemosensory stimuli is symptomology. Symptoms can represent a patient's subjective sensory experience (e.g., dyspnea, globus), which is often a primary motivation to seek medical care. During a medical history, clinicians spend much time obtaining details about symptoms because this information helps drive differential diagnosis. We propose that the following knowledge about psychophysics could be adapted for patients with disordered laryngeal-respiration symptoms. Appropriate modifications should be made to align with the purpose of a specific test, feasibility in a clinical setting, and patient tolerance to the presented chemosensory stimuli.

A major goal of psychophysics methodology is to quantify sensations.[110] In particular, the principles of psychophysics can accurately capture an individual's perceived intensities, either diminished or elevated, of sensory experiences.[86] These tools make it possible to convert the subjective nature of sensory-based symptoms to objective outcome measurements. The general application of psychophysical testing in chemosensation is to ask individuals to report their sensory experience when presented with a chemosensory stimulus. The protocols differ in the specific responses elicited, but they typically involve carefully training individuals to hone their awareness of the target sensation.

Psychophysical procedures can test an individual's thresholds as well as suprathreshold ratings.[92] For threshold testing, the goal is to determine the lowest concentration of a chemosensory stimulus that an individual can reliably detect. Similarly, recognition thresholds are the lowest concentrations that can be perceived well enough to provide a label based on a quality (e.g., fruity).[65] Thresholds can also be measured as a stimulus concentration that evokes a motor response such as a cough detection threshold.[111] Based on the measurements used in the chemical senses, 'chemical sensitivity' holds a specific meaning, referring to an individual's psychophysical test performance that indicates how attenuated or reduced their sensory function is compared to the general population.

In contrast to chemical sensitivity measured using threshold tests, suprathreshold testing relies on scaling procedures that measure the perceived intensity magnitudes of various sensations. In fact, any psychological attribute can be assigned to a chemosensory stimulus, including quality, strength, and hedonics.[103] Moreover, perhaps a more relevant problem that can be resolved using psychophysical testing is the ability to validly compare sensory experiences between different groups. Psychophysics methodology is able to account for the reality that an individual has unique sensory experiences that vastly differ from others.[112] An example of individual differences in sensation could be comparing the intensity of pain experienced during childbirth by two different women, or perhaps evaluating people's ranges in bitter taste perception while drinking coffee.[65] These inherent differences in sensation, which exist across individuals even in the absence of pathology, are likely more prominent among disordered populations. While a variety of scales exist, many chemosensory scientists rely on the general Labeled Magnitude Scale to collect suprathreshold intensity judgments.[103] Briefly, the general Labeled Magnitude Scale uses semantic labels from 'barely detectable' to 'strongest imaginable' sensation, which are spaced apart by a logarithmic scale,[113] and permits valid comparisons of sensory responses across groups of individuals and different types of sensations.[114] As such, this psychophysical measure has important clinical implications for differentiating patients with and without a given disorder based on the quantification of sensory-based symptoms. The stipulation with suprathreshold scaling procedures is that individuals must be properly trained, as well as cognitively able to participate. Finally, we end this review with a brief discussion that focuses on bridging scientific evidence from chemosensation with clinical relevance among patients with laryngeal-respiratory symptoms related to inhaled airborne stimuli.

4. Implications for Clinical Practice and Research

Based on the identified gaps in clinical practices related to laryngeal-respiratory disorders and the corresponding scientific evidence in chemosensation, we offer several key takeaways to bridge these concepts. The first theme revealed that many types and concentrations of triggering airborne stimuli contribute to symptoms of laryngeal impairment affecting respiration. Given that otolaryngologists and speech-language pathologists routinely describe the larynx as a protector of the airway,[26] clinicians are uniquely qualified to continue delivering patient education with the added benefit of providing scientific reasons to explain normal physiological laryngeal responses to inhaled stimuli. Clinicians who communicate this health information can help validate patients' experiences and address subsequent concerns regarding the safety of breathing airborne stimuli. For instance, patients who report that odorant and irritant chemical stimuli exacerbate their symptoms could be reassuringly counseled that the chemical sensory systems act, in part, as efficient defense mechanisms against airborne stimuli entering the airway. Furthermore, patients would appreciate recognizing that chemosensation is involved in at least three levels of airway protection, beginning with volitional behavior changes via learned associations between the perceptions of stimuli and interpretations of environmental danger[73] (e.g., patients who avoid fragrance aisles at retail establishments). Another level involves chemically-induced upper airway reflexes, including laryngeal movements, through nasal trigeminal chemesthesis[66] (e.g., patients who reflexively cough when inhaling paint fumes). As a final level of protection, extreme inhalation exposures can activate immune responses[67] (e.g., patients who develop signs of laryngeal tissue inflammation). These examples of education, which are founded in the science of chemosensation, would help reassure patients that their experiences, symptoms, and uncertainties may reasonably be explained and are recognized among scientists and clinicians as protective upper airway responses.

