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## Modern Psychophysics and the Assessment of Human Oral Sensation

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### Abstract

Psychophysical measures attempt to capture and compare subjective experiences objectively. In the chemical senses, these techniques have been instrumental in describing relationships between oral sensation and health risk, but they are often used incorrectly to make group comparisons. This chapter reviews contemporary methods of oral sensory assessment, with particular emphasis on suprathreshold scaling. We believe that these scales presently offer the most realistic picture of oral sensory function, but only when they are used correctly. Using converging methods from psychophysics, anatomy, and genetics, we demonstrate valid uses of modern chemosensory testing in clinical diagnosis and intervention.

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Psychophysical measures of experience have played a fundamental role in our understanding of sensory and hedonic processes. In the chemical senses, these measures have revealed the broad impact of oral sensation and dysfunction on health-related behaviors and overall quality of life [1]. Oral sensory disturbances may be relatively benign, but sometimes they are profoundly life altering. As such, chemosensory experience and its consequences represent an important clinical concern.

Assessing this experience, however, is an extremely challenging task. By definition, individual experience is subjective: we can *describe* our experiences and track them over time, but we cannot directly *share* the experiences of another person. Nevertheless, we use comparisons of real-world experience throughout life to communicate what is acceptable (e.g. pleasure, comfort) and what is not (e.g. disease, pain), so it is important to evaluate these experiences carefully. Recent advances in suprathreshold scaling capture sensory and affective

differences with improved accuracy, supporting the notion that perceptual experiences can be measured and compared.

In this chapter, we address methodological issues regarding threshold and suprathreshold measures of oral sensation. Using magnitude matching as an example, we argue that suprathreshold intensity scales provide a more complete picture of oral sensory function than do thresholds alone. Our efforts to identify useful suprathreshold tools include an examination of labeled scales, which are used (and misused) to compare experiences between individuals and groups. To confirm our psychophysical results, we demonstrate the use of parallel methods (e.g. multiple standards, genetic and anatomical tools). Finally, using techniques appropriate for comparison, we show how spatial taste testing has advanced our understanding of oral sensory function in health and disease.

### **Thresholds versus Intensity: How Should Oral Sensation Be Measured?**

When we enjoy a meal, we can easily tell if the soup is too salty or the cocktails watered down. These judgments demonstrate that intensity is continuous (i.e. strong or weak variants of stimulus strength) and not binary (i.e. present or absent). Some researchers believe that degrees of suprathreshold intensity are immeasurable or at best ordinal [2], but we contend that suprathreshold measures possess unique diagnostic and predictive capabilities.

#### *Indirect Psychophysics: Threshold Procedures*

Thresholds have been used for sensory evaluation ever since Fechner [3] codified them almost 150 years ago. Although thresholds present technical challenges, they are conceptually straightforward: the *absolute threshold* for a stimulus is the lowest concentration at which its presence can be detected as something, whether or not it is qualitatively discernible. The *recognition threshold* is the lowest concentration at which the quality of a stimulus (e.g. sweet, painful) can be identified. Finally, the *difference threshold* is the smallest increase in suprathreshold stimulus concentration that can be detected (i.e. the ‘just noticeable difference’).

Thresholds enjoy widespread use in research and clinical settings, mainly because they produce values suitable for comparison. Because thresholds are especially sensitive to sensory adaptation, subject fatigue, and criterion shift [4], abbreviated methods have been developed that provide reliable threshold estimates with fewer trials and minimal bias [5–7]. Even so, one of the most discouraging

features of thresholds is the time required to measure them: an up-down, forced-choice threshold procedure [7] takes approx. 20 min to administer, yielding only the lower boundary of the taste function; suprathreshold procedures approximate the entire taste function in much less time. Generally, the decision to use thresholds in lieu of suprathreshold measures is reasonable when there is strong concordance between threshold and suprathreshold experiences. However, psychophysical functions for taste stimuli show considerable variation that precludes reasonable predictions of suprathreshold sensation from threshold values alone [8].

As an alternative to chemical measures of taste sensitivity, electrogustometry involves the application of weak anodal electric currents to specific regions of the mouth [9]. Proponents of electrogustometry emphasize its convenience [10]; it is portable, avoids the use of chemical solutions, permits regional stimulation of taste bud fields, and provides values that can be compared across individuals, time points, locations within the mouth, or treatment conditions. Electric taste thresholds show high test-retest reliability and bilateral correspondence [11], and normative data have been described for some groups [12]. Accordingly, electrogustometry has been used to identify sizable taste losses associated with aging, denervation, and disease [11, 13, 14], but the following two disadvantages limit its use in more specific clinical assessments of taste function [15].

