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Oral Sensory Nerve Damage: Causes and Consequences

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Abstract

Oral sensations (i.e., taste, oral somatosensation, retronasal olfaction) are integrated into a composite sense of flavor, which guides dietary choices with long-term health impact. The nerves carrying this input are vulnerable to peripheral damage from multiple sources (e.g., otitis media, tonsillectomy, head injury), and this regional damage can boost sensations elsewhere in the mouth because of central interactions among nerve targets. Mutual inhibition governs this compensatory process, but individual differences lead to variation in whole-mouth outcomes: some individuals are unaffected, others experience severe loss, and some encounter sensory increases that may (if experienced early in life) elevate sweet-fat palatability and body mass. Phantom taste, touch, or pain sensations (e.g., burning mouth syndrome) may also occur, particularly in those expressing the most taste buds. To identify and treat these conditions effectively, emerging clinical tests measure regional vs. whole-mouth sensation, stimulated vs. phantom cues, and oral anatomy. Scaling methods allowing valid group comparisons have strongly aided these efforts. Overall, advances in measuring oral sensory function in health and disease show promise for understanding the varied clinical consequences of nerve damage.

Keywords

Taste; oral sensation; otitis media; tonsillectomy; phantom taste; burning mouth syndrome; obesity; intensity scale

1. Introduction

Oral sensations play a vital role in dietary health: they broadly govern flavor perception and food choice, which in turn contribute to long-term risk for chronic conditions such as obesity, cardiovascular disease, and cancer. In humans, the ability to perceive these sensations varies considerably, driven in large part by differences in oral anatomy and receptor expression. The relationships between oral physiology, sensation, and nutritional status remain to be fully understood, but the general consensus is that, as individuals, we live

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in diverse oral sensory worlds that shape both our interactions with food and the health impact of those interactions.

To complicate matters, another important source of oral sensory variation is damage to the nerves carrying it. Several cranial nerves convey oral sensory input, and compensatory interactions among them may mitigate the effects of regional damage on whole-mouth sensation – but for some individuals, these interactions may bring long-term changes in food-related sensation and affect, including unpleasant phantom sensations that lack an apparent source. Oral sensory dysfunction presents a diagnostic challenge because individual differences make it difficult to identify damage vs. normal function. Consequently, treatment and management options remain sparse.

In this review, we describe the causes of regional oral sensory nerve damage and their potential impact on whole-mouth sensation and food-related affect. We also discuss advances in the measurement tools used to evaluate oral sensation in health and disease, which have proven essential for comparing patients with healthy individuals. These tools include refined psychophysical scaling, visualization of oral anatomy, and spatial oral sensory testing. We believe that studying multiple aspects of function may enable differential diagnosis and more effective medical management of oral sensory complaints. More broadly, this strategy may also clarify how anatomy, genetics, and pathology interact to produce oral sensory variation.

2. Innervation of the mouth

The primary receptor organ for taste sensation is the taste bud, an onion-shaped structure that contains separate populations of cells specialized for transducing sweet, salty, sour, bitter, and umami taste cues. Taste buds are expressed throughout the mouth, but they are most commonly found in three types of papillae on the dorsal surface of the tongue. On the anterior, mobile portion of the tongue, fungiform papillae are round, elevated, mushroom-shaped structures that are distributed unevenly across the surface, with the highest density at the tongue tip. Foliate papillae are a series of folds on the rear edges of the tongue. Circumvallate papillae are large, round structures that form an arc across the posterior tongue with a central median papilla and 3-4 papillae on each side of it. (Filiform papillae, the most numerous type, serve no taste function but are involved in tactile sensation.) Taste buds are also found in the throat and at the junction of the hard and soft palates [1].

Several afferent nerves carry sensory information from the mouth, each carrying a specific array of information from a specific area. The chorda tympani (CT), a branch of the facial nerve (cranial nerve VII), carries taste information from fungiform papillae, while the lingual branch of the trigeminal nerve (cranial nerve V) carries pain, tactile, and temperature information from fungiform and filiform papillae in the same region [2, 3]. Multimodal information (i.e., taste, tactile, pain, and thermal cues) is carried from circumvallate papillae by the glossopharyngeal nerve (cranial nerve IX), from palatal taste buds by the greater superficial petrosal nerve (GSP, another branch of VII), and from the throat by the superior laryngeal branch of the vagus (cranial nerve X) [4-7]. Foliate papillae are innervated by the CT (taste) and V (tactile) in anterior regions and by IX (multimodal) in posterior regions [8,

9]. Overall, taste and oral somatosensory cues combine centrally with retronasal olfaction to produce the composite experience of flavor [e.g., 10].

