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REVIEW

Comparing Sensory Experiences Across Individuals: Recent Psychophysical Advances Illuminate Genetic Variation in Taste Perception

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Abstract

Modern psychophysics has traveled considerably beyond the threshold measures that dominated sensory studies in the first half of this century. Current methods capture the range of perceived intensity from threshold to maximum and promise to provide increasingly accurate comparisons of perceived intensities across individuals. The application of new psychophysical tools to genetic variation in taste allowed us to discover supertasters, individuals who live in particularly intense taste worlds. Because of the anatomy of the taste system, supertasters feel more burn from oral irritants like chili peppers, more creaminess/viscosity from fats and thickeners in food and may also experience more intense oral pain. Not surprisingly, these sensory differences influence food choices and thus health. A discussion of the milestones on the road to understanding genetic variation in taste must include discussion of some potholes as well. Often our failures have been as instructive as our successes in the effort to evaluate the impact of genetic variation in taste.

Introduction

Our current understanding of genetic variation in taste would not have been possible without the development of psychophysical techniques that permit comparisons across individuals. However, knowledge about this genetic variation has also contributed to the development of the techniques. This review examines how the study of genetic variation in taste has benefited from and fueled advances in psychophysical techniques.

Discovery of taste blindness for PTC (phenylthiocarbamide)

In 1931, Fox discovered taste blindness. While placing PTC in a bottle, some flew into the air and a colleague commented on how bitter it was, yet Fox tasted nothing (Fox, 1931). This discovery led to an exhibit at the 1931 meeting of the American Association for the Advancement of Science at which Blakeslee (a prominent geneticist of the day) and Fox recorded the taste qualities of PTC as perceived by more than 2500 participants. The results (28% tasteless; 65.5% bitter; the rest, other qualities) were published in the March 1932 issue of *The Journal of Heredity* (Blakeslee and Fox, 1932; Fox, 1932). The editor included a piece of paper impregnated with PTC so readers could report the taste qualities perceived by themselves and family members and for several years these papers were available from the journal for a small fee. Several additional studies on PTC appeared over the next few years, including a test of the Dionne quintuplets; they were tasters (Ford and Mason, 1941).

Family studies (Blakeslee and Salmon, 1931) led to the conclusion that PTC non-tasting is a Mendelian recessive characteristic, i.e. individuals with two recessive alleles (tt) are non-tasters and individuals with one dominant allele and one recessive allele (Tt or tT) and those with two dominant alleles (TT) are tasters. Recently, Reed and co-workers (Reed *et al.*, 1999) localized the *PROP* gene to chromosome 5; a region on chromosome 7 may also influence the phenotype.

Thresholds: a historical first step

Simply asking subjects to describe the taste of PTC seemed inadequate to Harris and Kalmus (Harris and Kalmus, 1949), so they introduced a threshold method that ultimately came to dominate early PTC studies [it was a variant of one of the classic threshold methods introduced by Fechner (Fechner, 1860)]. The Harris–Kalmus method was used to extend Fox's conclusion (Fox, 1932) that substances for which thresholds correlated highly with PTC thresholds all contained the N–C=S chemical group (Barnicot *et al.*, 1951). One of these substances was PROP (6-*n*-propylthiouracil). Kalmus (Kalmus, 1958) reasoned that tasters who had only taster siblings would be more likely to be homozygous for the dominant allele. Since these tasters had a lower average PTC threshold than did tasters with at least one non-taster sibling, Kalmus was able to argue that PTC tasting is an incomplete dominant. More recently, a different approach led to the same conclusion (Reed *et al.*, 1995). Mathematically, three distributions can be fitted to PROP threshold data. One is clearly associated with non-tasters; the two taster distributions overlap substantially. Thus, one can argue that PTC/PROP tasting is an incomplete dominant but thresholds cannot be used to classify individuals as homozygous or heterozygous for the dominant allele.

During these years, several studies suggested that females might be more responsive than males to PTC/PROP. Using modern statistics, we found overwhelming evidence for this sex effect in both early and current studies (Bartoshuk *et al.*, 1994). Variation in the frequency of PTC non-tasters and tasters across a variety of racial groups was commonly cited (Levine and Anderson, 1932; Parr, 1934) and is also supported by modern studies (Guo *et al.*, 1998).

In the 1960s, Fischer moved away from the focus on genetics and began to consider the behavioral implications of genetic variation in taste. He found associations between PROP tasting and drug sensitivities (Fischer *et al.*, 1965), personality type, food preferences and smoking habits (Fischer *et al.*, 1963). He was also the first to suggest the substitution of PROP for PTC, not only because PROP is odorless (PTC has a sulfurous odor) but also because PROP is less toxic than PTC (Fischer, 1971) [for a comparison of PROP and PTC see Lawless (Lawless, 1980)]. The belief that PTC/PROP tasting involved only the N–C=S group came into question. Anetholtrithione, a bitter compound not containing the nitrogen of the N–C=S group, was found to produce thresholds highly correlated with those for PTC (Dawson *et al.*, 1967).

The bitterness of PTC/PROP to non-tasters and tasters: scaling perceived intensity

The psychophysics of Fechner and Stevens

From a modern viewpoint, thresholds are an unsatisfying way to study sensory experience because they tell us only about the dimmest sensations not about the range of real world sensory intensities: a whisper, the sweetness of ice cream, the almost unbearable pain of a migraine. In order to provide a scale that could measure these suprathreshold intensities, the nineteenth century physicist Fechner turned to the jnd, the stimulus change necessary to produce a just noticeable difference. He assumed that the jnd could be considered a unit of sensation. The absolute threshold determined the bottom of the scale and one could count how many jnds were required to reach the suprathreshold intensity of interest.

A century later, a Harvard psychologist, S.S. Stevens, revolutionized psychophysics. In 1961, in a now classic paper ('To honor Fechner and repeal his law') Stevens quoted Fechner: 'The tower of Babel was never finished because the workers could not reach an understanding on how they should build it; my psychophysical edifice will stand because the workers will never agree on how to tear it down' (Stevens, 1961). Fechner was wrong. Stevens tore down Fechner's edifice by pointing out that if the jnd was really a unit of sensation, then the jnd scale would have ratio properties, i.e. a stimulus 10 jnds above threshold would be perceived to be twice as intense as one 5 jnds above threshold, but this is not the case. Each jnd does not add an equal increment of perceived intensity. Stevens and his students went on to provide the basic methodology for the new psychophysics.