- Because saliva is mildly acidic and contains salts, electrogustometry typically evokes sour or salty taste sensations [16]. However, oral sensory alterations are often quality specific, particularly affecting bitter taste [17, 18]. As such, electrogustometry may fail to identify clinically relevant damage.
- Electrogustometric thresholds correlate well with regional [12, 19] but not whole-mouth chemical taste thresholds [11]; suprathreshold functions for electrical and chemical taste also show poor agreement [20]. Thus, as with chemical taste thresholds (see above), electrogustometry cannot reflect real-world taste experience accurately.

### *Direct Psychophysical Scaling of Suprathreshold Intensity*

Thresholds provide only the lower limit of physical energy that can be perceived (e.g. decibels of sound, molar concentration), but suprathreshold or 'direct' scaling methods measure perceived intensity across the full dynamic range of sensation [21]. S.S. Stevens [22] introduced direct scaling methods with ratio properties, the most popular of which is magnitude estimation. In this procedure, subjects provide a number reflecting perceived stimulus intensity; they then give a number twice as large to a stimulus that is twice as intense, a number half

as large to a stimulus half as intense, and so on. The size of the numbers is irrelevant; only the ratios among numbers carry meaning. As a result, magnitude estimates describe only how perceived intensity varies with stimulus intensity *within* an individual; they cannot reflect meaningful differences of absolute perceived intensity *between* individuals or groups [23]. Because group comparisons are such a basic element of scientific analysis, this limitation has not been fully appreciated, but its consequences are severe. To illustrate, we now describe studies on individual differences in taste perception; these studies are especially noteworthy in terms of their contributions to comparative suprathreshold scaling.

### Genetic Variation in Oral Sensation: The Rise of Magnitude Matching

#### Taste Blindness: We Live in Different Oral Sensory Worlds

Discovered by the chemist A.L. Fox in 1931 [24], individuals differ significantly in their ability to taste thiourea compounds like phenylthiocarbamide (PTC) and 6-n-propylthiouracil (PROP) [25]; most individuals perceive bitterness (i.e. tasters), but others are ‘taste blind’ and perceive nothing (i.e. nontasters). Early reports suggested that taste blindness is a recessive trait inherited through a single genetic locus [26], while other studies measured the proportion of tasters by race, sex, and disease [27–29]. In the 1960s, behavioral experiments showed that PTC/PROP threshold sensitivity influences food preferences, alcohol and tobacco use, and body weight [30].

Buoyed by the potential benefits of direct scaling, Bartoshuk sought to compare the suprathreshold bitterness of PTC between nontasters and tasters. However, this comparison presents a problem: magnitude estimates have *relative* meaning when subjects are used as their own controls [31], but how can *absolute* bitterness rating be compared across groups? The answer to this question involves measuring PTC bitterness relative to an unrelated standard. Although magnitude estimates are often multiplied by a constant (i.e. ‘normalized’) in order to obtain group functions [32], this procedure is qualitatively different.

- To average magnitude estimates while maintaining the ratios among them, ratings must be brought into a common register so that one subject’s data are not unduly weighted just because that subject used larger numbers [23]. With this type of normalization, the standard is arbitrary, so group functions convey nothing about absolute perceived intensity.
- When the purpose of normalization is to permit group comparisons, the standard is assumed to be equally intense (on average) to the groups being compared. If this assumption holds, normalization yields valid across-group differences in absolute perceived intensity for stimuli of interest: if ‘10’ denotes the intensity of a standard to nontasters and tasters, PTC ratings of ‘40’ for tasters and ‘20’ for nontasters reflect a twofold intensity difference.

Because thioureas share the N–C=S chemical group [33], Bartoshuk reasoned that the taste intensity of a compound lacking the N–C=S group should be equal, on average, to nontasters and tasters. If so, group averages of PTC bitterness can be compared by rating it relative to, for example, NaCl saltiness. With this procedure, tasters find PTC and PROP more bitter than do nontasters [34, 35], and mounting data indicate that these individual differences reflect entirely different oral sensory worlds: tasters perceive more intense taste and oral tactile sensations overall [36], indicating that taste blindness extends far beyond the N–C=S group [30]. Of particular interest, a subset of tasters known as ‘supertasters’ consistently give the highest ratings to taste stimuli, oral irritants (e.g. capsaicin), fats, and food-related odors [37, 38].

