COMMENTARY

In Pursuit of Taste Phenotypes

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Abstract

Notable progress has been made relating individual differences in bitter taste sensitivity to specific alleles and TAS2R receptors, but psychophysical evidence of reliable phenotypes for other tastes has been more elusive. In this issue, Wise and Breslin report a study of individual differences in threshold sensitivity to sour and salty taste, which, though failing to find clear phenotypes, exemplifies the type of approach and analysis necessary to disentangle sources of variance inherent in the psychophysical measures applied from those attributable to true differences in sensitivity. Methodological and theoretical lessons that can be taken from this work are discussed in the context of the early and dramatic evidence of chemosensory phenotypes that belied the complexity of taste receptor genetics and focused attention solely on peripheral determinants of sensitivity.

Key words: genetics, individual differences, phenotypes, psychophysics, taste

Experimental evidence of chemosensory phenotypes dates from a serendipitous observation in 1918 by the plant geneticist Albert Blakeslee. While classifying the colors of species of flowering plants, Blakeslee discovered that he and his assistant disagreed about which of 2 color variants was more fragrant. Intrigued, he conducted a simple experiment during a staff meeting at what was then the Carnegie Station for Experimental Evolution in Cold Spring Harbor, NY. Asking the 7 colleagues present to sniff the 2 variants labeled A and B, he quickly confirmed that the different sensitivities of he and his assistant were shared by others. Blakeslee recruited more of his colleagues to the experiment and published a brief article in *Science* in which he reported that about one-third were "blind" to the odor of A and about two-thirds were "blind" to the odor of B (Blakeslee 1918). Thirteen years later, the chemist Arthur Fox (1931) published an account of his own serendipitous finding of the first taste phenotype. Initially confirming his observation with just 10 subjects, Fox determined that some people are "taste blind" to the bitterness of phenylthiocarbamide (PTC). In the following year, Blakeslee and Fox (1932) collaborated on a survey of the sensitivity to PTC at the meeting of the American Association for the Advancement of Science. Attendees were drawn to a "Taste Exhibit" by a sign asking "What Taste World Do You Live In?" There they placed a few PTC crystals on the tongue and "voted" (in an actual voting booth) whether the crystals were "tasteless, bitter, sour, or some other taste." This simplest of experiments showed that about two-thirds of the 2550 attendees who participated were "tasters," a value that agreed with Fox's initial, much smaller survey.

More than 80 years after Blakeslee's discovery, understanding of taste and olfactory genetics has advanced far beyond what he and Fox could have envisioned. So, too, have the methods of psychophysics advanced, with many more sensitive and sophisticated tools available to measure chemosensory phenotypes. But if Blakeslee and Fox were able to identify clear chemosensory phenotypes using such unsophisticated tests, one might reasonably ask why more sensitive methods are even necessary. Indeed, Lawless (1980) found several decades ago that 4 different psychophysical methods (forced-choice and method-of-limits detection

tasks, a recognition threshold task, and a suprathreshold category rating task) produced results that were so closely correlated that "no single method emerged as an unambiguous choice for PTC taster classification…" (p. 252). Lawless attributed this result to the robustness of the taster–nontaster dimorphism and noted that the least sensitive and easiest of the tasks he tested—category rating—was the most efficient way to screen for PTC and propylthiouracil (PROP) tasters.