One of Stevens's most important contributions, and one for which he is often not cited (Stevens, 1974), was the classification of scales of measurement. Although published in 1946, Stevens first presented his schema (Stevens, 1946) in 1940 to a meeting of the Psychological Round Table. Initially called The Society for Experimenting Psychologists (intended to pique the more senior members of the prestigious Society for Experimental Psychologists), the group was a 'youth-fired rebellion' founded in 1936 by six young experimental psychologists, including Stevens (Stevens, 1974). It was appropriate that Stevens presented his revolutionary ideas to a group that claimed as one of its objectives 'the maintenance of a constant vigil against the accumulation of dead wood' (Benjamin, 1977).

Stevens noted that there are nominal, ordinal, interval and ratio scales (Stevens, 1946). Nominal scales simply label (e.g. numbers on shirts of baseball players). Ordinal scales provide rankings (e.g. category scales such as one version of the Natick nine point scale in taste where 1 = very weak, 5 = medium and 9 = very strong) but do not provide information about the sizes of the intervals between numbers. Interval scales provide information permitting the sizes of intervals to be ranked (e.g. time as measured by dates on a calendar). The queen of the scales in Stevens's list is the ratio scale. Stevens wrote, 'Ratio scales are those most commonly encountered in physics' (e.g. length as measured in inches, mass as measured in pounds etc.) Stevens believed that it was possible to construct scales of sensation that had all the properties of ratio scales.

Stevens was famous for his psychophysical law: $\psi = \phi^{\beta}$, where ψ is the perceived intensity, ϕ is the stimulus and β is a value that depends on the sensory modality. Taking the log of both sides produces $\log\psi = \beta(\log\phi)$, the formula for a straight line of slope β. Thus, the slope of magnitude estimate data obtained from a given sensory modality plotted in log–log coordinates provides β, the exponent characteristic of that modality.

The most popular method that Stevens devised was magnitude estimation. Using this method, subjects are asked to assign numbers to perceived intensities such that one stimulus that is twice as intense as another is assigned a number twice as large. The numbers on this scale thus have ratio properties. Although this method is used widely, it is not always used correctly. Magnitude estimates cannot be compared across subjects because we cannot share one another's experience. Thus the scales of sensation that Stevens argued were like the scales used in physics have an odd limitation not found with scales in physics. Stevens's sensation scales measure relative intensities only within a subject, not across subjects. Stevens was primarily interested in comparisons across modalities, not across subjects (Borg, 1982). By the time he wrote his autobiography more than 40 sensory continua had been studied with magnitude estimation (Stevens, 1974).

Magnitude estimation applied to taste and smell

Beebe-Center (a colleague at Harvard) was the first to apply Stevens's method of magnitude estimation to taste; after Beebe-Center's death, Stevens, along with one of his students, J.C. Stevens (no relation), continued to work on taste (Stevens, 1960a,b, 1969). S.S. Stevens's revolution was appreciated by two of the pioneers in chemical senses at Brown University, Pfaffmann and Engen [see Engen (Engen, 1971) for a discussion of Fechner, Stevens and psychophysics]. Engen (Engen, 1961, 1964) shared the method with his own students in olfaction (Cain, 1970) and with McBurney (Engen and McBurney, 1964), one of Pfaffmann's students, who then used it to study adaptation in taste (McBurney, 1966). McBurney then shared the method with other Pfaffmann students (Bartoshuk, 1968). Magnitude estimation thus had a very early influence on the field of chemical senses.

Averaging magnitude estimates across subjects: the role of normalization

Magnitude estimation experiments have been done in two ways. Initially, investigators provided a standard stimulus at the beginning of a session and asked the subject to assign a particular number to it. For example, an investigator might present 0.3 M NaCl and ask all subjects to call it '10'. Subsequent stimuli were to be assigned numbers such that a stimulus that tasted twice as strong as the standard would be assigned the number '20' etc. The resulting magnitude estimates were averaged across subjects. Later, investigators began to allow subjects to use any numbers they liked as long as they assigned their numbers such that one sensation that was twice as intense as another was assigned a number twice as large etc. (Engen, 1971). This, however, raises problems for averaging across subjects, since some subjects might use very small numbers and others very large numbers. Normalization eliminates variability due to the size of the numbers.

Normalization consists of multiplying each subject's responses by a factor chosen to bring all subjects' numbers into a common range. For example, suppose we want to compare the sweetness of 1 M glucose and 1 M sucrose. One subject rates the glucose and sucrose as 4 and 8, respectively; a second subject provides 50 and 100, and a third 0.3 and 0.6. If we simply averaged the results, the larger numbers would be effectively weighted much more heavily than the smaller ones. In order to average across the three subjects, we want to first transform the data to remove variability due to the size of the numbers. Since we instructed the subjects to use numbers that reflected the appropriate ratios among the stimuli, if we multiply each subject's data by some factor, the ratios among that subject's ratings will stay the same. In this example let us make the transformed rating for sucrose equal to 25 for all three subjects. We would establish a factor for each subject such that factor = 25/sucrose rating; the factors would then be 3.12, 0.25 and 41.67, respectively. If we multiply each subject's data by her/his factor, the transformed ratings for glucose and sucrose are 12.5 and 25 for all subjects. Note that in this example we began with three sets of ratings where the ratio between glucose and sucrose was the same (0.5) but the sizes of the numbers were very different. The transformed ratings preserve the ratio of 0.5 between glucose and sucrose and all three subject's ratings are equally weighted.

In the example above, the third subject (who rated the sugars 0.3 and 0.6, respectively) could have experienced much more intense sweetness than did the first two. Neither the size of the original nor the transformed ratings reflect absolute perceived intensities. The techniques that get us closer to comparing absolute perceived intensities across individuals are discussed below.