The second theme described a lack of consistency across clinical provocation challenges to elicit signs of laryngeal and respiratory incoordination. Fortunately, the nature of provocation lends itself quite well to the use of chemosensory stimuli in clinical settings. For clinicians who currently use airborne stimuli during provocation challenges, we recommend entertaining the idea of implementing standardized chemosensory stimuli, described previously. Additionally, it is possible that this new knowledge about the standard presentations of chemosensory stimuli might remove logistical barriers for clinicians who previously hesitated to implement provocation challenges with patients. We acknowledge that no universal protocol is utilized across clinics and caution that its full clinical utility remains to be known. However, similar to regulating bolus consistencies during the assessment of swallowing function,[4] the main advantage of controlling the categories, concentrations, and delivery methods of airborne stimuli is the increased replicability both within and between patients, as well as available chemical safety data and ease of access to commercial products. In addition to standardizing assessment procedures, chemosensory stimuli have the potential to be used as therapeutic agents in behavioral speech therapy. If manipulating people's health beliefs regarding the safety of inhaled chemicals modifies cough sensations and upper airway responses,[90] this serves as evidence to support behavioral therapy techniques, such as respiratory retraining and cough suppression, implemented by speech-language pathologists.

The final theme demonstrated challenges associated with measuring vague laryngeal-based symptoms. Principles of human psychophysics that reveal how suprathreshold sensory ratings are interpreted could be an avenue of future research to help elucidate the driving mechanisms of disordered laryngeal-respiration. Specifically, sensory testing has the potential to guide clinical decisions such as which subgroups of patients would benefit most from different management approaches. For instance, greater fluctuations in suprathreshold intensity ratings, such as perceived dyspnea and the urge-to-cough, might be expected among patients with a non-organic etiology (e.g., primary functional laryngeal and airway disorders[115]). In contrast, patients with a predominant neurogenic etiology (e.g., chronic laryngopharyngeal neuropathy[14]) may exhibit less variation in the same suprathreshold intensity ratings based on the assumption that neuropathophysiology is the cause of symptoms, which should remain relatively consistent over time. Consequently, the notion of clinical subgroups of laryngeal-respiratory disorders is congruent with current management options that involve nonpharmacological (e.g., behavioral speech therapy) and pharmacological interventions (e.g., neuromodulating agents[13]), and deserves further investigation to optimize timely and effective treatment.

We acknowledge that while this review addressed only external stimuli, patients with impaired laryngeal and respiratory function frequently encounter internal triggering stimuli such as gastric refluxate.[116-119] Understanding similarities and differences in laryngeal responses between external and internal triggering stimuli would be a meaningful area of study. In addition, the distinction across functional laryngeal disorders is becoming more equivocal, as overlapping laryngeal symptomology (e.g., phonation, respiration, swallowing, upper airway defense reflexes) has been observed across different diagnoses including muscle tension dysphonia, muscle tension dysphagia, vocal cord dysfunction, and chronic cough.[30,120,121] As an alternative approach to diagnosing functional laryngeal disorders according to the predominant symptoms,[122] multiple upper airway symptoms may actually represent a larger continuum of functional disorders of the larynx.[123] It is our hope that future research about the role of the larynx during respiration, including the respiratory act of coughing, will better inform how to improve patient outcomes related to the overall category of functional laryngeal disorders.

5. Conclusion

Clinical practices have expanded in otolaryngology and speech-language pathology to include laryngeal disorders affecting respiration. This extension of services logically necessitates new training and incorporation of techniques specific to respiratory functions of the larynx. Here, we explored topics from the discipline of chemosensation based on notable gaps in clinical practice. We described relevant concepts including differentiating the three chemosensory systems, reliably delivering safe chemosensory stimuli, and measuring sensory perception using psychophysical testing. These concepts have the potential to be applied to patient education and counseling, provocation challenge testing, and differential diagnosis of clinical subgroups. Despite this new knowledge from another discipline, much of the clinical application will evolve as we continue to build upon the existing literature. We anticipate that additional research and clinical evidence, along with receptiveness to necessary modifications, will facilitate further growth in this clinical area and guide assessment and management of laryngeal-respiratory disorders. We encourage subsequent discoveries from other fields with the goal of synthesizing other relevant information to add relevant approaches that are not currently under consideration.

Acknowledgements

This work was supported by the National Institute on Deafness and Other Communication Disorders of the National Institutes of Health (NIH) under award number F32DC016805 (PI: CN) and the National Institute of Neurological Disorders and Stroke of the NIH under award number U19NS112953 (PI: JM). The research conducted by CN and AN was supported by training award number T32DC000014 (PIs: PD and JM). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. Additional research support was provided by a generous gift to the Monell Chemical Senses Center from Dr. Louise Slade. Special thanks to Drs. Karen Hegland, Adrianna Shembel, and Beverly Cowart for their constructive feedback.