The CT and the lingual branch of V exit the tongue together in a common sheath and proceed through the pterygomandibular space before separating. At this point, lingual V takes a fairly straight course to merge with the mandibular nerve before reaching the Gasserian ganglion and, ultimately, the brainstem [e.g., 11]. IX also takes a direct route, exiting the tongue along the styloglossus muscle and palatine tonsil to reach the inferior petrosal ganglion, then crossing the jugular foramen and the cerebellopontine angle into the brainstem. By comparison, the CT takes a more tortuous path; it traverses the middle ear along the medial aspect of the tympanic membrane, proceeds through a canal in the temporal bone, and joins the facial nerve to enter the geniculate ganglion, where it then joins GSP and approaches the brainstem as the nervus intermedius [e.g., 12]. As the next section details, these varied peripheral pathways make the taste system vulnerable to damage at several locations.

3. Causes of oral sensory nerve damage

Among the nerves carrying oral sensory input, the CT is particularly susceptible to damage due to its meandering path. Its course through the middle ear, where it crosses the auditory canal medial to the eardrum, presents the greatest risk; potential sources of damage include middle ear infection (i.e., otitis media) – which is extremely common, especially among children and despite emerging vaccines – and otologic surgery (e.g., tympanostomy, stapedectomy). Elsewhere, damage to the chorda tympani is a potential side effect of dental anesthesia, third-molar removal, laryngoscopy, and intubation procedures. Surgical resection of vestibular and auditory system tumors (e.g., acoustic neuroma) can compromise the nervus intermedius. Head trauma can damage the chorda tympani as it travels through the temporal bone, and vascular accidents (e.g., stroke) can impair brain regions receiving its input. Finally, medical conditions associated with facial nerve dysfunction (e.g., facial paralysis, herpes zoster infection) or broader craniofacial insult (e.g., temporomandibular joint disorder, reconstructive surgery) may inflict collateral damage on the CT [e.g., 13-18].

Meanwhile, the glossopharyngeal nerve's path along the palatine tonsil renders it prone to damage during tonsillectomy [19, 20]. A muscle layer interposed between IX and the tonsil often serves a protective function under these circumstances, but it is absent or discontinuous in some individuals [21]. Other surgical risks to IX include sleep apnea treatment and skull base surgery [22, 23], and posterior taste loss in the elderly suggests further nerve weaknesses that are not fully understood [24]. As with the CT, head trauma can cause lasting damage to the glossopharyngeal nerve, and stroke and other brain insults can affect its central targets.

4. Consequences of oral sensory nerve damage

The two major symptoms following damage to taste-related nerves are loss of sensation and the emergence of phantom oral sensations. Taste loss can occur throughout the entire mouth or in a specific region, it can affect a single taste quality or multiple ones, or it can target a

specific portion of the dynamic range (i.e., anywhere from threshold to maximum perceived intensity). Moreover, because taste, oral somatosensation, and retronasal olfaction interact centrally to produce flavor, taste-related nerve damage may induce changes in both taste and other oral sensations evoked by foods and beverages. Similarly, oral sensory phantoms can vary in quality (including taste, oral touch, and pain), location in the mouth, and perceived intensity. On the other hand, regional nerve loss goes unnoticed in many individuals because it does not always lead to whole-mouth sensory loss. Overall, the diversity and unpredictability of these outcomes have vexed clinical efforts for over a century, confounding a definitive model of oral sensory dysfunction [e.g., 25-27] and public health estimates of its prevalence [28, 29].