J.C. Stevens: cross-modality matching

At Harvard, J.C. Stevens pioneered studies showing that subjects were able to match the intensities of stimuli from different sensory continua (Stevens, and Marks, 1965; Marks and Stevens, 1966). In 1966, J.C. Stevens left Harvard and joined the Pierce Foundation in New Haven, CT, where he headed the group of psychophysicists (Adair, Cain and Marks) that I joined in 1970. Comparisons across individuals became of paramount importance when, in 1975, one of my students (Hall) and I began to study genetic differences in the ability to taste PTC.

PTC/PROP scaling

Hall was an undergraduate at Yale working in my laboratory on her senior thesis. J.C. Stevens urged us to scale the bitterness of PTC to see if non-tasters would be able to taste it at the highest concentrations. At that time we believed that the ability to taste PTC was unrelated to the ability to taste other substances like NaCl. Cross-modality matching told us that we could ask our subjects to rate the bitterness of PTC and the saltiness of NaCl on the same scale using magnitude estimation. By normalizing the data to NaCl, we could compare the bitterness of PTC across tasters and non-tasters; we found that tasters perceived much greater bitterness than did non-tasters across all PTC concentrations (Hall *et al.*, 1975). Note that the logic here does not require that every individual perceive exactly the same intensity from the NaCl standard. Rather, one need only assume that there is no relation between the perceived intensities of NaCl and PTC. This would ensure that NaCl would, on average, be equally intense to tasters and non-tasters.

Hall's experiment included caffeine, a compound that does not contain the N–C=S group, yet the bitterness of dilute caffeine was more intense to tasters than to non-tasters, further evidence that non-tasters do not simply lack a receptor for N–C=S. This point was reinforced with the results of a study including saccharin and sucrose (Bartoshuk, 1979). Incidentally, in this study we followed Fischer's advice and switched from PTC to PROP. The saccharin tasted more bitter to tasters of PROP (explaining why only some consumers complain of its bitter taste). Saccharin and sucrose were also sweeter to tasters. This made the genetic variation much more interesting and motivated subsequent studies (Gent and Bartoshuk, 1983; Bartoshuk *et al.*, 1988).

The use of adjectives

Prior to Stevens's development of direct scaling methods, sensory intensities were compared across individuals using labeled category scales [see Kamen (Kamen, 1959) for an early version of the Natick nine point scale]. Investigators assumed that adjectives like 'weak' and 'strong' referred to the same sensory intensities for all subjects. Moskowitz (Moskowitz, 1977), also a student of S.S. Stevens, combined the use of adjectives with magnitude estimation. At the end of each experiment, he asked subjects to provide the estimates that they would have used to describe stimuli that were 'weak', 'strong' etc. He then normalized to the adjectives. However, adjectives do not always convey the same meaning. For example, strong coffee and strong pain suggest different absolute intensities. Concern about this was one of the factors motivating the development of magnitude matching (see below).

Discovery of supertasters

As we continued to do studies with PROP, we saw remarkable variability in the psychophysical functions for PROP among tasters. We began to suspect that the tasters could be subdivided into two groups: medium tasters who perceived saturated PROP as only moderately bitter and supertasters who perceived it as extremely bitter (Bartoshuk, 1991). We suggested the use of a ratio of PROP to NaCl to discriminate medium tasters from supertasters. For example, 0.0032 M PROP (close to saturated at room temperature) is much more bitter than 1 M NaCl is salty to supertasters; medium tasters find the two stimuli to be similar in intensity (Bartoshuk *et al.*, 1994). We suspect, but have yet to prove, that supertasters have two dominant alleles (TT) while medium tasters have one dominant allele (tT or Tt). If we are correct, then suprathreshold scaling has done what Kalmus's thresholds could not do: distinguish between heterozygous and homozygous tasters.

Magnitude matching

Marks worked with J.C. Stevens at Harvard on cross-modality matching, although Marks did his PhD research with George Miller (Stevens, and Marks, 1965; Marks and Stevens, 1966). Fifteen years later they extended their work to develop a method they called magnitude matching (Marks and Stevens, 1980; Stevens, and Marks, 1980). They compared magnitude estimates of lights and sounds under two conditions. In one, lights and tones both varied in intensity from low to high values. In the other, all of the lights but only the low to moderate tones were tested; this duplicates the experience that a person with a hearing impairment would have when given all of the stimuli. When the subjects got only the low to moderate intensity sounds, they essentially matched them to the low to moderate intensity lights just as they did when given the whole range of sounds. The relative stability of this matching demonstrated that suprathreshold scaling could be done with a standard of modality different from the one under study.

It is unlikely that we will ever find a standard that is genuinely perceived identically by all subjects. For example, the ability to hear obviously varies so that an auditory standard cannot be identical to all. However, if we can assume that the standard does not vary systematically with the stimuli of interest, magnitude matching can reveal differences across groups.

Magnitude matching was first used for the chemical senses to compare taste and smell in old and young subjects (Rifkin and Bartoshuk, 1980; Stevens, *et al.*, 1982, 1984; Bartoshuk *et al.*, 1984, 1986). Using sound as the standard modality, these studies showed that aging takes a greater toll on olfaction than on taste. Magnitude matching was also used to reveal taste losses in patients with head trauma and upper respiratory infection (Solomon *et al.*, 1991). Magnitude matching was to play a dramatic role in studies on PROP tasting. Using a non-taste standard provided the key to understanding the *magnitude* of the differences across individuals.

Marks's context effects: is NaCl a good standard for PROP studies?

Magnitude matching (with tone intensity as the standard modality) allowed us to test whether or not NaCl was a good standard for PROP studies. The early results were encouraging; 0.32 and 1 M NaCl appeared to taste equally intense to all (Marks *et al.*, 1988). Unfortunately, that study was done before we understood that PROP might alter the intensities of other taste qualities via a context effect. We now know that perceived intensities vary as a function of the intensities that precede them (Marks, 1992). For example, a moderately loud tone will sound relatively louder if it follows intense tastes. In the 1988 study, tones, PROP and NaCl were randomly interspersed. For tasters, the intense bitterness of PROP probably intensified the loudness of the tones. Since data were normalized to tones, NaCl would have seemed relatively less intense to the tasters, thus concealing non-taster–taster differences. Presenting PROP last (to prevent context effects) while scaling NaCl, tones and PROP showed that NaCl tastes more intense to supertasters (Bartoshuk *et al.*, 1998a). Thus, although using NaCl as a standard will reveal many differences across non-tasters, medium tasters and supertasters, the size of those differences may be underestimated. Incidentally, a ratio of PROP bitterness to NaCl saltiness (using a scale with ratio properties) remains a good way to differentiate medium tasters from supertasters because this process orders the subjects with regard to PROP ability only and the magnitude of the differences is not involved.