But advances in the genetics of taste have taught us that merely identifying tasters and nontasters provides little information about underlying genotypes. Bufe et al. (2005) elegantly showed that the genetics, biology, and psychophysics of PROP and PTC sensitivity are more complicated than was suggested by earlier work. Using a sophisticated combination of molecular genetics and psychophysics, these authors found that sensitivity was most heavily influenced by 3 haplotypes of the hTAS2R38 receptor gene, which they concluded coded for 3 variants of the TAS2R38 receptor with different sensitivities. But the study also revealed that haplotype alone was not always a consistent predictor of phenotype, particularly at suprathreshold levels: Some individuals homozygous for the PROP nontaster haplotype rated high concentrations of PROP just as bitter as did individuals who were homozygous for the taster haplotype. Conversely, these results demonstrated that no single psychophysical method can reveal the phenotypic complexity of taste perception. This would only be possible if a single receptor were solely responsible for perception of a given taste stimulus throughout the entire perceptual range. In fact, Blakeslee and Fox (1932) saw evidence that this was not the case in their own studies, noting that "People differ apparently in the intensity of sensation they experience which seems to have little relation to the thresholds at which they can first detect the substance" (p. 101). Bartoshuk (1978, 2000) later discussed possible explanations for this phenomenon and emphasized the importance of suprathreshold psychophysics for understanding taste perception, pointing out that focusing solely on threshold sensitivity can "…tell us only about the dimmest sensations, not about the range of real world sensory intensities…" (Bartoshuk, 2000, p. 448).

So, it is now clear that to characterize human taste perception fully requires measuring it in multiple ways. Yet, if different methods yield different phenotypes, we are faced with the considerable challenge of how to identify the sources and the meaning of these differences. A study by Wise and Breslin published in this issue takes a commendable step toward meeting this challenge by conducting a thoughtful examination of how the psychophysical methods and procedures they used might have contributed to the results they found. In some respects, their work follows the lead of another carefully executed study by Galindo-Cuspinera et al. (2009), which returned to the question of which psychophysical method is best for assessing PROP taster status. But the 2 studies have important differences. Wise and Breslin moved on from PROP

to study sour and salty taste, for which the transduction mechanisms in humans remain unclear. They too employed multiple psychophysical methods but limited their study to measurement of detection and recognition thresholds. In experiment 1, detection thresholds were obtained using a modified 2-alternative forced-choice method, and recognition thresholds were estimated using a modified Harris–Kalmus method (Harris and Kalmus 1949; Kalmus 1958). Importantly, replicate measurements were collected from each subject to assess the test–retest reliability of the 2 methods. This seemingly minor methodological detail proved crucial for interpreting their results: Although the relationship between detection and recognition thresholds for both salty and sour was weak, the test–retest reliability for both measures was high. The high test–retest reliability meant that the failure to find a significant correlation between the 2 kinds of thresholds was not due to excessive variability in one or both methods. This enabled Wise and Breslin to conclude that the 2 methods measure different perceptual abilities that are mediated by different, or partially overlapping, physiological mechanisms. But Wise and Breslin also reasoned that the low correlation between the 2 thresholds could have been due to the fact that the staircase method estimates only a single point on the psychometric function. It was possible that other points on the function, which would reflect different decision criteria, might be more highly correlated with the recognition threshold. In a second experiment conducted on 19 of the 22 subjects of experiment 1, the authors employed a much more rigorous (and time consuming) forced-choice method of constant stimuli (FC-MCS) to estimate the complete psychophysical function. Although the results did not offer clear support for their hypothesis, they did reveal interesting relationships between the FC-MCS data and the detection and recognition thresholds of experiment 1. Most notable was an inversion in the points of convergence on the psychophysical functions for sensitive versus insensitive subjects that reflected a smaller range of individual differences in the staircase data compared with the FC-MCS data. Wise and Breslin speculated that a procedural detail in the up–down staircase task might have led to this difference: The same (moderate) starting concentration was used for all subjects, which would tend to produce more taste adaptation in sensitive subjects than in insensitive subjects, and may cause the staircase for insensitive subjects (who do not detect the starting concentration) to converge on lower thresholds. This problem could be reduced by increasing the time between stimuli in the staircase or by using individualized starting concentrations determined by estimating the sensitivity of each subject in an initial ascending series. Wise and Breslin further point out that individual differences in other factors, such as how well subjects attend to the task and how quickly they master it, could also add variability in amounts that depend on the nature of the psychophysical task and the specific procedure used.

