Individual Differences in Odor Perception

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A perfumer's ability to make fine distinctions among similar odors and to identify individual chemical components in a mixture is recognized as more art than science. This is true because the manner in which the olfactory system works is complex and at times baffling to scientists. Some knowledge is available about the anatomy and neurophysiology of the olfactory system and about the physical and chemical properties of the odorants. However, neither the initial step of interaction between the odorant and the receptor, nor the nature of the receptor, nor the process of olfactory coding within the brain is well understood.

To be perceived as an odorant, a molecule must be volatilized from its source, inhaled into the nasal cavity and dissolved in the protective mucus layer lining the epithelium which contains the olfactory sensory cells. It is believed that the molecule then must be bound by a protein receptor on hair-like protrusions (cilia) from the cell. The presumed binding process results in dramatic changes within the cell initiating olfactory nerve impulses which travel from the sensory cell to the olfactory lobe of the brain. Finally, in what is probably an extremely complex process, the brain interprets the incoming signals by associating them with a previous olfactory experience in order to assign an odor descriptor. The phenomenon of odorant-receptor binding, the type of neurotransmitters involved in nerve-lobe communication, and the correlation between odor quality and regional neural activity within the olfactory lobe and other parts of the brain are all active areas of research.

In spite of its complexities, olfactory perception is not a random event, and the fact that molecules can be classified on the basis of their three dimensional structure and polarity into odor groups (musky, sweaty, etc.) holds promise for a future system of structure/odor-quality predictive relationships, but the number of such groupings will not be trivial. There are many parameters that influence olfactory evaluation of an odorant. Sensitivity varies with the nature of the molecule and is influenced by its volatility, solubility in the mucus layer, and strength and specificity of binding to the receptor. Some examples of variation in sensitivity include dimethylsulfide and natural musk, both with de-

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tection thresholds of less than 1 ppb in air, compared with isobutanol and camphor, both with thresholds greater than 1000 ppb in air.

The context in which an odor is perceived can also determine whether an odorant gives a positive or negative response. Methyl mercaptan and isovaleric acid are unacceptable when associated with humans (for example, in breath and axillary odors) but are desirable in certain foods (for example, in cheeses). Furthermore, most natural odors are complex stimuli, that is, they are combinations of many chemicals which are interacting with many receptors. Thus, synergistic and antagonistic effects must also be considered.

To further complicate matters, trigeminal nerves in the nasal cavity are also stimulated by odorants. However, unlike olfactory cells, these nerves respond to the irritating aspects of odorants. The coolness of menthol, the sting of ammonia, and the burn in pepper are among some of the odor-induced perceptions which are mediated by the trigeminal system. Most odorants stimulate both the olfactory and trigeminal systems so that the overall perceived sensory quality is attributable to both of these systems. In addition, research has shown that there is an inverse relationship between the trigeminal and olfactory systems. Increases in trigeminal stimulation result in decreases in the perceived intensity of an odor detected via the olfactory system and *vice versa.*

A perfectly tuned and educated olfactory system, in addition to experiencing pleasurable sensations, is capable of sensitive, exact olfactory measurements and can outperform vision and hearing in detecting changes in stimulus intensity. Furthermore, in most situations, the nose is more sensitive than many instruments designed to detect odors. For the majority of the adult population, however, there are flaws in this otherwise exquisite system, some of which are inborn or inherited errors. Most serious are situations where the olfactory lobe is missing as a result of congenital abnormalities, or the olfactory nerves are severed during head trauma or destroyed as a result of viral infection. Less serious, because they are usually correctable, are situations where access of odorous molecules to the olfactory epithelium is blocked by nasal polyps, deviated septum or other anatomical anomalies. Regardless, people with any of these disorders are incapable of smelling, as most people experience it, although they may be able to detect trigeminally mediated qualities. Such people are anosmic.

Unlike total anosmia, hyperosmia and hyposmia refer respectively to a generalized heightened or diminished odor sensitivity and are usually associated with disease and/or illness. For example, hyperosmia has been reported in association with schizophrenic episodes, while hyposmia, probably experienced by each of us, usually accompanies a head cold or hay fever.

More common are specific or selected anosmias where perception of only certain odor qualities is altered. Specific anosmia is the condition in which a person of otherwise normal olfactory acuity cannot perceive a particular compound at a concentration such that its odor is obvious to most other people. It is unknown whether these specific anosmias result from an inability of the odorant molecule to reach the receptor sheet, involve a missing receptor, are a result of problems in nerve transduction, or involve odor recognition at the cognitive level.

These rather specific types of olfactaory deficits were discussed in a 1918 report by A. F. Blakeslee, who described varying sensitivities among people to the odor of pink and red Verbena flowers. Some people, including Blakeslee, were able to smell the pink flowers but could not detect a fragrance in the red flowers. Other people, including Blakeslee's assistant, could smell the red flowers but could not detect a fragrance in the pink flowers. Still other people detected a fragrance from both types of flowers.

Blakeslee, in 1935, also reported the results of a survey which he performed at an international flower show. More than 8,000 people sniffed various types of Freesia flowers. About 19% of males and 17% of females could not smell at least one of the flower types. Most of these people claimed to have a good olfactory sense.