#### Magnitude Matching: Non-oral Standards Enable Oral Sensory Comparisons

If supertasters perceive NaCl more intensely than do others, then NaCl is a poor standard for oral sensory comparisons, meaning that observed differences between taster groups are inaccurate (albeit conservatively so). This problem was resolved by experiments on cross-modality matching, in which stimuli from unrelated modalities are compared [39]; by assuming that taste and hearing are unrelated, taste intensity can be rated relative to auditory intensity. This ‘magnitude matching’ procedure [40] confirmed the suspicion that the saltiness of NaCl varies with taster status [41]. Magnitude matching addresses the problem of group comparisons by changing the task: oral sensations cannot be compared directly across PROP taster groups, so subjects rate stimuli of interest relative to a non-oral sensory standard. As long as variability in the standard remains unrelated to variability in PROP bitterness, oral sensory experiences are comparable across groups.

The ability to observe accurate differences in oral sensation has revealed associations between sensory experience, dietary behavior, and disease risk. For example, PROP bitterness is linked to decreased vegetable preference and intake [42, 43], a known risk factor for colon cancer; it also associates with an increased number of colon polyps [44]. PROP intensity also predicts avoidance of high-fat foods, so supertasters have lower body mass indices and more favorable cardiovascular profiles [45–47].

#### PTC/PROP Genetics: Supertasting Is Not Explained by a Single Gene

Early family studies indicated that nontasting is a recessive trait with a single locus [26], while the discovery of supertasters led to additive models in which supertasters are homozygous dominant and medium tasters heterozygous [48]. Based on modern genetic analysis, oral sensory variation may in fact involve multiple alleles and/or loci [49]: candidate genes reside on chromo-

somes 5p15, 7, and 16p [50, 51], and subsequent mapping of chromosome 7q has identified sequence polymorphisms in a putative PTC receptor gene (TAS2R38) that account for observed threshold differences [52]. While medium tasters and supertasters have similar PROP thresholds [36], homozygous dominant individuals for TAS2R38 find PROP slightly more bitter than do heterozygotes, but this relationship is imperfect [53]. In other words, supertasting cannot be explained completely by threshold sensitivity or TAS2R38 expression – additional factors (i.e. oral anatomy, pathology, other genetic markers) must contribute [54]. Specifically, supertasting appears to depend on two conditions: the ability to taste PTC/PROP (which means that taste buds express PTC/PROP receptors) and a high density of fungiform papillae (i.e. structures containing taste buds) on the anterior tongue (which maximizes oral sensory input). As data continue to amass, oral anatomy may prove a better biological index of supertasting than PTC/ PROP receptor expression.

#### Best Practices and the Perils of Classification

Valid consensus values for PROP classification are lacking, mainly because continuing advances in genetic and psychophysical testing supersede previous estimates. Consequently, existing criteria are idiosyncratic and variable, resulting in a vigorous debate over which classification scheme best reflects differences in oral sensation [45, 55, 56]. At the center of this issue, the validity of any boundary value depends on the instrument used to measure it; when suprathreshold psychophysical tools produce distorted comparisons, the sorting criteria derived from those tools are also distorted. (Thresholds have remained a popular clinical measure for precisely this reason, even though they too distort real-world sensory experience.)

Broadly speaking, the most effective assessment strategies integrate multiple correlates of function. As advances in anatomy and genetics permit more nuanced studies, the best methods for oral sensory evaluation will encompass an array of techniques that complement and enrich sophisticated psychophysical measurement [57]. We have used this multivariate approach to develop the following guidelines for contemporary PROP classification.

- Nontasters and tasters are easily distinguished by genetic analysis of TAS2R38 (i.e. nontasters are recessive, tasters are dominant) [52], which reflects PROP threshold differences (i.e. above 0.2 mM for nontasters, below 0.1 mM for tasters [58, 59]). In a database of over 1,400 healthy lecture participants living in the USA, these differences roughly correspond to a general Labeled Magnitude Scale (gLMS) boundary value of ‘weak’ (i.e. approx. 17 out of 100) for filter papers impregnated with saturated PROP (approx. 0.058 M) [unpublished data]. Consistent with previous estimates [59, 60], this cutoff yields approx. 25% nontasters in the sample.

- Supertasters are distinguished from medium tasters by psychophysical criteria. Existing population estimates of PROP taster status are based on a single-locus model, so this boundary value will remain arbitrary until all genetic loci related to taste blindness are identified. In the database described above, nontasters represent the lowest 25% of PROP paper ratings, so a working definition of supertasting might include the top 25% of ratings; this logic suggests a gLMS boundary value of approx. 80.
- Individuals with taster genotypes and nontaster PROP ratings probably reflect oral sensory pathology (see below). In these cases, oral anatomy can often be used to identify supertasters [1], who show high fungiform papilla density (i.e. over 100 papillae/cm<sup>2</sup> [59]) and low PROP responses when taste function is compromised.