Context effects can be relatively large. An experiment comparing olfactory perception in young and old subjects (Marks *et al.*, 1988) showed that the magnitude of the difference between young and old was doubled when context effects were diminished. Thus we might expect to see greater differences among non-tasters, medium tasters and supertasters when context effects are removed.

Green's Labeled Magnitude Scale

Building on the work of earlier psychophysical scale development (Moskowitz, 1977; Gracely *et al.*, 1978; Borg, 1982; Marks *et al.*, 1988), Green and his students (Green *et al.*, 1993, 1996) constructed the Labeled Magnitude Scale (see Figure 1) with intensity adjectives spaced so that the scale would have ratio properties (i.e. a stimulus rated at 50 is twice as intense as one at 25). Thus this scale (hereafter called the Green scale) can be used in place of magnitude estimation. Most importantly, the top of the scale is labeled 'strongest imaginable'. If that label were to reflect similar perceived intensities across individuals, as Borg suggested (Borg, 1982), then the Green scale could be used to compare absolute perceived intensities across individuals. This cannot be proven, however, in our current PROP experiments the Green scale is revealing differences among non-tasters, medium tasters and supertasters that are similar to those found using magnitude matching with a sound control. Since magnitude matching has no ceiling, agreement between magnitude matching and the Green scale suggests that the Green scale avoids a ceiling effect. Further, note that the assumptions made by the two methods are very different. Magnitude matching rests on the assumption that there is no systematic relation between hearing and taste. Our use of the Green scale rests on the assumption that 'strongest imaginable' refers to the same perceived intensity, on average, across non-tasters, medium tasters and supertasters. The fact that both lead to the same conclusion about the size of the differences across non-tasters, medium tasters and supertasters strengthens belief in both assumptions.

It is important to note that we are using 'strongest imaginable' to refer to the strongest sensation of *any kind*. The Green scale was originally used such that 'strongest imaginable' referred only to oral sensations (Green *et al.*, 1993). Since supertasters perceive not only more intense tastes but also more intense oral pain and oral touch as well (see below), 'strongest imaginable oral sensation' would be more intense to supertasters than to non-tasters. The Green scale will be successful in comparing perceived intensities across non-tasters, medium tasters and supertasters only to the extent that the adjectives have the same meaning, on average, to all three groups. The domain to which adjectives are applied clearly affects the absolute intensities to which the adjectives apply. As noted above, 'strong pain' suggests a more intense experience than does 'strong coffee'. Yet the order of intensity adjectives and possibly the ratios among them within a domain are stable. For example, 'strong coffee' always denotes a more intense experience than 'weak coffee'. The anchor 'strongest imaginable' referring to sensations of any kind establishes the domain as the entire range of perceived intensities.

Assessment of genetic variation: potential artifacts

Context effects

When context effects intensify a standard, the ability to reveal differences among non-tasters, medium tasters and supertasters is diminished. This is the mistake we made when we first attempted to use magnitude matching to test our assumption that NaCl was a good standard in PROP studies. However, in experiments that do not contain a standard, context effects could produce apparent PROP effects that are not real in the following way. If subjects taste concentrated PROP, supertasters will have the most intense experiences of bitterness; subsequently, other stimuli that they taste (or hear etc.) may be perceived to be too strong. Obviously, this would lead to untrue associations between PROP tasting and other stimuli. Consequently, it is essential that PROP be tasted after other stimuli or on separate days. It is not yet known how much time is required for these context effects to dissipate.

Ceiling effects

The Green scale has provided insights about the severity of ceiling effects in psychophysical studies. Ceiling effects can conceal variations in perceived intensity. Figure 1 demonstrates how the ceiling effect in the nine point scale prevents proper sorting of medium tasters from supertasters. Subjects rated the bitterness of PROP papers

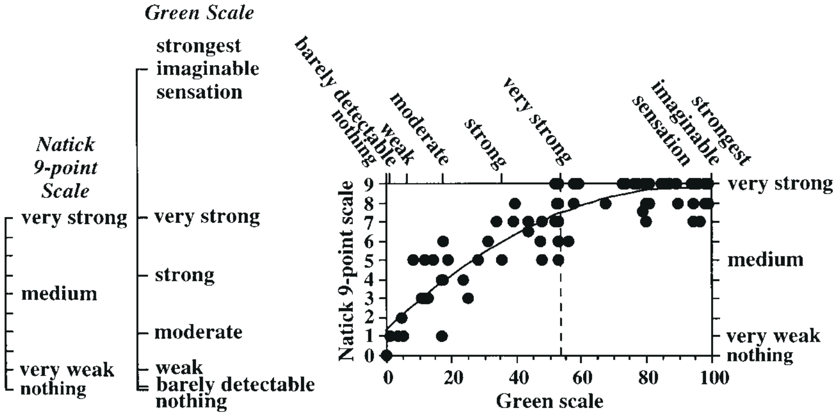

Figure 1 Bitterness of PROP paper (3 cm circles of filter paper each impregnated with 1.6 mg PROP). Green scale versus nine point scale (scales shown on the left) for 97 subjects (85 females, 12 males). The polynomial regression produced $r = 0.92$, $P < 0.0001$. Note that in the plot on the left side of the dotted line (marking 'very strong' on the Green scale) the two scales show considerable agreement. To the right of the dotted line, the nine point scale fails to distinguish among subjects who give differing ratings with the Green scale. Portions of these data were published previously (Bartoshuk *et al.*, 1999a).