In 1948, a Frenchman, M. Guillot, published a pivotal paper suggesting that specific anosmias ("anosmies parielles") were related to fundamental odor groups. More recently, the chemist J. E. Amoore contributed to this concept with his hypothesis that primary odors could be established by studying specific anosmias. Amoore developed procedures for testing the sensitivity of individuals to many types of odorants and documented six classes of specific anosmia.

Determination of Specific Anosmia

In a typical sensory evaluation, subjects are presented with a series of dilutions of the stimulus and with one or more blanks. Beginning with the lowest concentration, the sensory detection threshold level of the stimulus is determined. Each subject is required to choose the

odor-containing vessel. Threshold is often defined as the lowest concentration at which the person begins to correctly discriminate the odor-containing vessel from the blanks.

A bar graph (figure 1) of people's thresholds to the odor of pyridine, determined in this forced choice manner, shows that the thresholds of the subjects fall within narrow limits; there are very few normal people who cannot smell pyridine. However, when tested with androstenone, an odorous steroid, the distribution of thresholds for these same people looks very different. A glance at figure 2 shows that extremes are common. These subjects were not chosen because of these vast differences. Indeed, in the general population, approximately 50% of adults cannot smell androstenone. (Androstenone has been proposed as a human pheromone. Although this is quite controversial, it is generally accepted that this compound does function as a pheromone in another species, the domestic pig. Receptive sows must first smell this substance, and its alcohol form, androstenol, which are both found in the saliva of boars, prior to their assuming the mating stance. In the absence of these odors, the sows will resist insemination.)

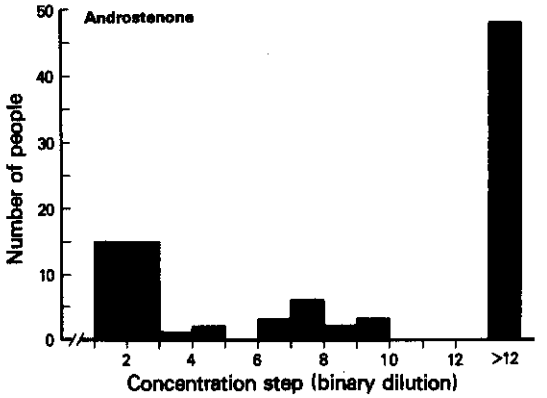

Figure 2. Distribution of detection thresholds for the same people as in figure 1 but now tested with androstenone. People in the group on the far left are the most sensitive. People in the middle group also smell androstenone but react differently. People in the group on the far right do not detect an odor.

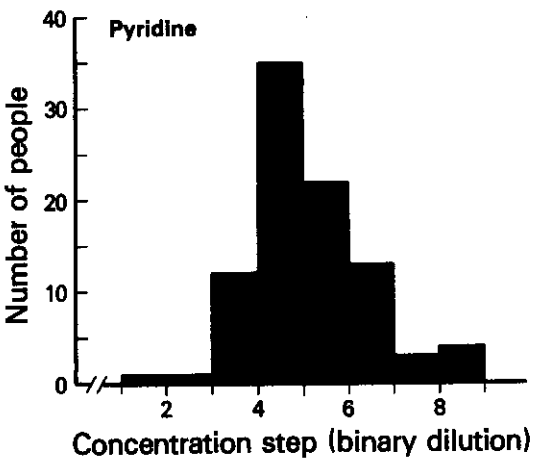

Figure 1. Distribution of detection thresholds for a group of people tested with 8 concentration steps of pyridine. The 8 concentration steps were established by a binary dilution series from step 8, the most concentrated (0.003% v/v in mineral oil).

Step 12 of figure 2 represents a concentration of androstenone of 0.1% w/v in light mineral oil, and each dilution step is ½ of the previous concentration. The total range of the concentration series exceeds 4000 fold. Individuals failing to detect an odor at the highest concentration of androstenone also fail to detect an odor when presented with crystalline androstenone, a powerful odorant for those capable of smelling it.

As seen in figure 2, people who smell androstenone fall into one of two groups. People in the very sensitive group (at the low end of the concentration series) can detect the odor of androstenone at less than 10 parts per trillion in air; at higher concentrations, these people are offended by what they describe as a powerful, stale urine odor. People in the other group, in addition to being less sensitive than members of the previous group, also have a much different perception of the odor. These people use descriptors such as sweet, musky, woody or perfume-like and are not offended by the odor. Hence, even among smellers of androstenone, there is both quantitative and qualitative variation.