References

1. Franco RA, Andrus JG. Common diagnoses and treatments in professional voice users. Otolaryngologic Clinics of North America. 2007;40(5):1025–1061, vii. [PubMed: 17765694]
2. Stachler RJ, Francis DO, Schwartz SR, et al. Clinical practice guideline: Hoarseness (dysphonia) (update) executive summary. Otolaryngology-Head and Neck Surgery. 2018;158(3):409–426. [PubMed: 29494316]
3. Miller RM, Groher ME. Speech-language pathology and dysphagia: A brief historical perspective. Dysphagia. 1993;8(3):180–184. [PubMed: 8359037]
4. Pennman JP, Thomson M. A review of the textured diets developed for the management of dysphagia. Journal of Human Nutrition and Dietetics. 1998;11:51–60.
5. Martin-Harris B, Jones B. The videofluorographic swallowing study. Physical Medicine and Rehabilitation Clinics of North America. 2008;19(4):769–785, viii. [PubMed: 18940640]
6. Altman KW, Irwin RS. Cough: A new frontier in otolaryngology. Otolaryngology-Head and Neck Surgery. 2011;144(3):348–352. [PubMed: 21493194]
7. Altman KW, Lane AP, Irwin RS. Otolaryngology aspects of chronic cough. The Journal of Allergy and Clinical Immunology: In Practice. 2019;7(6):1750–1755. [PubMed: 31078514]
8. Patel RR, Venediktov R, Schooling T, Wang B. Evidence-based systematic review: Effects of speech-language pathology treatment for individuals with paradoxical vocal fold motion. American Journal of Speech-Language Pathology. 2015;24(3):566–584. [PubMed: 25836980]
9. American Speech-Language-Hearing Association. Scope of Practice in Speech-Language Pathology. https://www.asha.org/policy/sp2016-00343/. 2016.
10. Stemple JC, Fry LT. Voice therapy: Clinical case studies. 3rd ed. San Diego, CA: Plural Publishing; 2010.
11. Vertigan AE. The larynx as a target for treatment in chronic refractory cough. Current Otorhinolaryngology Reports. 2019;7:129–136.
12. Hess HE, Barone NA, Daniero JJ. Predicting patient needs for interdisciplinary services in a voice and swallowing center. Journal of Voice. 2020;34(3):435–441. [PubMed: 30401577]
13. Cohen SM, Misono S. Use of specific neuromodulators in the treatment of chronic, idiopathic cough: A systematic review. Otolaryngology-Head and Neck Surgery. 2013;148(3):374–382. [PubMed: 23300226]
14. DePietro JD, Jang M, Sjogren EV, Dikkers FG, Cohen SM, Noordzij JP. Management of chronic laryngopharyngeal neuropathy in the United States and Europe. The Annals of Otology, Rhinology, and Laryngology. 2015;124(4):305–311. [PubMed: 25358612]