(adapted from *The Journal of Heredity*, 1932) at the beginning and end of an hour long lecture using both a nine point scale and the Green scale (counterbalanced so that half of the subjects used the nine point scale first and half used the Green scale first). They were instructed to use the Green scale such that 'strongest imaginable' referred to the strongest sensation they could imagine in any modality. Using the nine point scale, subjects could give no stronger rating than 'very strong'. Given the greater freedom of the Green scale, over half of the 97 subjects rated the bitterness of the paper above 'very strong' (note that this predominantly female sample contained relatively few non-tasters). The Green scale reveals that 'very strong' is too weak a descriptor for many tasters of PROP. Supertasters and some medium tasters use the top of the nine point scale so they cannot be discriminated from one another. Incidentally, the negative curvature of the plot in Figure 1 is a well-known result when category scales are plotted against ratio scales (Stevens and Galanter, 1957).

Initially we used the nine point scale for clinical (Solomon *et al.*, 1991) and PROP studies (Bartoshuk *et al.*, 1996). However, once we had a comparison of the nine point scale with the Green scale, we could see the dire consequences of this. Whenever differences among individuals are of interest (e.g. clinical pathologies, genetic variation), scales with ceiling effects should not be used. To demonstrate the dangers of using such scales with PROP, sucrose sweetness was scaled with both the Green scale and Drewnowski's nine point scale (note the slightly different labeling: 1 = 'not at all', 9 = 'extremely') with a sensory evaluation panel (Lucchina *et al.*, 1998a). The Green scale showed an association ($r = 0.32$, $P < 0.001$) and the nine point scale did not ($r = 0.09$, not significant).

Ceiling effects can actually reverse PROP effects. For example, if supertasters are required to rate tastants on a scale with a severe ceiling effect, they will place the strongest stimuli at the top of the scale and proportionately reduce their ratings of weaker stimuli. Depending on the shape of the underlying psychophysical functions, tasters may seem to experience less intense tastes than non-tasters at some concentrations, even though, in reality, the tasters experience more intense tastes [see for example the caffeine intensity data in figure 4 in Smagghe and Louis-Sylvestre (Smagghe and Louis-Sylvestre, 1998) and see figure 1 in Prutkin and co-workers (Prutkin *et al.*, 2000) for an example from our work].

Sampling problems

In order to test for PROP effects, an investigator must be certain that the subjects represent the genetic diversity that exists. Since thresholds do not necessarily predict suprathreshold perception (see below), suprathreshold scaling is required to ensure that supertasters are sampled. If subjects are sorted into categories with insensitive suprathreshold methodologies, then there is no way to determine whether or not they are sufficiently different with regard to PROP tasting to show differences for any other stimuli. This problem is exacerbated by small sample sizes.

Threshold errors

Errors in threshold methodology pose a serious hazard in PROP studies. For example, McBurney and Collings (McBurney and Collings, 1977) introduced the up–down procedure with forced choice into modern taste psychophysics. Subjects are given two stimuli (water and a given concentration of the tastant of interest) and asked to choose the one with a taste. If they choose incorrectly, the concentration is raised on the next trial. If they choose correctly, the same concentration is repeated; the concentration is lowered only after two consecutive correct trials. This generates runs of incorrect and correct choices. The first reversal point is discarded and the geometric mean of an even number (usually six) of subsequent reversal points determines the threshold. Ending a run after two correct choices or one wrong choice produces a threshold that is roughly halfway between chance and perfect performance (Wetherill and Levitt, 1965). Increasing the required number of correct choices required increases the reliability of the threshold. Unfortunately, it also increases the length of the procedure, thus risking subject fatigue. A recent study suggests that requiring three correct choices may prove to be a useful compromise [for a discussion see Marks and Wheeler (Marks and Wheeler, 1998)]. In addition, J.C. Stevens reminds us that brief threshold tests are, at best, only estimates of a subject's sensitivity; averages over multiple threshold measurements will further ensure reliable assessments (Stevens, *et al.*, 1995).

If the up–down threshold procedure is used with only one correct choice and the procedure is begun below the subject's true threshold, the 'threshold' that results can be much lower than the subject's true threshold. To see how this could occur, consider running the procedure with water as both stimuli. On each trial, the subject has a 50% chance of selecting the 'correct' solution. A series of reversals can occur leading to a 'threshold' even if the subject never actually tastes anything (L.E. Marks, personal communication). The distorted threshold distribution that will result from such an error can lead to misinterpretations. For example, in one such study (Smagghe and Louis-Sylvestre, 1998) the distorted distribution appeared to have an antimode at a concentration well into the taster range. The authors mistakenly considered those subjects with thresholds above the false antimode to be non-tasters.

Errors in the choice of standard

For PROP studies it is critical to avoid standards that are known to vary with PROP tasting; such an error can produce apparent PROP effects in the wrong direction. For example, in one study (Schifferstein and Frijters, 1991) subjects were instructed to rate bitterness on a 150 mm line. All subjects were given 0.0003 M quinine and told to place its bitterness at the maximum, 150 mm. Thus no matter how bitter 0.0003 M quinine actually tasted, the subjects had to place it at the same point, the top of the scale. Not surprisingly, the average quinine functions for tasters and non-tasters were the same. Subjects tasted KCl as well as quinine in this study; the KCl functions for tasters and non-tasters were different but, remarkably, the non-tasters appeared to perceive more intense bitterness than did the tasters. This would be expected if quinine and KCl both taste more bitter to tasters but the magnitude of the difference is greater for quinine. Without the artificial anchoring of 0.0003 M quinine at the top of the scale, the taster function for quinine would have been considerably above that for the non-tasters. Similarly, the KCl function would have been above that for the non-tasters, however, the distance between the KCl functions would have been smaller than that for the quinine functions.

The error discussed here has also occurred in other fields where comparisons between groups are critical [for studies on taste and aging see Bartoshuk and Duffy (Bartoshuk and Duffy, 1995); for studies on taste and cancer see Duffy and co-workers (Duffy *et al.*, 1998)].

Dissociation between threshold and suprathreshold measures

That thresholds do not predict suprathreshold experience has been known for many years [see Amerine (Amerine *et al.*, 1965) for the early history of this idea in food science and Moskowitz, Bartoshuk and Pangborn for examples in taste (Moskowitz, 1974; Bartoshuk, 1978; Pangborn, 1980)]. This is illustrated in Figure 2, which shows PROP functions from subjects grouped by both threshold and suprathreshold PROP ratings. Compare function 2 with function 4. Subjects producing function 2 had non-taster thresholds and those producing function 4 had taster thresholds. However, the perceived bitterness of 0.0032 M PROP was greater on function 2 than 4. How are these subjects to be classified? Ultimately, genetic studies will answer this question. What we know now is that the family studies that relied on thresholds to classify subjects must have classified some non-tasters as tasters and vice versa.