Definition of Anosmia Defect

The anosmias that have been characterized include urinous, sweaty, musky, fishy, spermous,

Table I. Frequency of Occurrence of Olfactory Deficits to Some Odorants

Odorant	Characteristic Smell	Percent of Humans Not Detecting the Odor
5 alpha-androst-16-en-3-one	urinous	45-50
4-chloroaniline	mixed	41
isobutyraldehyde	malty	36
1,8-cineole	camphoraceous	33
1-pyrroline	spermous	16
omega-pentadecalactone	musky	10
trimethylamine	fishy	6
isovaleric acid	sweaty	3
L-carvone	minty	-

malty, minty and camphor. Table I lists the compounds which best represent these odor classes and are associated with the largest differences between normal and anosmic people. Androstenone represents one of the largest defects. Indeed, as noted above, many people are true anosmics, incapable of smelling any odor associated with this compound. Other compounds in this class include androsta-4,16-dienone and androstan-3-one. Interestingly, two non-steroidal analogs of androstenone have been synthesized which mimic its three dimensional structure and polarity. These have been shown to have the same odor quality and the same anosmia distributions. Whether they act as pheromones in pigs, as does androstenone, has yet to be determined.

People who are anosmic to isovaleric acid also respond similarly to butyric, isobutyric, valeric and other short-chain aliphatic acids. However, this "specific anosmia" is more statistical in nature. The "anosmia" to L-carvone, which characterizes the minty odor, is similar. People classified as anosmic to this compound have only a weak defect. In many of these specific anosmia conditions, the "anosmic" person can detect the compound if the concentration is significantly above the normal threshold. These people are certainly not the same as others with regard to their sensitivity to the compound of interest. However, these specific anosmias might be better called selective hyposmias.

Additional work has shown that at least some specific anosmias have a genetic component. Many people cannot smell the musky odor of ω-pentadecalactone (see Table I). Dr. Amoore's research group determined that this specific anosmia was familial and appeared to be inherited as a recessive trait. More recently, Charles Wysocki and G. K. Beauchamp determined that the ability to smell androstenone also was inherited. Philadelphia area twins were asked to smell androstenone. All identical twins but only one half of the non-identical twins were alike in their sensitivity to androstenone. This is exactly what would be expected of a genetic trait: identical twins have 100% of their genes in common, while non-identical twins have only 50%.

Specific Anosmia in Laboratory Animals: Models of Human Conditions

As mentioned above, some people have a specific anosmia to the sweaty smell of isovaleric acid. Tests with laboratory animals have demonstrated that a similar phenomenon occurs in mice. This offers researchers a significant advantage in studying specific anosmias and, perhaps more importantly, the basic mechanisms of olfaction. It is far easier to do anatomical, physiological and biochemical studies on materials from mice than from humans. Few people would agree to surrendering part of their olfactory apparatus or of having an electrode placed on their epithelium to determine whether the receptors of anosmics interact with or respond to the odor. Work is underway to find other mimics of human specific anosmias.

Conclusions

Most people have some olfactory deficits about which they are unaware. These may cause only minor problems in their daily lives, for example, the inability to detect certain nuances in foods.

Of major concern are life-threatening situations, for example, the inability of sewer workers to smell hydrogen cyanide gas. (Anosmia to hydrogen cyanide occurs in approximtely 10-20% of Caucasians.) It has been suggested that there are many uncharacterized anosmias for which the subject population has not yet been identified. The existence of unrecognized specific anosmias may have important consequences for safety in the work environment and certainly has an impact on product evaluations.

Many of the known specific anosmias are related to human odors and popular flavors/fragrances. This may be a spurious correlation: much more research has been conducted with these odors. Four of these relate directly to human odor sources including vaginal/skin (isovaleric acid), metabolites of semen (pyrolline) and axilla (androstenone, androstenol and isovaleric acid). Thus, individuals who are unable to recognize any one of these odor qualities would have difficulty in determining the efficacy of certain products, such as deodorants. Similarly, fragrances with musky or minty odorants would be perceived as qualitatively or quantitatively different in individuals who are insensitive to these compounds. We suggest that all members of testing panels be screened, not only with the flavors/fragrances added to test formulations, but also with the odors which will ultimately interact with the product.

References

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1. J. E. Amoore. Olfactory genetics and anosmia. In: Handbook of Sensory Physiology: Olfaction. L. M. Beidler, ed. (Springer Verlag, New York, 1971)
2. J. E. Amoore. Specific anosmia and the concept of primary odors. Chemical Senses and Flavor, **2,** 267 (1977)
3. J. E. Amoore, P. Pelosi, and J. Forrester. Specific anosmias to 5 α-androst-16-en-3-one and ω-pentadecalactone: The urinous and musky primary odors. Chemical Senses and Flavor, **2,** 401 (1977)
4. M. Beets and E. Theimer. Odor similarity between structurally related odorants. In: Ciba Foundation Symposium on Taste and Smell Vertebrates. G. Wolstenholme and J. Knight, eds. (J & A Churchill, London, 1970)
5. J. N. Labows. Our most mysterious sense. In: World Book Encyclopedia Science Annual (World Book Inc., New York) 1983
6. A. Sherman, J. E. Amoore and V. Weigel. The pyridine scale for clinical measurement of olfactory threshold: A quantitative re-evaluation. Otolaryngology and Head and Neck Surgery, **87,** 717 (1979)
7. C. J. Wysocki, G. Whitney and D. Tucker. Specific anosmia in the laboratory mouse. Behavior Genetics, **7,** 171 (1977)