Despite considerable evidence, some researchers persistently claim that oral sensation has little effect on sensation, food behavior, or health [55, 61, 62]. In nearly every case, these dissenting reports fail to show effects of interest because their methods are incapable of showing effects of interest. Many of these reports involve the inappropriate use of labeled intensity scales.

#### Labeled Scales: Valid (and Invalid) Comparisons

Measurement scales labeled with intensity descriptors – including Likert, 9-point, and visual analog scales (VAS) [63–65] – are widely used throughout the medical, scientific, and consumer disciplines. Although many category scales have been ‘validated’, the fact that a scale measures what it was intended to measure does not guarantee its ability to produce valid group comparisons.

#### Properties of Intensity Labels: Spacing, Relativity, and Elasticity

We commonly use intensity descriptors to compare our experiences with the experiences of those around us (e.g. ‘This solution tastes *strong* to me. Does it taste *strong* to you?’). Because we use these words so frequently, they have been incorporated as labels in intensity scales. These labels have special properties that warrant discussion.

- Generally, ratings from category scales have ordinal but not ratio properties [66], because intensity descriptors are not equally spaced [67]. Several investigators have produced scales with labels spaced empirically to provide ratio properties [68]; this spacing has been replicated across multiple sensory and hedonic attributes [69–72], indicating that sensory and hedonic experiences possess similar intensity properties.
- Intensity descriptors are relative by definition: because adjectives modify nouns, they have no absolute meaning until their antecedents are specified. Nevertheless, many group comparisons implicitly assume that scale

descriptors denote the same absolute intensity regardless of the object described [73, 74].

- Intensity descriptor meanings vary among groups of people just as they do among different sensory modalities. In a study assessing the magnitudes denoted by scale descriptors for taste perception [37], the spacing among descriptors appears proportional for nontasters and supertasters, but the supertaster range is expanded (fig. 1a).

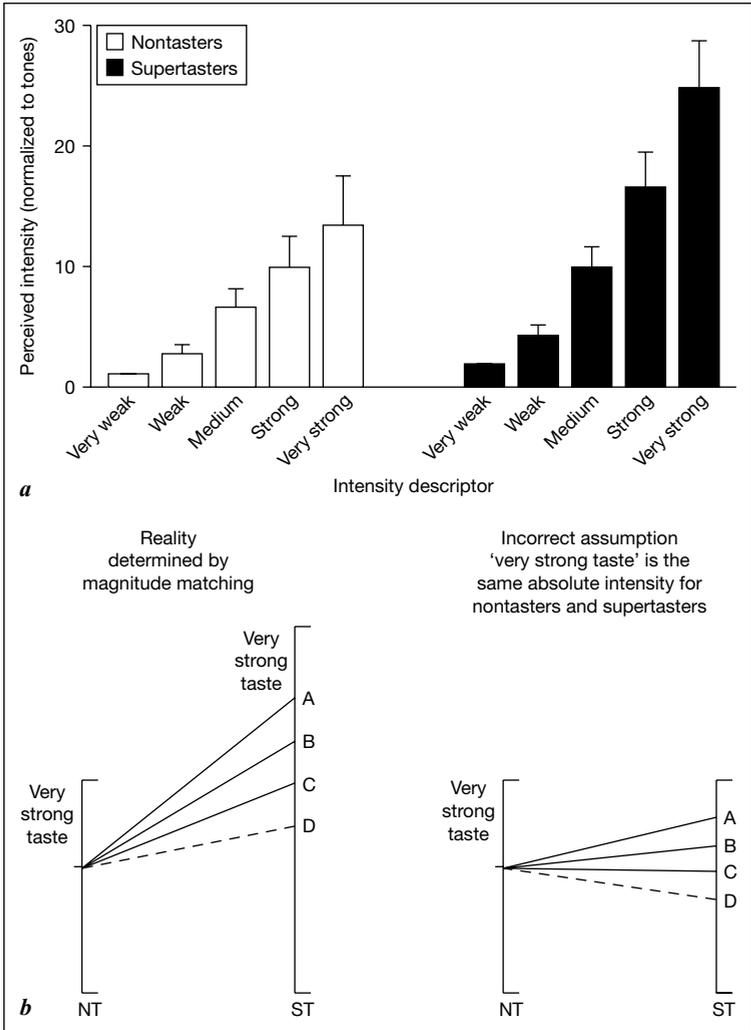
In short, intensity labels maintain their relative spacing, but they are elastic in terms of the domain to be measured and individual experiences within that domain. Because labeled scales fail to account for this elasticity, they are inappropriate whenever subject classification (e.g. sex, age, weight, clinical status) produces groups for which scale labels denote different absolute intensities.