When oral sensory complaints occur following head/neck and other medical procedures, they typically resolve on their own over several months [e.g., 30]. In cases involving CT trauma sustained during otologic surgery, advances in technique have eased the recovery process: Oral sequelae are less frequent when the CT is stretched rather than cut [31-37] and recovery rates following transection are highest when the cut ends are reattached [38, 39]. Still, in these and other cases of CT damage, follow-up taste testing often reveals persistent change and incomplete recovery of function [e.g., 36, 40, 41]. These results coincide with structural data from patients with sectioned CT nerves: Regeneration occurs in many cases, but microscopy shows significant fibrosis and fewer intact nerve cells [42]. Clinical evaluation of taste loss often occurs years after presumptive damage, and most efforts to mitigate or reverse long-term taste loss have been unsuccessful. Notably, taste-related nerve damage may carry especially robust and long-lasting consequences for bitterness, as the nerve fibers conveying it are small, unmyelinated, and susceptible to environmental insult [43-45].

4.1. Taste loss, taste constancy, and oral disinhibition

While the impact of oral sensory nerve damage varies among individuals, its consequences stem from inhibitory connections among the central targets of oral sensory nerves. The earliest evidence that these circuits exist came from Halpern and Nelson [46], who anesthetized the CT in rats and found increased signal in brainstem neurons receiving glossopharyngeal nerve input. Over time, experiments like these led to an “oral disinhibition” or “release of inhibition” model in which the sensory nerves of the mouth partially and mutually suppress one another, so that damage to one nerve disinhibits those that remain, resulting in increased activity that effectively compensates for regional loss. In human experiments supporting this view, CT anesthesia in humans enhances taste cues on the contralateral posterior tongue (innervated by IX) [47-49]. Other observations indicate that glossopharyngeal nerve loss drives CT disinhibition in a similar manner [50], and that damage to either nerve leads to elevated somatosensory input from the trigeminal nerve [e.g., 51].

Oral disinhibition may explain the phenomenon known as “taste constancy”, which has been documented as a medical and gastronomic curiosity for at least two centuries: Whole-mouth sensation is remarkably impervious to regional nerve loss. Abundant clinical evidence details the rapid decline of anterior taste sensation following CT damage [e.g., 40, 41, 52,

53] and posterior taste and tactile sensation following IX damage [e.g., 54], yet whole-mouth sensation is often unaffected. Taste cues are perceptually referred to sites in the mouth that are touched [55-57], so a parsimonious explanation for taste constancy is that regional nerve damage augments remaining taste cues, which are experienced throughout the mouth – even in the denervated area, because it is touched during whole-mouth stimulation.

Clinical evaluations and experimental oral anesthesia suggest that the varied effects of oral sensory loss on whole-mouth sensation depend in part on the spatial extent of taste loss. Individuals with damage to a single nerve (i.e., CT or IX loss, but not both) experience the strongest disinhibitory effects, including elevated whole-mouth taste, retronasal olfaction, and oral somatosensation (e.g., chili peppers, fats). However, oral disinhibition cannot sustain these sensations when multiple nerve fields are compromised (i.e., CT + IX), so whole-mouth sensation falls [e.g., 47, 49]. Similar results are found in individuals with health histories involving otitis media (i.e., CT damage), tonsillectomy (i.e., IX damage), head trauma (i.e., CT and/or IX damage), and combinations of these conditions (i.e., CT + IX damage) [58, 59].

Individual differences in the capacity to perceive oral sensation may also contribute to the impact of oral sensory loss. These differences, first discovered as “taste blindness” to the bitterness of phenylthiocarbamide (PTC) and its chemical relative 6-*n*-propylthiouracil (PROP) [60], occur for most oral sensory stimuli and stem from polymorphisms at the receptor level [e.g., 61, 62], which are further amplified by differences in the number of fungiform papillae expressed on the anterior tongue. With this variation, “supertasters” generally experience the most intense taste sensations because they express the most fungiform papillae (and thus the most taste buds). Non-supertasters (also known as “medium tasters” and “nontasters”) express fewer fungiform papillae and perceive less intense taste sensations [63, 64]. Fungiform papillae are innervated by both taste and tactile nerve fibers [65], so supertasters also experience the strongest oral pain, burn (e.g., chili peppers), and viscosity (e.g., fats) [e.g., 66-68]. These differences can influence long-term dietary health; for example, PROP supertasters tend to avoid high-fat foods, leading to lower body mass and more favorable cardiovascular profiles [69, 70]. With regard to pathology, supertasters naturally have the most oral sensation to lose, so they may encounter the most robust disinhibitory effects following nerve damage, including taste constancy and phantom sensations. Supporting this view, unilateral CT anesthesia augments contralateral oral burn only in supertasters [51], and it fails to produce taste constancy in nontasters [71].