15. DePietro JD, Stein DJ, Calloway N, Cohen SM, Noordzij PJ. U.S. practice variations in the treatment of chronic laryngopharyngeal neuropathy. The Laryngoscope. 2014;124(4):955–960. [PubMed: 24122867]
16. Shembel AC, Sandage MJ, Verdolini Abbott K. Episodic laryngeal breathing disorders: Literature review and proposal of preliminary theoretical framework. Journal of Voice. 2017;31(1):125.e127–125.e116.
17. Andrianopoulos MV, Gallivan GJ, Gallivan KH. PVCM, PVCD, EPL, and irritable larynx syndrome: What are we talking about and how do we treat it? Journal of Voice. 2000;14(4):607–618. [PubMed: 11130117]
18. Brooks SM. Vocal cord dysfunction after an inhalation exposure. Journal of Allergy and Therapy. 2017;8(3):1000261.
19. Dailey SH, Mai JP. Chronic Cough. In: Carroll TL, ed. Overview of Chronic Cough and its Impact on Health Care. San Diego, CA: Plural Publishing; 2019:1–19.
20. Gillespie A, Gartner-Schmidt J. Odor induced laryngeal hypersensitivity. Perspectives on Voice and Voice Disorders (SIG 3). 2006;16:10–15.
21. Morrison M, Rammage L, Emami AJ. The irritable larynx syndrome. Journal of Voice. 1999;13(3):447–455. [PubMed: 10498060]
22. Morrison M, Rammage L. The irritable larynx syndrome as a central sensitivity syndrome. Canadian Journal of Speech-Language Pathology and Audiology. 2010;34(4):282–289.
23. Tomares SM, Flotte TR, Tunkel DE, Pao M, Loughlin GM. Real time laryngoscopy with olfactory challenge for diagnosis of psychogenic stridor. Pediatric Pulmonology. 1993; 16(4) :259–262. [PubMed: 8265275]
24. Vertigan AE, Gibson PG. Speech pathology management of chronic refractory cough and related disorders. Braunton, Devon, UK: Compton Publishing; 2016.
25. Guss J, Mirza N. Methacholine challenge testing in the diagnosis of paradoxical vocal fold motion. The Laryngoscope. 2006;116(9):1558–1561. [PubMed: 16954978]
26. Hodges HL. Speech therapy for the treatment of functional respiratory disorders. In: Functional Respiratory Disorders: When Respiratory Symptoms Do Not Respond to Pulmonary Treatment. Anbar RD (editor), New York, NY: Humana Press; 2012.
27. Pacheco KA, Chenworth E, Blager FB. Diagnosis of vocal cord dysfunction by irritant challenges. Journal of Allergy and Clinical Immunology. 2011;127(2):AB20.
28. Tay TR, Hoy R, Richards AL, Paddle P, Hew M. Inhaled mannitol as a laryngeal and bronchial provocation test. Journal of Voice. 2017;31(2):247.e219–247.e223.
29. Taramarcaz P, Seebach JD, Motteli L, Benaim C, Schwitzguebel AJ. Spirometry and provocation tests for vocal fold dysfunction diagnosis: A retrospective case series. Swiss Medical Weekly. 2018;148:w14692. [PubMed: 30667518]
30. Vertigan AE, Kapela SM, Kearney EK, Gibson PG. Laryngeal dysfunction in cough hypersensitivity syndrome: A cross-sectional observational study. Journal of Allergy and Clinical Immunology In practice. 2018;6(6):2087–2095. [PubMed: 29729441]
31. Bartlett D Jr. Respiratory functions of the larynx. Physiological Reviews. 1989;69(1):33–57. [PubMed: 2643125]
32. Ludlow CL. Laryngeal reflexes: Physiology, technique, and clinical use. Journal of Clinical Neurophysiology. 2015;32(4):284–293. [PubMed: 26241237]
33. Troche MS, Brandimore AE, Godoy J, Hegland KW. A framework for understanding shared substrates of airway protection. Journal of Applied Oral Science : revista FOB. 2014;22(4):251–260. [PubMed: 25141195]
34. Donzelli J, Brady S. The effects of breath-holding on vocal fold adduction: Implications for safe swallowing. Archives of Otolaryngology-Head & Neck Surgery. 2004;130(2):208–210. [PubMed: 14967752]
35. Martin BJ, Logemann JA, Shaker R, Dodds WJ. Normal laryngeal valving patterns during three breath-hold maneuvers: A pilot investigation. Dysphagia. 1993;8(1):11–20. [PubMed: 8436017]
36. Mendelsohn MS, Martin RE. Airway protection during breath-holding. The Annals of Otology, Rhinology, and Laryngology. 1993;102(12):941–944. [PubMed: 8285515]

37. Pstras L, Thomaseth K, Waniewski J, Balzani I, Bellavere F. The Valsalva manoeuvre: Physiology and clinical examples. Acta Physiologica (Oxford, England). 2016;217(2):103–119. [PubMed: 26662857]
38. Chung KF, Bolser D, Davenport P, Fontana G, Morice A, Widdicombe J. Semantics and types of cough. Pulmonary Pharmacology & Therapeutics. 2009;22(2):139–142. [PubMed: 19136069]
39. Hegland KW, Troche MS, Brandimore AE, Davenport PW, Okun MS. Comparison of voluntary and reflex cough effectiveness in Parkinson's disease. Parkinsonism & Related Disorders. 2014;20(11):1226–1230. [PubMed: 25246315]
40. Altman KW, Simpson CB, Amin MR, Abaza M, Balkissoon R, Casiano RR. Cough and paradoxical vocal fold motion. Otolaryngology-Head and Neck Surgery. 2002;127(6):501–511. [PubMed: 12501100]
41. Forrest LA, Husein T, Husein O. Paradoxical vocal cord motion: Classification and treatment. The Laryngoscope. 2012;122(4):844–853. [PubMed: 22434681]
42. Vertigan AE, Theodoros DG, Gibson PG, Winkworth AL. Efficacy of speech pathology management for chronic cough: A randomised placebo controlled trial of treatment efficacy. Thorax. 2006;61(12):1065–1069. [PubMed: 16844725]
43. Hull JH, Backer V, Gibson PG, Fowler SJ. Laryngeal dysfunction: Assessment and management for the clinician. American Journal of Respiratory and Critical Care Medicine. 2016;194(9) :1062–1072. [PubMed: 27575803]
44. Vertigan AE, Theodoros DG, Gibson PG, Winkworth AL. The relationship between chronic cough and paradoxical vocal fold movement: A review of the literature. Journal of Voice. 2006;20(3):466–480. [PubMed: 16274959]
45. Slovarp L, Loomis BK, Glaspey A. Assessing referral and practice patterns of patients with chronic cough referred for behavioral cough suppression therapy. Chronic Respiratory Disease. 2018;15(3):296–305. [PubMed: 29430939]
46. Allan PF, Abouchahine S, Harvis L, Morris MJ. Progressive vocal cord dysfunction subsequent to a chlorine gas exposure. Journal of Voice. 2006;20(2):291–296. [PubMed: 16293397]
47. Bhargava S, Panitch HB, Allen JL. Chlorine induced paradoxical vocal cord dysfunction. Chest. 2000;118(suppl):295S–296S.
48. Cummings KJ, Fink JN, Vasudev M, Piacitelli C, Kreiss K. Vocal cord dysfunction related to water-damaged buildings. The Journal of Allergy and Clinical Immunology: In Practice. 2013;1(1):46–50. [PubMed: 24229821]
49. de la Hoz RE, Shohet MR, Bienenfeld LA, Afilaka AA, Levin SM, Herbert R. Vocal cord dysfunction in former World Trade Center (WTC) rescue and recovery workers and volunteers. American Journal of Industrial Medicine. 2008;51(3):161–165. [PubMed: 18213642]
50. Galdi E, Perfetti L, Pagella F, Bertino G, Ferrari M, Moscato G. Irritant vocal cord dysfunction at first misdiagnosed as reactive airway dysfunction syndrome. Scandinavian Journal of Work, Environment & Health. 2005;31(3):224–226.
51. Gartner-Schmidt JL, Rosen CA, Radhakrishnan N, Ferguson BJ. Odor provocation test for laryngeal hypersensitivity. Journal of Voice. 2008;22(3):333–338. [PubMed: 17512171]
52. Herin F, Poussel M, Renaudin JM, et al. A 38-year-old hairdresser with irritant-associated vocal cord dysfunction. The International Journal of Tuberculosis and Lung Disease. 2012;16(1):138–139. [PubMed: 22236860]
53. Hoy RF, Ribeiro M, Anderson J, Tarlo SM. Work-associated irritable larynx syndrome. Occupational Medicine. 2010;60(7) :546–551. [PubMed: 20871021]
54. Huggins JT, Kaplan A, Martin-Harris B, Sahn SA. Eucalyptus as a specific irritant causing vocal cord dysfunction. Annals of Allergy, Asthma & Immunology. 2004;93(3):299–303.
55. Marcinow AM, Thompson J, Forrest LA, deSilva BW. Irritant-induced paradoxical vocal fold motion disorder: Diagnosis and management. Otolaryngology-Head and Neck Surgery. 2015;153(6):996–1000. [PubMed: 26307573]
56. Munoz X, Roger A, De la Rosa D, Morell F, Cruz MJ. Occupational vocal cord dysfunction due to exposure to wood dust and xerographic toner. Scandinavian Journal of Work, Environment & Health. 2007;33(2):153–158.