Pathology can reduce or increase the perceived bitterness of PROP leading to misclassifications (Bartoshuk *et al.*, 1996). For example, a loss in the ability to taste bitter could make a supertaster seem like a non-taster. Mattes and co-workers (Mattes *et al.*, 1986) noted that the loss of taste with thyroid disease may have led to the belief that these patients tend to be non-tasters. On the other hand, if taste damage is localized to the chorda tympani nerve, bitter taste mediated by the glossopharyngeal nerve can be intensified (see the discussion on release of inhibition below). This might change the classification of some individuals (e.g. medium tasters might appear to be supertasters). The proportion of individuals that could be misclassified is unknown, however, common ailments (e.g. head trauma, upper respiratory infections, otitis media) are known to damage taste (Solomon *et al.*, 1991; Bartoshuk *et al.*, 1996).

Although we cannot eliminate all classification errors, some can be avoided. For example, Reed and co-workers (Reed *et al.*, 1999) using the Green scale classified individuals as tasters only if they rated the bitterness of PROP paper as 'strong' or greater. This ensured that no non-tasters would be classified as tasters. Further, she classified individuals as non-tasters only if they rated the bitterness of PROP paper as 'weak' or less. This eliminated the individuals who have non-taster thresholds but who taste concentrated PROP as bitter nonetheless.

Figure 2 illustrates the variability among tasters that first led us to suggest a distinction between medium and supertasters (Anliker *et al.*, 1991; Bartoshuk, 1991;

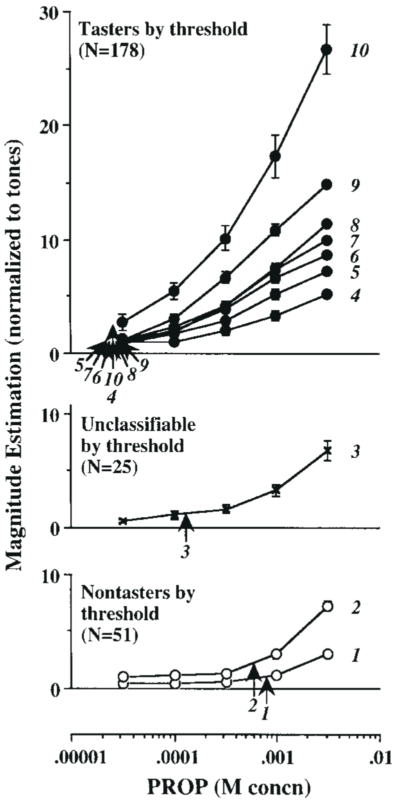

Figure 2 Magnitude estimates of PROP (normalized to tones) plotted versus concentration of PROP. Data from 254 subjects were ranked by the magnitude of the response to 0.0032 M PROP and then sorted into groups of roughly 25 subjects each. The average PROP functions for each group are numbered from 1 (lowest responses to 0.0032 M PROP) to 10 (highest responses to 0.0032 M PROP). Average thresholds for each group are indicated by the arrows. For the tasters, the average thresholds and suprathreshold responses to 0.0032 M PROP were not associated, in fact, the average thresholds for functions 4 and 10 were the same, 0.000027 M PROP. Portions of these data were published previously (Bartoshuk *et al.*, 1994).

Bartoshuk *et al.*, 1992). Cut-offs between these groups will remain arbitrary until genetic studies can determine with certainty which subjects carry two copies of the dominant allele. For most analyses relating PROP tasting to other tastes, correlation analyses between the perceived intensities of PROP and other tastants will provide the most sensitive test for associations. If experimenters choose to group subjects, one rational strategy would be to calculate the expected frequency of homozygous tasters given the frequency of non-tasters in a given data set. Since the frequency of non-tasters is close to 0.25 in the USA, such cut-offs are ~25, 50 and 25% for non-tasters, medium tasters and supertasters, respectively. By this logic, roughly the top two functions (functions 9 and 10) are those produced by supertasters. Note, however, that these figures must be adjusted if a sample contains predominantly females or males; more females are supertasters than are males (Bartoshuk *et al.*, 1994).

Studies on PROP and sweetness assessed by methodology

Since so many studies on PROP were done without the benefit of the recent insights on methodological problems, their conclusions must be reassessed. For example, consider 15 studies in which the sweetness of sucrose was scaled in subjects classified by their ability to taste PROP or PTC.

Seven studies were done prior to the discovery of supertasters. Five (Bartoshuk, 1979; Gent and Bartoshuk, 1983; Marks *et al.*, 1988, 1992; Miller and Reedy, 1990) found that sucrose was sweeter to tasters than to non-tasters. Two found no PROP effects: in one (Lawless, 1979) PTC was interspersed with other stimuli so a context effect could have concealed any PTC effects and the other (Frank and Korchmar, 1985) used a scale that we now know has a ceiling effect.

Eight studies were done after the discovery of supertasters. Five [comprising (Bartoshuk *et al.*, 1992; Drewnowski *et al.*, 1997a; Lucchina *et al.*, 1998a,b) and data collected by Prutkin (Prutkin, 1997) and cited elsewhere (Bartoshuk *et al.*, 1999a; Prutkin *et al.*, 1999b)] found differences consistent with the expected direction (supertasters > medium tasters > non-tasters). Three (Drewnowski *et al.*, 1997c, 1998; Smagghe and Louis-Sylvestre, 1998) found no PROP effects; use of the nine point scale affected both the classification of subjects (i.e. medium and supertasters could not be completely separated) and the scaling of sweetness in these studies.