4.2. Phantom oral sensations

Phantom oral sensations, which occur in the absence of obvious stimulation, are another consequence of oral disinhibition. Taste phantoms are associated with several neurological disorders [e.g., 72, 73], and clinical accounts link them to conditions involving oral sensory nerve damage [50]. About 40% of healthy subjects experience taste phantoms during CT anesthesia; these sensations are usually localized to the contralateral posterior tongue (i.e., IX) and vary in quality and intensity, fading with the anesthetic. Whole-mouth topical anesthesia abolishes these “release-of-inhibition phantoms” [49], presumably by suppressing spontaneous neural activity at their source [74]. Meanwhile, a case report describes a bitter

phantom that arose bilaterally at IX following tonsillectomy. Spatial testing indicated complete IX loss, yet the phantom became more intense with whole-mouth topical anesthesia. This “nerve-stimulation phantom” was probably caused by surgical damage to IX and further disinhibited by CT anesthesia [50]. Although it remains uncertain why some individuals develop nerve-stimulation phantoms with oral sensory nerve damage, others develop release-of-inhibition phantoms, and others experience no taste disturbance at all, the defining feature of these complaints is that local suppression produces or enhances a taste illusion elsewhere in the mouth (i.e., oral disinhibition).

In recent years, oral pain phantoms have also been linked to regional oral sensory nerve damage [75-79]. Oral pain phantoms take several different forms, but the one most often described is burning mouth syndrome (BMS), a condition found primarily in post-menopausal women and marked by severe oral pain in the absence of visible pathology [e.g., 80, 81]. After systemic, infectious, and local explanations are exhausted, so-called “idiopathic” BMS is usually described as psychogenic [e.g., 82], but sensory testing reveals a different and less prejudicial story. Based on several clinical studies, patients with idiopathic BMS tend to be supertasters with bitter taste loss and trigeminal hyperalgesia on the anterior tongue, consistent with CT loss [83-87]. Many of these patients also reported taste phantoms at IX [88, 89], and topical anesthesia intensified their taste and oral pain symptoms [90]. These findings imply that, in many cases, idiopathic BMS is an oral pain phantom generated by CT loss and subsequent trigeminal disinhibition. Consistent with this profile, GABA_A agonist medications (e.g., clonazepam, gabapentin) often suppress both taste phantoms and BMS pain, presumably by restoring lost inhibition from absent taste cues [e.g., 91]. Recent data indicate that BMS involves both release-of-inhibition and nerve-stimulation phantoms [92], which would explain why some patients respond well to systemic GABA_A therapy [93] and others to peripheral treatments (e.g., topical GABA_A agonists, oral desensitization, peripheral nerve block) [94-97]. As these varied results suggest, oral sensory damage does not preclude other factors linked to BMS, but it offers a novel mechanism for specific cases viewed previously as intractable. Overall, phantom oral sensations appear to be consistent with phantom sensations in other sensory systems (e.g., orofacial pain, phantom limb, tinnitus), all of which are associated with nerve damage [e.g., 98-100].

4.3. Long-term changes in food choice and body mass

Flavor perception plays an essential role in food choice, which in turn guides long-term nutritional outcomes [e.g., 101]. Accordingly, health risks may shift over time when nerve damage alters the sensory components of flavor, particularly when food preferences are emerging early in life. Otitis media is the most common disease among children in the USA [102], despite promising vaccination efforts [e.g., 103, 104]. Severe forms of OM induce chronic degeneration in CT neurons [105-108], and children show reduced anterior taste function following surgical treatment for severe OM [109]. Under these circumstances, the intensity of dietary fats may rise due to trigeminal disinhibition [110, 111], as fats are detected in the mouth principally by their texture (although taste may play a role) [e.g., 112, 113]. Association studies suggest that childhood obesity and a high-fat diet are risk factors for OM [114-119], but the opposite may also be true: OM-related changes in the balance of

flavor cues may amplify obesity risk by sharpening avidity for energy-dense foods during critical periods for food learning, similar to developmental models of sweet overconsumption [e.g., 120].