57. Perkner JJ, Fennelly KP, Balkissoon R, et al. Irritant-associated vocal cord dysfunction. Journal of Occupational and Environmental Medicine. 1998;40(2):136–143. [PubMed: 9503289]

58. Reddy PV, Solomon D, Truncale T. Vocal cord dysfunction after chlorine inhalation. Chest. 2004;126:999S.

59. Tonini S, Dellabianca A, Costa C, Lanfranco A, Scafa F, Candura SM. Irritant vocal cord dysfunction and occupational bronchial asthma: Differential diagnosis in a health care worker. International Journal of Occupational Medicine and Environmental Health. 2009;22(4):401–406. [PubMed: 20053620]

60. Weinberger M, Doshi D. Vocal cord dysfunction: A functional cause of respiratory distress. Breathe. 2017;13(1):15–21. [PubMed: 28289447]

61. Selner JC, Staudenmayer H, Koepke JW, Harvey R, Christopher K. Vocal cord dysfunction: The importance of psychologic factors and provocation challenge testing. The Journal of Allergy and Clinical Immunology. 1987;79(5):726–733. [PubMed: 3571766]

62. Bahrainwala AH, Simon MR. Wheezing and vocal cord dysfunction mimicking asthma. Current Opinion in Pulmonary Medicine. 2001;7(1):8–13. [PubMed: 11140406]

63. Morris MJ, Allan PF, Perkins PJ. Vocal cord dysfunction: Etiologies and treatment. Clinical Pulmonology Medicine. 2006;13(2):73–86.

64. Pinto JM. Olfaction. Proceedings of the American Thoracic Society. 2011;8(1):46–52. [PubMed: 21364221]

65. Reed DR, Knaapila A. Genetics of taste and smell: Poisons and pleasures. Progress in Molecular Biology and Translational Science. 2010;94:213–240. [PubMed: 21036327]

66. Green BG. Chemesthesis and the chemical senses as components of a "chemofensor complex". Chemical Senses. 2012;37(3):201–206. [PubMed: 22210122]

67. Bruning T, Bartsch R, Bolt HM, et al. Sensory irritation as a basis for setting occupational exposure limits. Archives of Toxicology. 2014;88(10):1855–1879. [PubMed: 25182421]

68. Jette ME, Clary MS, Prager JD, Finger TE. Chemical receptors of the arytenoid: A comparison of human and mouse. Laryngoscope. 2020;130(2):423–430. [PubMed: 30908677]

69. Gent JF, Goodspeed RB, Zagraniski RT, Catalanotto FA. Taste and smell problems: Validation of questions for the clinical history. Yale Journal of Biology and Medicine. 1987;60(1):27–35. [PubMed: 3564547]