Studies done after context and ceiling effects were understood (Prutkin, 1997; Lucchina *et al.*, 1998a,b; Bartoshuk *et al.*, 1999a; Prutkin *et al.*, 1999b) provide the best estimates of the size of the PROP effect. Figure 3 illustrates the ease with which sweet–PROP associations can be demonstrated even in a lecture setting. Two hundred and sixty-one attendees at lectures were given a piece of candy, a PROP paper and a questionnaire containing Green scales. First they tasted the candy and rated its sweetness; then they tasted the PROP paper and rated its bitterness. Figure 3 shows that perceived sweetness increased as ability to taste PROP increased. Among tasters only (removing the 25% of subjects with the lowest PROP ratings) the association remains ($r = 0.3$, $P < 0.001$), i.e. supertasters perceived greater sweetness than did medium tasters.

In sum, of 16 studies (including the data shown in Figure 3), 11 showed a sucrose–PROP association and five did not. However, each of the five failures is easily explained if we take into account the limitations of the psychophysical procedures in use at the time.

PROP tasting and tongue anatomy

Miller and Reedy (Miller and Reedy, 1990) discovered anatomical differences between non-tasters and tasters using dyes (including blue food coloring) that differentially stain structures on the tongue. Dyes fail to stain fungiform papillae (the structures resembling button mushrooms that

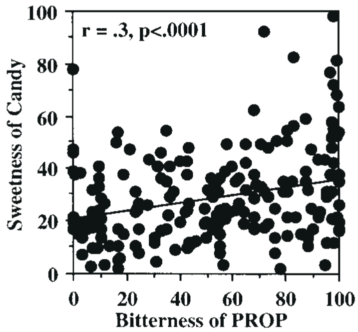

Figure 3 Sweetness of Stop and Shop Butterscotch Buttons plotted versus bitterness of PROP paper (Green scale).

contain the taste buds of the anterior tongue) so they can be counted. Dyes stain taste pores (conduits leading to the taste buds) so these can be counted under magnification. Miller and Reedy found that PROP tasters had more taste pores than did non-tasters. In collaboration with them (Reedy *et al.*, 1993; Bartoshuk *et al.*, 1994), we extended their observations to supertasters; supertasters had the most fungiform papillae and taste pores. The association between number of fungiform papillae and bitterness of PROP has been further supported by more recent studies (Hosako-Naito *et al.*, 1996; Tepper and Nurse, 1997).

Not surprisingly, since females are more likely than are males to be supertasters they have, on average, more fungiform papillae (and thus more taste pores) than do males (Bartoshuk *et al.*, 1994). In a sample of 71 females and 51 males, 17% of the females had more taste pores than any males in the sample (Prutkin *et al.*, 2000).

Perception of oral pain/irritation and touch

Twenty-five percent of the innervation of fungiform papillae comes from the chorda tympani nerve and 75% from the trigeminal nerve (Beidler, 1969). The chorda tympani nerve fibers synapse with cells in the taste buds. Trigeminal nerve fibers surround each taste bud and terminate in the apex of the fungiform papilla, an area less keratinized and thus possibly providing better access to pain stimuli. The location of the trigeminal fibers coupled with the presence of substance P and CGRP (neurotransmitters associated with pain) supports the conclusion that many mediate pain sensations (Nagy *et al.*, 1982; Whitehead *et al.*, 1985; Finger *et al.*, 1994; Whitehead and Kachele, 1994). Given this anatomy, it is not surprising that supertasters perceive the greatest irritation/pain from oral irritants like capsaicin (chili peppers), piperine (black pepper) and ethanol on the anterior tongue (Karrer, 1991; Karrer and Bartoshuk, 1991; Bartoshuk *et al.*, 1993a; Snyder *et al.*, 1996; Prutkin *et al.*, 1999a; Cunningham, 2000). Supertasters also perceive the greatest irritation/pain from ethanol on the circumvallate papillae (Cunningham, 2000); just as with the fungiform papillae, immunohistochemical studies show nerve fibers in the circumvallate papillae containing substance P and CGRP (Finger, 1986; Finger *et al.*, 1994).

Supertasters also perceive more intense sensations from substances that provide tactile stimulation in the mouth. For example, supertasters perceive the most intense sensations from fat in dairy products (Duffy *et al.*, 1996), fat in salad dressings (Tepper and Nurse, 1997), canola oil and guar gum, a thickener used in foods (Prutkin *et al.*, 1999a). The exact anatomy of the tactile innervation of fungiform papillae is not known. However, the association between number of fungiform papillae and perception of viscous stimuli suggests that tactile perception in humans depends, at least in part, on fungiform papillae. It is interesting that in the human the two point tactile threshold approximates the distance between fungiform papillae, i.e. a subject perceives two points if each one contacts a different papilla (Prutkin, 1997).

Interactions between taste and oral burn

The anatomical variation across non-tasters, medium tasters and supertasters has consequences beyond the simple relation between number of fungiform papillae and perceived intensity of burn. We have previously shown that there are central inhibitory interactions between the chorda tympani (front of the tongue) and glossopharyngeal (back of the tongue) nerves (Bartoshuk *et al.*, 1993b; Catalanotto *et al.*, 1993; Lehman *et al.*, 1995; Yanagisawa *et al.*, 1998). Damage to one releases inhibition leading to intensified taste responses from the other as well as taste phantoms. We now suspect that there are also inhibitory interactions between taste and somatosensation such that damage to taste can release inhibition of oral pain leading to intensified oral burn as well as pain phantoms. In particular, we suggest that the pain disorder called burning mouth syndrome is an example of such a phantom. We have evaluated burning mouth syndrome patients and found that they showed damage to the chorda tympani nerve and that the intensity of the pain experienced was proportional to the number of fungiform papillae on their tongues, i.e. patients with the most intense pain tended to be supertasters (Bartoshuk *et al.*, 1998b, 1999). In support of this, unilateral anesthesia of the chorda tympani intensifies perception of oral burn on the contralateral anterior tongue; supertasters experienced the largest effect (Tie *et al.*, 1999). This interaction is presumably central since the two sides of the tongue are innervated independently.

Tongue anatomy can tell us which psychophysical scales produce the best comparisons across individuals

Given that intensity of taste varies with the number of fungiform papillae, we can compare psychophysical scales to determine which produces the best correlation between perceived taste intensity and number of papillae. A preliminary study [Gardner, cited in Prutkin *et al.* (Prutkin *et al.*, 2000)] suggests that the Green scale performs as well as (and possibly better than) magnitude estimation and far better than scales with ceiling effects.