#### Consequences of Invalid Comparisons: Distortion and Reversal

Figure 1b shows errors resulting from the false assumption that intensity descriptors denote the same absolute intensity to everyone. (This figure is idealized, but effects have been verified using taste and food stimuli [1].) The left side shows stimuli that produce equal perceived intensities to nontasters. The diverging lines connecting nontaster and supertaster ratings indicate PROP effects of differing sizes; the intensity difference between groups for the label ‘very strong taste’ is the same difference shown in figure 1a. When the label ‘very strong taste’ is treated as if it denotes the same average intensity to nontasters and supertasters, supertaster data are compressed relative to nontaster data, as shown on the right side.

- Stimulus A appears more intense to supertasters than to nontasters, but the magnitude of the effect is blunted.
- The difference between nontasters and supertasters for stimulus C is equal to the difference between the labels, so it disappears.
- For stimulus D, the actual difference between nontasters and tasters is smaller than the difference in meaning for ‘very strong taste’, so group differences appear to go in the opposite direction. This phenomenon is known as a *reversal artifact* [75].

Despite this problem, some investigators argue that group effects with significant biological impact should be sufficiently robust to be detected with any and all methods [55]. Claims like these are distortions themselves: biological effects exist whether they are measured or not, but measurement tools are useless if they cannot detect those effects realistically. Moreover, the popularity of a scale does not necessarily make it the right tool for the task at hand. Although improved labeled scales show promise, contrary reports arising from invalid scaling methods remain significant obstacles to health-related research efforts.



**Fig. 1.** Nontasters (NT) and supertasters (ST) inhabit different oral sensory worlds. **a** The perceived intensity of scale descriptors for NT and ST. **b** Consequences of invalid group comparisons. On the left, taste functions reflect actual differences between NT and ST measured with magnitude matching. On the right, the same taste functions are distorted by the incorrect assumption that 'very strong taste' indicates the same absolute perceived intensity to NT and ST: valid effects appear truncated and may reverse direction inaccurately. Modified from Bartoshuk et al. [37].

### Building a Better Scale: A Quest for Appropriate Standards

Category scales assume ratio properties when the spacing among categories reflects real-world experience. If this common intensity scale were stretched to its maximum, might it produce a labeled scale allowing valid comparisons of oral sensory intensity? To test this idea, Bartoshuk and colleagues replaced the top anchor of the LMS [71] with the label ‘strongest imaginable sensation of any kind’. This scale, now known as the general LMS (gLMS), produces similar group differences in PROP bitterness as magnitude matching [76], indicating that the top anchor functions as a suitable standard for oral sensory assessment. Considering that sensory and affective intensity labels are similarly spaced [68], a bipolar version of the gLMS has proven particularly useful for hedonic measurement [77].

The standards used in the laboratory often require cumbersome and expensive equipment. Because scale labels rely on memories of perceived intensity, remembered sensations have been proposed as standards for magnitude matching. Although the precise relationship between real and remembered intensity is unclear [78], remembered oral sensations appear to reflect effects seen with actual stimuli [79]. Meanwhile, the term ‘imaginable’ found in many intensity scales is a poor standard, as recent data show individual differences in the intensity of imagined experiences [80]. Thus, in a more radical approach to scaling, perhaps all labels should be abandoned except for those at the ends of the scale. The resulting scale – a line denoting the distance from ‘no sensation’ to the ‘strongest sensation of any kind ever experienced’ – is essentially a VAS encompassing all sensory modalities; we have proposed calling it the general/global VAS (gVAS) [81].

Overall, we have used labeled scales with success because we include both real and remembered sensations as standards. By using raw gLMS scores and/or normalizing those scores to other standards, we are able to confirm our conclusions across a variety of assumptions.

### **Clinical Assessment of Oral Sensory Function**

Disorders of oral sensation are both widespread and variable, yet useful resources and appropriate medical treatment are frustratingly sparse [82]. Because taste cues influence nutritional health, metabolism, and affect [83], their loss can be traumatic, yet in other cases taste loss is hardly noticed [84]. Gustatory disturbances are often associated with specific disorders and treatment interventions, but just as often they are of unknown origin and unpredictable onset [85]. Thus, oral sensory evaluations require a thorough examination of physical (e.g. oral anatomy, oral and salivary pathology, neurological damage), sensory

(e.g. taste, oral somatosensation, retronasal olfaction), and emotional aspects of chemosensation (e.g. psychopathology, quality of life).