70. Zhao K, Dalton P. The way the wind blows: Implications of modeling nasal airflow. Current Allergy and Asthma Reports. 2007;7(2):117–125. [PubMed: 17437682]

71. Lundstrom JN, Boesveldt S, Albrecht J. Central processing of the chemical senses: An overview. ACS Chemical Neuroscience. 2011;2(1):5–16. [PubMed: 21503268]

72. Stevenson RJ. An initial evaluation of the functions of human olfaction. Chemical Senses. 2010;35(1):3–20. [PubMed: 19942579]

73. Wilson DA, Stevenson RJ. Learning to smell: Olfactory perception from neurobiology to behavior. Baltimore, MD: The Johns Hopkins University Press; 2006.

74. Silver WL. Physiological factors in nasal trigeminal chemoreception. In: Green BG, Mason JR, Kare MR, eds. Chemical Senses. Vol 2: Irritation. New York, NY: Marcel Dekker, Inc.; 1990.

75. Kjaergaar SK, Hodgson M. The assessment of irritation using clinical methods and questionnaires. AIHAJ. 2001;62(6):711–716. [PubMed: 11767936]

76. Finger TE, Bottger B, Hansen A, Anderson KT, Alimohammadi H, Silver WL. Solitary chemoreceptor cells in the nasal cavity serve as sentinels of respiration. Proceedings of the National Academy of Sciences of the United States of America. 2003;100(15):8981–8986. [PubMed: 12857948]

77. Viana F Chemosensory properties of the trigeminal system. ACS Chemical Neuroscience. 2011;2(1):38–50. [PubMed: 22778855]

78. Doty RL, Cometto-Muniz JE, Jalowayski AA, Dalton P, Kendal-Reed M, Hodgson M. Assessment of upper respiratory tract and ocular irritative effects of volatile chemicals in humans. Critical Reviews in Toxicology. 2004;34(2):85–142. [PubMed: 15112751]

79. Bucca CB, Bugiani M, Culla B, et al. Chronic cough and irritable larynx. The Journal of Allergy and Clinical Immunology. 2011;127(2):412–419. [PubMed: 21167571]

80. Bradley RM. Sensory receptors of the larynx. The American Journal of Medicine. 2000;108 Suppl 4a:47s–50s. [PubMed: 10718452]

81. Tizzano M, Cristofoletti M, Sbarbati A, Finger TE. Expression of taste receptors in solitary chemosensory cells of rodent airways. BMC Pulmonary Medicine. 2011;11:1–12. [PubMed: 21214899]

82. Johnson BN, Mainland JD, Sobel N. Rapid olfactory processing implicates subcortical control of an olfactomotor system. Journal of Neurophysiology. 2003;90(2):1084–1094. [PubMed: 12711718]

83. Sbarbati A, Merigo F, Benati D, Tizzano M, Bernardi P, Osculati F. Laryngeal chemosensory clusters. Chemical Senses. 2004;29(8):683–692. [PubMed: 15466813]

84. Sasaki CT, Weaver EM. Physiology of the larynx. The American Journal of Medicine. 1997;103(5a):9s–18s. [PubMed: 9422616]

85. Pathak S, Slovarp L, Clary MS, Jette ME. Laryngeal chemoreflex in health and disease: A review. Chemical Senses. 2020;45(9):823–831. [PubMed: 33247587]

86. Bartoshuk LM, Beauchamp GK. Chemical senses. Annu Rev Psychol. 1994;45:419–449. [PubMed: 8135507]

87. Bartoshuk LM, Sims CA, Colquhoun TA, Snyder DJ. What Aristotle didn't know about flavor. American Psychologist. 2019;74(9):1003–1011. [PubMed: 31829675]

88. Mazzone SB, Farrell MJ. Heterogeneity of cough neurobiology: Clinical implications. Pulmonary Pharmacology & Therapeutics. 2019;55:62–66. [PubMed: 30763726]

89. Van den Bergh O, Van Diest I, Dupont L, Davenport PW. On the psychology of cough. Lung. 2012;190(1):55–61. [PubMed: 22120902]

90. Janssens T, Brepoels S, Dupont L, Van den Bergh O. The impact of harmfulness information on citric acid induced cough and urge-to-cough. Pulmonary Pharmacology & Therapeutics. 2015;31:9–14. [PubMed: 25634521]

91. Jaen C, Dalton P. Asthma and odors: The role of risk perception in asthma exacerbation. Journal of Psychosomatic Research. 2014;77(4):302–308. [PubMed: 25280827]

92. Doty RL. Measurement of chemosensory function. World Journal of Otorhinolaryngology-Head & Neck Surgery. 2018;4(1):11–28. [PubMed: 30035257]

93. Doty RL, Deems DA, Frye RE, Pelberg R, Shapiro A. Olfactory sensitivity, nasal resistance, and autonomic function in patients with multiple chemical sensitivities. Archives of Otolaryngology-Head & Neck Surgery. 1988;114(12):1422–1427. [PubMed: 2461210]