The correlation between number of fungiform papillae and taste function will never be perfect. Fungiform papillae are relatively stable anatomical structures; they may prove to be the most stable measure of original genetic endowment in taste. However, taste sensations depend not only on the number of fungiform papillae but also on the integrity of the taste buds within the papillae as well as the nerve carrying information from the papillae to the brain. In an extreme example, patients in whom the chorda tympani nerve has been severed unilaterally (peripheral to the geniculate ganglion) perceive no taste on the side of the cut (revealed by spatial taste testing). Yet in a number of such patients, there was no difference in the number of fungiform papillae between the two sides of the tongue (Janjua, 1996; Schwartz, 1998). We suspect that the loss of fungiform papillae seen in human subjects who suffer damage to both the chorda tympani and the trigeminal nerves (Zuniga and Miller, 1994) is due to damage to the trigeminal nerve. Other pathologies (e.g. otitis media) and hormonal variation can also be expected to affect taste and not the number of fungiform papillae. However, even imperfect correlations between perceived intensity and number of fungiform papillae will suffice to determine how well psychophysical scales compare perceived intensities across individuals.

Supertasters, the perception of foods and food preferences

Advances in psychophysical methodology reveal that the magnitudes of differences among non-tasters, medium tasters and supertasters are greater than originally supposed. Given the size of these sensory differences, it is not surprising that they affect behavior. The general dislike of bitterness led early investigators to suspect that tasters would tend to dislike bitter foods [see review by Drewnowski (Drewnowski, 1990)]. Drewnowski and his colleagues (Akella *et al.*, 1997; Drewnowski *et al.*, 1997b) have related PROP status to dislike of bitter compounds in foods that confer health benefits. For example, they have suggested that tasters might avoid foods containing bitter substances useful for cancer prevention. This is particularly interesting in the light of work done 30 years ago; patients with carcinoma of the cervix were more likely to be tasters (Milunicová *et al.*, 1969). However, another study (Ahuja *et al.*, 1977) found the opposite result; patients with cancer of the cervix were more likely to be non-tasters. These studies were done in very different cultures. Given cultural variation in available foods as well as food preparation methods, PROP tasters might be at less risk in some cultures and more risk in others. Some studies suggest that smokers and alcoholics are more likely to be non-tasters than would be expected by chance (Fischer *et al.*, 1963; Pelchat and Danowski, 1992). The greater intensity of oral irritation and bitterness that supertasters would be expected to experience from these activities might provide some protection, i.e. non-tasters would be less likely to reject smoking and/or drinking because of unpleasant sensory experiences (Bartoshuk *et al.*, 1993a; Dicarlo and Powers, 1998).

The earlier investigators did not have the advantage of knowing that PROP tasting also associates with perception of sweet and fat, sensations that are normally liked. However, the degree of liking sweet and fat might be expected to vary with the intensity of these sensations, i.e. some sweet sensations and/or sensations from fat may be too intense and thus less pleasant. The associations between PROP tasting and liking/disliking sweet and/or high fat foods have been examined by using preference questionnaires (Duffy and Bartoshuk, 1996; Duffy *et al.*, 1999) as well as by having subjects sample sweet (Looy and Weingarten, 1992; Drewnowski *et al.*, 1997a,c; Peterson *et al.*, 1999) or high fat (Tepper and Nurse, 1997, 1998; Drewnowski *et al.*, 1998) foods. Most of these studies report a negative relationship between PROP tasting and a liking for sweet and/or high fat foods (Looy and Weingarten, 1992; Duffy and Bartoshuk, 1996; Tepper, 1998; Tepper and Nurse, 1998; Duffy *et al.*, 1999; Peterson *et al.*, 1999). Some also found that the negative association between PROP tasting and a liking for sweet or high fat foods was strongest in women (Looy and Weingarten, 1992; Duffy and Bartoshuk, 1996; Duffy *et al.*, 1999; Peterson *et al.*, 1999).

Some of the preference studies above were conducted with hedonic scales designed to profit from the psychophysical advances in sensory scales. For example, one study (Duffy and Bartoshuk, 1996) was based on a scale devised by Marks (Marks *et al.*, 1988), which preceded development of the Green scale. The Marks scale consists of a horizontal line labeled '0' at the left end and 'extremely' about two-thirds of the way to the right end. We used this as a hedonic scale by first asking subjects to circle 'like' or 'dislike' and then indicate the intensity of their hedonic reaction on the Marks scale. Other studies (Duffy *et al.*, 1999; Peterson *et al.*, 1999) were based on the Green scale. The center of the line was labeled 'neutral' and Green scales extended to the left and the right with 'strongest imaginable' at each end. The left side of the scale was labeled 'dislike' and the right side 'like'.

Some inconsistencies among the hedonic studies will likely be related to the psychophysical methodologies but other factors are also important. Hedonic responses depend on sensation but they also depend on many other variables as well. Thus resolution of apparent disagreement among the hedonic studies will be harder to achieve than resolution among the sensory studies.

If some supertasting females find high sweet, high fat foods less pleasant, do they then eat less of them and possibly weigh less? In small samples of elderly women (Lucchina *et al.*, 1995) as well as younger women (Dabrila *et al.*, 1995) supertasters tended to be thinner. More recently, in a larger study ($n = 596$) (Duffy *et al.*, 1999), both female and male supertasters were thinner among subjects with normal body weight. In addition, both female and male supertasters were thinner in a sample where restrained eaters were excluded (Tepper and Ullrich, 1999).

Conclusions

Accurate measurement is fundamental to any science. The ability to make comparisons of sensory and hedonic experiences across subjects will lead to new discoveries in a variety of fields. This review has traced the development of new psychophysical insights in the context of one of the scientific questions that motivated some of the advances: genetic variation in taste.

Blakeslee and Fox (Blakeslee and Fox, 1932) first spoke of the 'different taste worlds' produced by genetic variation. The psychophysical advances reviewed here substantially improve comparisons of these worlds. Since the chemical senses play a role in a wide variety of behaviors that affect disease risk (e.g. food choices, alcohol intake, smoking) accurate measures of sensory variation will allow us to assess the true contribution of chemosensory experience to overall health and well-being.

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