Several afferent nerves carry sensory information from the mouth, each carrying a particular array of information from a particular area. The chorda tympani (CT), a branch of the facial nerve (VII), carries taste information from the anterior tongue; the lingual branch of the trigeminal nerve (V) carries pain, tactile, and temperature information from the same region. The greater superficial petrosal nerve, another branch of nerve VII, carries taste cues from the palate. Multimodal information (i.e. taste, touch, pain, temperature) is carried from the posterior tongue by the glossopharyngeal nerve (IX) and from the throat by the vagus (X) [86]. Taste and oral somatosensory cues combine centrally with retronasal olfaction to produce the composite experience of flavor [87]. This spatial distribution of input has led researchers to consider the clinical relevance of localized oral sensory damage (see below), so modern protocols for oral sensory evaluation typically include judgments of intensity and quality for both regional and whole-mouth stimuli.

### *Whole-Mouth Oral Sensation*

In whole-mouth gustatory testing, chemical stimuli are sampled and moved throughout the mouth, stimulating all oral taste bud fields simultaneously; subjects rinse with water prior to each stimulus. Laboratory tests of oral sensation involve the presentation of chemical solutions at multiple concentrations spanning the functional range of perception [41, 88], but most clinical tests have streamlined this process to a single stimulus for each of the common taste qualities (i.e. sucrose, NaCl, citric acid, quinine hydrochloride) [89]. In addition, multiple concentrations may be used to derive suprathreshold taste functions, and other oral stimuli may be included to evaluate oral tactile sensation (e.g. capsaicin, alcohol) or individual differences (e.g. PROP). Having discussed the disadvantages of thresholds, we favor suprathreshold measurements involving magnitude matching or the gLMS/gVAS with appropriate standards, so stimuli unrelated to oral sensation (e.g. sound, remembered sensations) should be incorporated.

Aqueous solutions are inconvenient for field and clinical use, so alternative methods of stimulus delivery have been explored, including paper strips and tablets [90–92]. With respect to whole-mouth testing, the most enduring example of these methods is the use of PROP papers as a screening tool for taste blindness. In early studies, PTC crystals were placed directly on the tongue [33] or delivered on saturated filter papers [93]. Today, PROP papers are made by soaking laboratory-grade filter papers in a supersaturated PROP solution heated to just below boiling. When dry, each paper contains approx. 1.6 mg PROP [94]; patients with

hyperthyroidism are prescribed 100–300 mg daily [95]. Variants of this method have been described [96], but all share the common goal of introducing a small amount of crystalline PROP to the tongue surface. Although PROP papers are convenient and portable, their technical flaws warrant consideration.

- To produce a taste, the filter paper must be completely moistened with saliva, which requires healthy salivary function and a sufficient period of contact with the tongue [55].
- Some studies [35] report excessive false-positive and false-negative responses to PTC/PROP filter papers. These response rates probably result from minor testing variations that affect response bias.
- Filter paper testing shows only moderate concordance with threshold sensitivity [97]. As described above, threshold and suprathreshold measures almost always dissociate when proper scaling is used.

Despite these concerns, filter paper ratings and laboratory PROP assessments show significant agreement and high test-retest reliability [94, 96, 98], perhaps because the effective concentration of PROP is unimportant provided it is high. Comparisons of PROP paper and solution bitterness suggest that the concentration dissolved from paper into saliva approaches maximum solubility [unpublished data]. Because functions of PROP bitterness for nontasters, medium tasters, and supertasters diverge [36], the most efficient way to sort subjects is to use the highest concentration possible, so papers made from saturated PROP [94] may be preferable to those made from lower concentrations.

### *Oral Sensory Anatomy: Videomicroscopy of the Tongue*

Multiple reports indicate that differences in taste bud density account for human oral sensory variation [45, 59]. To explore this idea further, Miller and Reedy [99] developed a method for visualizing the tongue in vivo. Human tongues are coated with large, raised, circular structures (i.e. fungiform papillae) that hold taste buds [100]; blue food coloring applied to the tongue surface fails to stain these papillae, which subsequently appear as pink circles against a blue background. Fungiform papillae can be counted with a magnifying glass and a flashlight, while videomicroscopy allows resolution of pores at the apical tips of taste buds. This method has revealed positive associations between PROP intensity, fungiform papilla density, and taste bud density [59, 99]. Fungiform papillae are dually innervated by CT and nerve V [101], which accounts for the elevated taste and oral tactile sensations experienced by supertasters [45, 102].