Of course, the contribution of higher-level neural processes to variability in psychophysical measurements has long been a concern, whether the goal has been to measure the limits of sensitivity or to quantify sensation magnitude. Possible cognitive biases in the staircase method and how they might be avoided were considered long ago (Cornsweet 1962), and reducing cognitive factors lies at the heart of the Theory of Signal Detection (Green and Swets 1966) and the "criterion-free" methods (e.g., the FC-MCS) that it forged. Cognitive biases in intensity measurement have similarly led to innovation (and controversy) in the development and use of psychophysical scaling methods (e.g., Bartoshuk and Marks 1986; Parducci and Wedell 1986; Borg and Borg 1987; Green et al. 1993; Green et al. 1996; Bartoshuk 2000). But higher-level processes can also add "variance" that is part and parcel of perceptual phenotypes. Both threshold and suprathreshold stimuli must activate all levels of the taste pathway that are necessary for conscious experience of taste, with different tasks presumably engaging somewhat different neural circuits within the pathway. Wise and Breslin alluded to this likelihood when they surmised that low correlations between detection and recognition thresholds could reflect separate or overlapping physiological processes that serve the 2 kinds of thresholds. For example, once detected, recognition of the quality evoked by a taste stimulus might depend on a pattern-matching mechanism, perhaps located in gustatory cortex, which would involve a form of memory. Given the individual differences that are typical in the performance of memory tasks, it is likely that individuals also differ in their ability to recognize weak and fleeting taste stimuli. In addition, evidence of individual differences in taste intensity perception, which were independent of taste modality and thus could not have arisen from differences in peripheral taste mechanisms, led to the hypothesis of a "central gain" mechanism in taste (Green and George 2004). It was proposed that such a mechanism, for which evidence has also been found in auditory perception (Parker et al. 2002; Schneider et al. 2011), contributes to individual differences in the responsiveness to suprathreshold taste stimulation, including the "super-taster" phenomenon (Green and George 2004; Green et al. 2005; Lim et al. 2008). Thus, as we continue to learn more about the complex genetics and biology of taste transduction (e.g., Bufe et al. 2005; Meyerhof et al. 2010; Reed et al. 2010; Cabras et al. 2012), it is important to keep in mind the potential contributions to taste phenotypes of processes within the central nervous system that are also likely to be under some degree of genetic control. Sorting out these effects requires more complicated study designs, including tests not only with multiple taste stimuli but also with nongustatory stimuli to reveal whether a phenotype is specific to a taste stimulus, a taste quality, the taste system, or reflects a more general perceptual or cognitive process.

Unfortunately, the need for more rigorous psychophysical studies to identify perceptual phenotypes comes at a time when psychophysics is increasingly taking a backseat to biological and genetic studies of taste mechanisms. Although the power, importance, and value of the great strides being made in biology and genetics are undisputed, the more data that come from in vitro and animal models the greater is the need for psychophysical studies to relate those findings to human perception. Perhaps the most important lesson to be taken from papers like Wise and Breslin's is that this translation cannot be accomplished without studies that are informed by knowledge of the strengths, weaknesses, and pitfalls of the available psychophysical methods. There is clear danger in viewing these methods as easy-to-use tools that can be taken down from the shelf and used as if following a recipe. As these authors warn, "…individual differences in sensitivity seem to interact with the methodological differences" (p. 20), a fact that researchers must keep in mind when considering which psychophysical method to use, the procedural details that need to be tailored to the conditions and objectives of the study, and how to interpret the results.

This warning may sound discouraging, but it should not be interpreted in a negative way. Instead, the study by Wise and Breslin serves to remind us of both the complexity inherent in efforts to identify reliable sensory phenotypes and the progress that can be made if appropriate methods are carefully selected and used with sufficient rigor. Proof of the success that can be achieved lies in the progress that has already been made toward this goal for bitter taste (e.g., Kuhn et al. 2004; Bufe et al. 2005; Reed et al. 2010; Mennella et al. 2011; Cabras et al. 2012). Moreover, this is not to say that important discoveries can no longer be made with simple experiments. It merely warns that after the flowers have been sniffed or the crystals tasted, our work has just begun. The good news is that there have never been more opportunities (or a greater need) for psychophysics to make significant contributions to understanding the biological mechanisms and genetics of human taste perception.

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