Supporting this view, several measures of past OM exposure and severity have been linked to elevated sweet-fat preferences, adiposity, and body mass in children [121-124]. These changes may be especially long-lasting, as they also occur in adults with a childhood history of severe otitis media [125, 126], along with reduced anterior taste function [127-132] and manifestations of oral disinhibition that include elevated glossopharyngeal, trigeminal, and whole-mouth intensity [58, 110, 127, 133, 134]. As with other outcomes of oral sensory nerve damage, these effects may occur preferentially in supertasters [e.g., 125, 126], and they suggest that oral disinhibition has consequences that emerge and shift over time, depending on the timing and nature of injury and the individual afflicted.

5. Measuring oral sensory nerve damage

Careful measurement is an axiom of good science. Unfortunately, several measurement issues have impeded progress in understanding the consequences of taste-related nerve damage. Comparisons of perceived oral sensory intensity have been flawed by the use of scaling methods that cannot provide valid comparisons of patients and normal controls. Individual differences in oral sensation, based on oral anatomy and genetics, present a challenge in distinguishing normal vs. abnormal function. Central inhibition in the oral sensory system adds complexity to sensory profiles of nerve damage, so clinical tests examining only whole-mouth sensation can conceal localized taste losses with long-term and potentially traumatic consequences (e.g., phantoms). In this section, we describe these problems and propose refinements to chemosensory evaluation that may enable better diagnosis and management of oral sensory dysfunction.

5.1. Psychophysical scaling

Intensity scales have been used since antiquity, and several types have been developed for clinical, scientific, and consumer applications. Popular examples in contemporary use include Likert's 5-point scale to measure attitudes (1 = strongly disagree, 2 = disagree, 3 = neither agree nor disagree, 4 = agree, 5 = strongly agree) [135] and several iterations of the 10-point pain scale (0 = no pain, 10 = worst possible pain) used commonly in medical practice [e.g., 136]. These category scales do not have ratio properties because, for example, a pain intensity of "8" is not necessarily twice as intense as an intensity of "4". An example of a scale with ratio properties is the visual analogue scale (VAS), a line labeled at its endpoints with the minimum and maximum intensities of a given attribute (e.g., "not at all" vs. "extremely" liked) [137, 138]. As an alternative to these fixed scales, measurement theorists developed the method of magnitude estimation, in which individuals freely assign numbers to sensations in ratios corresponding to their perceived intensity; by definition, "8" is twice as strong as "4" [e.g., 139].

To identify functional loss, most clinical tests have benchmarks that define normal vs. abnormal data. However, intensity scales present a special problem because they must be used in the same way by everyone (e.g., patients vs. controls) to produce valid comparisons

that allow those benchmarks to be defined and understood. Category scales, the VAS, and magnitude estimation were originally devised to compare responses to different stimuli (e.g., brands of soft drink), not differences in response among groups of people (e.g., males vs. females, elderly vs. young, obese vs. thin). When attention turned to such comparisons, it was simply assumed that these scales produce valid differences – but they cannot do so because we cannot perceive the conscious experience of another person, even though we often speak as though we can. For example, one might ask, “This candy tastes very sweet to me; does it taste very sweet to you?” but the answer is merely a rough estimate because neither party knows how intense “very sweet” actually is to the other person. Put another way, if “8” means searing pain to one person and a light tingle to another, then the distinction between “8” and “4” has little useful meaning.

To address this problem, efforts over several years have centered on identifying standards equally intense to all groups of interest; differences expressed relative to a standard may be interpreted as true intensity differences rather than methodological artifacts, a technique pioneered in early work on genetic variation in taste [140] and now known as “magnitude matching” [141, 142]. For example, individual differences in taste perception emerge when an auditory standard is used, under the assumption that hearing and taste are unrelated [143]. Similarly, ratio scales like the VAS can be modified to enable magnitude matching; the VAS typically describes a single attribute (e.g., “no sweetness” vs. “strongest sweetness”), but changing the frame of reference to all sensory experience (e.g., “no sensation” vs. “strongest sensation of any kind ever experienced”) yields valid comparisons of oral sensation because taste and oral tactile cues are almost never cited as the strongest sensations a person has ever experienced. These developments have culminated in the rising use of “global” intensity scales for both sensory and affective measurement [e.g., 144-149].

5.2. Spatial and whole-mouth testing

Medical assessments of chemosensory function typically use a whole-mouth “sip and spit” test, but it may not be the best tool for clinical evaluation of nerve damage. As we have described, compensatory oral disinhibition often leads to normal whole-mouth sensation, masking regional nerve damage that may explain clinical symptoms (e.g., phantoms). Consequently, spatial testing of individual nerve fields (in concert with whole-mouth testing) offers a more complete picture of oral sensory function.