94. Zucco GM, Militello C, Doty RL. Discriminating between organic and psychological determinants of multiple chemical sensitivity: A case study. Neurocase. 2008;14(6):485–493. [PubMed: 19012169]

95. Doty RL. Olfaction. Annual Review of Psychology. 2001;52:423–452.

96. Engen T Odor sensation and memory. New York, NY: Praeger Publishers; 1991.

97. Tremblay C, Frasnelli J. Olfactory and trigeminal systems interact in the periphery. Chemical Senses. 2018;43(8):611–616. [PubMed: 30052799]

98. Hummel T Assessment of intranasal trigeminal function. International Journal of Psychophysiology. 2000;36(2):147–155. [PubMed: 10742569]

99. Wise PM, Radil T, Wysocki CJ. Temporal integration in nasal lateralization and nasal detection of carbon dioxide. Chemical Senses. 2004;29(2):137–142. [PubMed: 14977810]

100. Hummel T, Sekinger B, Wolf SR, Pauli E, Kobal G. 'Sniffin' sticks': Olfactory performance assessed by the combined testing of odor identification, odor discrimination and olfactory threshold. Chemical Senses. 1997;22(1):39–52. [PubMed: 9056084]

101. Ebihara S, Izukura H, Miyagi M, Okuni I, Sekiya H, Ebihara T. Chemical senses affecting cough and swallowing. Current Pharmaceutical Design. 2016;22(15):2285–2289. [PubMed: 26881438]

102. Lundström JN, Gordon AR, Alden EC, Boesveldt S, Albrecht J. Methods for building an inexpensive computer-controlled olfactometer for temporally-precise experiments. International Journal of Psychophysiology. 2010;78(2):179–189. [PubMed: 20688109]

103. Doty RL, Laing DG. Psychophysical measurement of human olfactory function. In: Doty RL, ed. Handbook of Olfaction and Gustration. 3rd ed. Hoboken, NJ: John Wiley & Sons, Inc.; 2015.

104. Doty RL. Olfactory dysfunction and its measurement in the clinic. World Journal of Otorhinolaryngoly-Head Neck Surgery. 2015;1(1):28–33.

105. Doty RL, Shaman P, Dann M. Development of the University of Pennsylvania Smell Identification Test: A standardized microencapsulated test of olfactory function. Physiology & Behavior. 1984;32(3):489–502. [PubMed: 6463130]

106. Kobal G, Hummel T, Sekinger B, Barz S, Roscher S, Wolf S. "Sniffin" sticks": Screening of olfactory performance. Rhinology. 1996;34(4):222–226. [PubMed: 9050101]

107. Dalton P, Doty RL, Murphy C, et al. Olfactory assessment using the NIH Toolbox. Neurology. 2013;80(11 Suppl 3):S32–36. [PubMed: 23479541]

108. Pellegrino R, Sinding C, de Wijk RA, Hummel T. Habituation and adaptation to odors in humans. Physiology & Behavior. 2017;177:13–19. [PubMed: 28408237]

109. Heymann H A personal history of sensory science. Food, Culture & Society. 2019;22(2):203–223.

110. Doty RL. Psychophysical testing of smell and taste function. Handbook of Clinical Neurology. 2019;164:229–246. [PubMed: 31604550]

111. Wise PM, Breslin PA, Dalton P. Sweet taste and menthol increase cough reflex thresholds. Pulmonary Pharmacology & Therapeutics. 2012;25(3):236–241. [PubMed: 22465565]

112. Bartoshuk LM, Duffy VB, Chapo AK, et al. From psychophysics to the clinic: Missteps and advances. Food Quality and Preference. 2004;15(7-8):617–632.

113. Green BG, Dalton P, Cowart B, Shaffer G, Rankin K, Higgins J. Evaluating the 'Labeled Magnitude Scale' for measuring sensations of taste and smell. Chemical Senses. 1996;21(3):323–334. [PubMed: 8670711]

114. Bartoshuk LM. Psychophysics: A journey from the laboratory to the clinic. Appetite. 2004;43(1):15–18. [PubMed: 15262013]

115. Misono S, Dietrich M, Piccirillo JF. The puzzle of medically unexplained symptoms: A holistic view of the patient with laryngeal symptoms. JAMA Otolaryngology-Head & Neck Surgery. 2020;146(6):550–551. [PubMed: 32352490]

116. George S, Suresh S. Vocal cord dysfunction: Analysis of 27 cases and updated review of pathophysiology & management. International Archives of Otorhinolaryngology. 2019;23(2):125–130. [PubMed: 30956693]

117. Loughlin CJ, Koufman JA. Paroxysmal laryngospasm secondary to gastroesophageal reflux. Laryngoscope. 1996;106(12 Pt 1):1502–1505. [PubMed: 8948611]