Clinically, videomicroscopy is useful in confirming CT damage (see below), which often appears as a discrepancy between high fungiform papilla density and low taste sensation on the anterior tongue [1]. In addition, the association

between taste intensity and oral anatomy among healthy subjects can be used to evaluate the ability of various scales to provide valid across-group comparisons: the gLMS and magnitude matching produce robust correlations between taste intensity and fungiform papillae density, but category scales are severely limited in this regard [103].

### *Spatial Taste Testing*

Because different nerves innervate different regions of the oral cavity, oral sensation may be absent in one area but intact in others. Remarkably, individuals with extensive taste damage are often unaware of it unless it is accompanied by tactile loss [84], presumably because taste cues are referred perceptually to sites in the mouth that are touched [104–106]. As a result of this ‘tactile referral’, regional taste loss rarely produces whole-mouth taste loss, yet it remains clinically significant as a precursor to altered, heightened, and phantom oral sensations. Measures of regional taste function are an important tool for identifying the source of these complaints.

The integrity of specific taste nerves is assessed clinically via spatial testing [8], in which suprathreshold solutions of sweet, sour, salty, and bitter stimuli are applied with cotton swabs onto the anterior tongue tip, foliate papillae (i.e. posterolateral edges of the tongue), circumvallate papillae (i.e. raised circular structures on the posterior tongue), and soft palate. (A spatial taste test involving filter paper strips impregnated with taste stimuli has also been described [92].) Stimuli are presented on the right and left sides at each locus, and subjects make quality and intensity judgments using magnitude matching or the gLMS. Special care must be taken to avoid stimulating both sides of the mouth simultaneously (which impedes localization), triggering a gag reflex during circumvallate stimulation, or allowing palate stimuli to reach the tongue surface (which leads to inflated palate ratings). Following regional testing, subjects swallow a small volume of each solution and rate its intensity, thereby enabling comparisons of regional and whole-mouth sensation.

### Regional Taste Sensation: The ‘Tongue Map’ Is False

Comparisons of psychophysical functions across oral loci indicate that taste is perceived at similar intensity on all tongue areas holding taste buds, but less so on the palate [107]. Thus, oral sensory losses can be detected as significant local variations from otherwise stable perception across the tongue surface.

For many years, the only spatial feature of taste mentioned in textbooks was a map showing the areas on the tongue sensitive to each of the four basic

tastes: sweet on the tip, salt and sour on the edges, and bitter on the rear. This inaccurate ‘tongue map’ arose from a misunderstanding of the work of Hänig [108], who examined taste thresholds at various tongue loci. Hänig showed that thresholds for the four basic tastes vary slightly at different loci, but he did not find that taste modalities are restricted to specific regions of the tongue surface. The misunderstanding occurred years later when Boring [109] plotted the reciprocal of Hänig’s threshold values as a measure of regional sensitivity. Subsequent readers failed to realize that the reciprocals actually represented very small threshold differences, and a myth was born.

### Clinical Correlates of Localized Taste Loss

Spatial taste testing is most powerful when used in combination with genetic and anatomical data, as it reveals discrepancies between heredity and experience that arise via pathology [57]. The following examples illustrate conditions in which modern oral sensory testing may facilitate diagnosis or intervention.

#### Disinhibition in the Mouth: A Model for Taste and Oral Pain Phantoms

Dysgeusia refers to a chronic taste that occurs in the absence of obvious stimulation [110]. Many clinical complaints of dysgeusia result from taste stimuli that are not readily apparent to the patient (e.g. medications tasted in saliva, crevicular fluid, or blood [111–113]), but some chronic oral sensations, known as phantoms, appear to arise centrally.

*Glossopharyngeal Disinhibition: Taste Phantoms.* Neurological disorders can lead to taste phantoms [114], but CT damage appears to be a primary factor in clinical accounts [84]. Moreover, electrophysiological recordings from rodents and dogs show that blocking CT input produces elevated activity in brain regions receiving input from nerve IX [115, 116]. These data indicate that CT inhibits nerve IX normally, so CT loss should disinhibit nerve IX. Human psychophysical data support this model.

- In patient cohorts (e.g. head injury, craniofacial tumors, ear infections) and healthy subjects under anesthesia, unilateral CT loss leads to increased whole-mouth perceived bitterness via increased contralateral taste sensation at nerve IX [18, 117–119]. Oral sensory input rises ipsilaterally into the CNS [120], so these contralateral effects appear to involve central modulation.
- About 40% of healthy subjects experience taste phantoms while under CT anesthesia. These phantom sensations are localized contralaterally to nerve IX, vary in quality and intensity, and fade with the anesthetic. Whole-mouth topical anesthesia abolishes these release-of-inhibition phantoms [119], presumably by suppressing spontaneous neural activity at their source.