Electrogustometry, the application of mild electric current to the oral surface, may be the best-known method for localized stimulation of the mouth [e.g., 150-152], but it has two key limitations. First, electrogustometry measures only taste thresholds, which fail to predict suprathreshold function at levels experienced in everyday life [153]. Second, electrogustometry evokes a limited subset of oral sensations that can be multimodal and difficult to describe (e.g., bitter-sweet and irritation) [154, 155]. Taste dysfunction may affect any taste quality, so electrogustometry may miss relevant deficits. Nevertheless, it has proven useful for assessing the specific integrity of the CT [156].

The most complete evaluation of oral sensory function involves spatial taste testing [157], in which suprathreshold solutions of sweet, sour, salty, and bitter stimuli are applied with cotton swabs onto the anterior tongue tip, foliate papillae, circumvallate papillae, and soft

palate. (A spatial taste test involving filter paper strips impregnated with taste stimuli has also been described [158].) High stimulus concentrations (e.g., 1.0 M NaCl, 1.0 M sucrose, 0.032 M citric acid, 0.001 M quinine hydrochloride) enable easy identification of taste loss. Stimuli are presented on the right and left sides at each site, and subjects make quality and intensity judgments using magnitude matching or a global intensity scale. Following regional testing, subjects swallow a small volume of each solution and rate its intensity, which allows comparisons of regional and whole-mouth sensation; discrepancies between the two (e.g., low regional sensation + high whole-mouth sensation) are a sign of nerve damage. Abbreviated versions of this protocol have recently been incorporated into federally-funded health surveillance efforts, including the National Health and Nutrition Examination Survey (NHANES) [159, 160] and the NIH Toolbox for Assessment of Neurological and Behavioral Function [161].

5.3. Oral anatomy

Oral sensation shows broad individual differences under healthy conditions, so it can be difficult to distinguish sensory outcomes of nerve damage from normal sensation, particularly at low levels (which occur, for example, in both healthy nontasters and in supertasters with severe loss). Measures of oral anatomy, in particular the density of fungiform papillae on the anterior tongue, have proven useful in clarifying this distinction. We quantify fungiform papilla density by staining the tongue with blue food coloring; papillae appear under magnification as pink circles against a blue background, which are counted in a standardized area at either side of the midline tongue tip [64, 162-164]. These measures have consistently yielded robust associations between oral anatomy and sensation in healthy individuals [e.g., 64, 164-166], which have been used to validate the ability of psychophysical scales to provide valid group differences [153].

Videomicroscopy of the tongue has also enabled identification of some forms of oral sensory pathology. Transection of the CT in humans leads to taste bud degeneration and corresponding taste loss, but fungiform papillae remain intact because they are structurally supported by the trigeminal nerve [167, 168]. Accordingly, we treat fungiform papilla density as a stable index of innate, pre-existing oral sensory capacity, and we interpret sensory deviations from it (e.g., high density + low sensation) as the effect of nerve damage [e.g., 169]. This dissociation may explain recent reports challenging the relationship between oral anatomy and sensation [170-172]; nerve damage obscures this relationship, yet these studies failed to assess it and probably included unhealthy sensory profiles in their samples [173].

6. Conclusion

Oral sensory nerve damage has complex effects on whole-mouth sensation and food behavior that have resisted easy clinical interpretation for over a century, but we believe that better understanding has already arisen from careful chemosensory measurement of a broader nature than previous efforts have explored. In particular, the disinhibitory model we describe requires rigorous assessment of individual differences in oral anatomy and sensation to identify healthy function vs. patterns of regional dysfunction. Accomplishing

this task has led us to reconsider the instruments used to measure sensory and affective differences, with the goal of ensuring that they render true variation rather than methodological artifacts. Although progress has been made in the management of some of the most striking sequelae of oral sensory nerve damage (e.g., phantom oral pain), other symptoms remain elusive in current medical practice (e.g., nerve regeneration). Nevertheless, we remain confident that advances in oral sensory assessment will yield improved health outcomes, as they yield highly predictive and highly comparable profiles of flavor-related experience in health and disease.

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