118. Murry T, Tabaee A, Aviv JE. Respiratory retraining of refractory cough and laryngopharyngeal reflux in patients with paradoxical vocal fold movement disorder. Laryngoscope. 2004;114(8):1341–1345. [PubMed: 15280705]

119. Poelmans J, Tack J, Feenstra L. Paroxysmal laryngospasm: A typical but underrecognized supraesophageal manifestation of gastroesophageal reflux? Digestive Diseases and Sciences. 2004;49(11-12):1868–1874. [PubMed: 15628718]

120. Kang CH, Hentz JG, Lott DG. Muscle tension dysphagia: Symptomology and theoretical framework. Otolaryngology-Head and Neck Surgery. 2016;155(5):837–842. [PubMed: 27352887]

121. Kang CH, Zhang N, Lott DG. Muscle tension dysphagia: Contributing factors and treatment efficacy. Annals of Otology, Rhinology, and Laryngology. 2020:3489420966339. doi: 10.1177/0003489420966339. Online ahead of print.

122. Murry T, Milstein CF. Laryngeal movement disorders and their treatment. Perspectives on Voice and Voice Disorders. 2016;1(Part 3):75–82.

123. McGarey PO Jr., Barone NA, Freeman M, Daniero JJ. Comorbid dysphagia and dyspnea in muscle tension dysphonia: A global laryngeal musculoskeletal problem. OTO Open. 2018;2(3):2473974x18795671.

Table 1.

Studies Demonstrating Temporal Relationships between Exposures to Airborne Stimuli and Development of Laryngeal Disorders Affecting Respiration.

Reference	Study Design	N	Patient Descrintion	Triggering Stimulus	Exposure Description	Diagnosis
Allan et al. (2006)[46]	Case report	1	49-year-old male firefighter	Chlorine gas	Single, accidental occupational exposure 15,000 gallons Duration 6 hours	Vocal cord dysfunction
Bhargava et al. (2000)[47]	Case report	1	17-year-old male student athlete	Swimming pool chlorine	Chronic recreational exposure	Paradoxical vocal cord dysfunction
Cummings et al. (2013)[48]	Case series	2	47-year-old female and 31-year-old female office workers	Indoor mold growth in water-damaged buildings	Chronic, accidental occupational exposure	Vocal cord dysfunction
de la Hoz et al. (2008)[49]	Case series	10	6 male and 4 female 9/11 World Trade Center rescue workers and volunteers (age range 35-70 years)	Variety of irritants and compounds from 9/11 World Trade Center disaster	Chronic, accidental occupational exposure Duration range 3-23 weeks	Vocal cord dysfunction
Galdi et al. (2005)[50]	Case report	1	47-year-old female nurse	Glutaraldehyde	Single occupational exposure Duration 20-30 minutes	Vocal cord dysfunction
Gartner-Schmidt et al. (2008)[51]	Case report	1	53-year-old female	Paint fumes	Single occupational exposure	Laryngeal hypersensitivity
Herin et al. (2012)[52]	Case report	1	38-year-old female hairdresser	Bleaching agents	Chronic occupational exposure	Irritant-associated vocal cord dysfunction
Hoy et al. (2010)[53]	Case series	14	3 males and 11 females in manufacturing, sales, business, and construction (mean age 50.6 years)	Perfumes Cleaning agents Paint fumes Dust Exhaust Unspecified odors and fumes	Single and chronic occupational and recreational exposure	Work-associated irritable larynx syndrome
Huggins et al. (2004)[54]	Case report	1	46-year-old female nurse	Eucalyptus plant	Chronic occupational exposure	Vocal cord dysfunction
Marcinow et al. (2015)[55]	Case series	34	3 males and 31 females (age range 27-73 years)	Not reported	Single exposure	Irritant-induced paradoxical vocal fold motion disorder
Munoz et al. (2007)[56]	Case report	1	26-year-old male carpenter	Iroko and western red cedar wood dust	Chronic occupational exposure	Vocal cord dysfunction
Perkner et al. (1998)[57]	Case series	11	3 males and 8 females in manufacturing, housekeeping, health care, transportation, farming, clerical, safety inspection, and food service (mean age 45 years)	Ammonia Cleaning chemicals Solder fumes Smoke Machine fluid Ceiling tile dust Unspecified odors	Single occupational and recreational exposure	Irritant-associated vocal cord dysfunction
Reddy et al. (2004)[58]	Case report	1	25-year-old female	Chlorine gas	Single, accidental occupational exposure	Vocal cord dysfunction
Tonini et al. (2009)[59]	Case report	1	45-year-old female nurse	Isopropylic alcohol Formaldehyde Glutaraldehyde	Chronic occupational exposure	Occupational irritant-induced vocal cord dysfunction

Reference	Study Design	N	Patient Descrintion	Triggering Stimulus	Exposure Description	Diagnosis
				Peracetic acid Hydrogen peroxide Sodium hypochlorite		
Weinberger et al. (2017)[60]	Case report	1	15-year-old female corn detasseler	Sodium hypochlorite Cornfield	Single occupational exposure	Vocal cord dysfunction