- In one report [121], a bitter taste phantom arose bilaterally at nerve IX following tonsillectomy. Spatial testing indicated complete nerve IX loss, yet the phantom became more intense with whole-mouth topical anesthesia. This nerve stimulation phantom was probably caused by surgical damage to nerve IX and disinhibited further by CT anesthesia.

*Trigeminal Disinhibition: Oral Pain Phantoms.* CT taste input also appears to inhibit cues from nerve V. This interaction may suppress oral pain during intake, and it may facilitate tactile referral of taste information following localized taste damage. Because supertasters have the most taste and trigeminal input, CT damage may lead to adverse sensory consequences due to extreme disinhibition of nerve V: following unilateral CT anesthesia, supertasters show increased ratings for the burn of capsaicin on the contralateral anterior tongue [122].

Oral pain phantoms are another serious consequence of nerve V disinhibition. The identification of burning mouth syndrome (BMS) as such a phantom vividly illustrates the clinical relevance of modern oral sensory testing. BMS, a condition most often found in postmenopausal women, is characterized by severe oral pain in the absence of visible pathology [123]. BMS is often described as psychogenic, but systematic psychophysical testing tells a different story. Most BMS patients show significantly reduced bitterness for quinine on the anterior tongue, consistent with CT damage [124]. Nearly 50% of BMS patients experience taste phantoms at nerve IX [17]; topical anesthesia usually intensifies BMS-related taste and oral pain [125]. Finally, the peak intensity of BMS pain correlates with fungiform papillae density, indicating that BMS is most prevalent among supertasters. Taken together, these data strongly suggest that BMS is an oral pain phantom generated by CT damage. Grushka et al. [126] have shown that agonists to the inhibitory neurotransmitter  $\gamma$ -aminobutyric acid suppress BMS pain, presumably by restoring lost inhibition from absent taste cues.

### Clinical Considerations

Laboratory and clinical data support the use of topical anesthesia in the mouth to determine the locus of oral sensory dysfunction. However, interpretations of topical anesthesia must be made carefully, as incomplete anesthesia will impede differential diagnosis. In topical anesthesia, patients hold approx. 5 ml of 0.5% dyclone in the mouth for 60 s, rest for 60 s, rinse with water, and describe any oral sensations experienced for the duration of the sensory block [121].

If a taste or oral pain complaint becomes more intense with oral anesthesia, it does not arise from normal stimulation of oral sensory receptors. Certain therapeutic agents promote venous taste and other dysgeusias, so medication and supplement use should be reviewed. Another possibility is that the nerve innervating the region of sensory disturbance has sustained physical damage. If damage is peripheral to nerve cell bodies, the resulting neuroma may produce a

nerve stimulation phantom; topical anesthesia exacerbates nerve stimulation phantoms via central disinhibition. Conclusions involving nerve damage should be confirmed by further neurological examination.

When local anesthesia abolishes a taste or oral pain complaint, an actual stimulus may be present in the mouth. To test for the presence of such a stimulus, the patient should attempt to rinse it from the mouth; if the offending sensation subsides at all, an actual stimulus should be considered. Alternatively, nerve damage unrelated to the complaint may be disinhibiting input related to it; topical anesthesia suppresses these central release-of-inhibition phantoms, presumably by inhibiting spontaneous activity. Spatial testing should reveal localized taste loss at a site distant from the phantom.

## **Conclusion**

Human psychophysics is a powerful aspect of clinical and basic science that offers a window onto neurobehavioral processes often inaccessible by other means. As such, our goal in exploring psychophysical methodology is to craft measurement tools that reflect individual differences accurately and allow adaptive use in clinical, research, and other assessment settings. Conservative approaches to this task emphasize threshold measures, but we have embraced suprathreshold techniques in the hope of measuring biologically relevant sensations, and we have carefully evaluated these techniques in the process. Our overall approach has been to refine existing methods continuously, incorporating real-world reference points in order to represent perception as faithfully as possible. These refinements have posed a constant challenge to remain user friendly; our use of sophisticated scaling tools in laboratory research shows that untrained subjects learn to use them quickly and skillfully, and our clinical research indicates that these tools are accessible to patients. Finally, our systematic use of techniques from psychophysics, anatomy, neurology, and genetics has allowed us to explore complex relationships between oral sensation, affect, behavior, and disease at multiple levels of analysis. In our view, these effects confirm that our methods reflect highly predictive and highly comparable aspects of sensory and hedonic experience.

## **Acknowledgements**

This research is supported by a grant from the US National Institutes of Health (DC 00283) to L.M.B.. D.J.S. is supported by funding from the US National Science Foundation and the Rose Marie Pangborn Sensory Science Fund.

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