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REVIEW ARTICLE

Olfactory dysfunction and its measurement in the clinic

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Abstract The sense of smell is largely taken for granted by laypersons and medical professionals alike. Indeed, its role in determining the flavor of foods and beverages, as well as in warning of, or protecting against, environmental hazards, often goes unrecognized. This is exemplified, in part, by the fact that most patients presenting to medical clinics with "taste" problems are typically subjected to complex brain imaging and gastroenterological tests without the sense of smell even being tested or considered as a basis of the problem. Aside from frank deficiencies in sweet, sour, bitter, salty and savory (umami) sensations, "taste" disorders most commonly reflect inadequate stimulation of the olfactory receptors via the retronasal route; i.e., from volatiles passing to the receptors from the oral cavity through the nasal pharynx. This article describes the two most common procedures for measuring the sense of smell in the clinic and provides examples of the application of these tests to diseases and other disorders frequently associated with smell loss. Basic issues related to olfactory testing and evaluation are addressed. It is pointed out that smell loss, particularly in later life, can be a harbinger for not only a range of neurodegenerative diseases, but can be a prognostic indicator of early mortality.

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Introduction

Smell loss or distortion is a common problem encountered by the otolaryngologist. Such dysfunction is often reflected in complaints of "taste" loss, with many patients noting that food "tastes like cardboard" or no longer has hedonic appeal. Diminished smell sensitivity influences food selection and nutrient intake, and compromises safety from food poisoning and toxic agents. Indeed, a disproportionate number of the elderly die in fires, gas explosions, and toxic exposures as a result of being unable to detect smoke or odorous warning agents added to natural gas.[1] Smell dysfunction can be devastating for those who depend upon this sense for their safety or livelihood, such as cooks, homemakers, plumbers, fire fighters, perfumers, fragrance sales persons, wine merchants, food and beverage distributors, and employees of numerous chemical, gas, and public works industries. Indeed, according to medical regulations, anosmics are not allowed into the U.S. armed forces, reflecting the importance of smell function in the operation of complex machinery and the potential for exposures to toxic agents in the battlefield.

As is the case with vision and hearing, quantitative testing is essential to (a) determine the validity and nature of a patient's complaint, (b) accurately monitor changes in function over time (including influences of pharmacological, surgical, or immunological interventions), (c) detect malingering, and (d) establish disability compensation. Fortunately, largely as a result of funding from the U.S. National Institutes of Health in the early 1980's, significant advances have been made in the development and application of easy-to-use and reliable clinical tests of olfactory function — advances described in this paper. It is clearly is no longer tenable to simply ask a patient whether a few odorants placed under the nose can be identified, since this approach can result in misleading conclusions, as it is not quantifiable, lacks reliability, has no normative referent, and is easily faked by malingerers.

Basic considerations in measuring smell function

The sense of smell is sensitive to thousands, if not millions, of odorants. While accurate testing of such a sense appears, at first glance, to be daunting, smell function is relatively easy to measure. Thus, with some exceptions, when psychophysical thresholds are increased to one odorant they tend to be increased to others, reflecting the commonality and distribution of the receptor cells and their propensity for injury.[2] Analogous phenomena are present for the identification of different odorants. Injury to more central neural structures similarly influences pathways that code or transmit information from more than one class of receptor cell. For these reasons, responses to only a few well-chosen target odorants need to be evaluated to establish an accurate assessment of the overall functioning of the system. The reader is referred elsewhere for detailed information on the anatomy and physiology of the olfactory system.[3]

In recent years, both psychophysical and electrophysiological tests have been developed to quantify olfactory function in the clinical setting. Additionally, modern structural and functional imaging procedures have been applied to better define the underpinnings of functional losses, such as damage to or the lack of olfactory bulbs and tracts.[4] However, olfactory tests vary in terms of sensitivity and practicality, ranging from brief tests of odor identification to sophisticated olfactometers yoked to electrophysiological recording equipment capable of quantifying odor-induced changes in electrical activity at the level of the olfactory epithelium (the electro-olfactogram; EOG) and cortex (odor event-related potentials; OERPs). Psychophysical tests are more practical and less costly than electrophysiological tests, making them much more popular, particularly in light of technical issues with electrophysiological testing. For example, the EOG cannot be reliably measured in all patients, given epithelial sampling issues and the intolerance of some subjects to electrodes that are placed within their non-anesthetized noses. Since the EOG is present in some anosmics and can be recorded even after death, it cannot be used, by itself, as a reliable indicator of general olfactory function. Unlike the auditory brainstem evoked potential, the OERP is presently incapable of localizing anomalies within the olfactory pathways. OERP recording sessions can be quite long since relatively long inter-stimulus intervals are needed to prevent adaptation.[5]

Some physicians, as well as attorneys seeking to denigrate psychophysical test results, divide sensory tests into "subjective" and "objective" classes. The former require a conscious response on the part of the examinee, whereas the latter assess involuntary reactions, such as altered electrical or autonomic nervous system activity. However, as pointed out for audition by the Nobel laureate Georg von Bekesy nearly 50 years ago, such a dichotomy is misleading and laden with a value judgment, since objective always trumps subjective.[6] In fact, most psychophysical olfactory tests provide a more sensitive assessment of function than do electrophysiological measures. While it is presumed that "subjective" tests are easier to malinger than "objective" tests, forced-choice psychophysical tests can detect most malingerers on the basis of improbable responses,[7] and many so-called "objective" olfactory tests are not immune to malingering. For example, reliable measurement of electrophysiological responses requires considerable subject cooperation, such as sitting very still during recording sessions.

Modern psychophysical olfactory tests

The utility of a clinical olfactory test depends upon its reliability (consistency, stability), validity (accuracy in measuring dysfunction), and practicality (administration time and effort). Related to its validity are its sensitivity (ability to detect abnormalities), specificity (ability to detect abnormalities with a minimum of false positives), and positive predictive value (the proportion of all positive tests that are true positives). Unfortunately, too few data are available to allow for statistically valid comparative assessment of such parameters among the dozens of olfactory tests that are presently available,[2] although, in general, the more trials contained in a test, the higher its

reliability and sensitivity[8]; see Fig. 1. Even though some very short olfactory tests are statistically reliable, such reliability comes at a price of lessened sensitivity or specificity, as brief tests can only clump patients into very broad dysfunction categories. This is analogous to the difficulty of using of a flashlight to determine differing degrees of visual disturbances, ultimately limiting classifications to total blindness or lack of total blindness.

Most modern clinical tests of olfactory function assess odor identification, threshold detection, discrimination, or memory.[2] It should be noted, however, that such nominally disparate tests are not mutually exclusive and generally correlate with one another. At our center we largely rely upon forced-choice odor identification and single staircase detection threshold tests for assessing dysfunction in patients, as they are reliable and conceptually measure somewhat different elements of olfactory processing. These tests are briefly described below, followed by examples of their application to clinical disorders.

Odor identification: The University of Pennsylvania Smell Identification Test (UPSIT)

The UPSIT, developed in the early 1980's, was derived from basic test measurement theory and focuses on the comparative ability of individuals to identify odors at the suprathreshold level.[9] Its popularity is due, in large part, to its high sensitivity, reliability (test–retest $r = 0.94$), and practicality, such as its ability to be self-administered in a waiting room in ~10 min and scored by a technician, nurse, or secretary in less than a minute. Physically it is comprised of four test booklets, each containing 10 pages (Fig. 2). A strip embedded with a microencapsulated odorant is present on the bottom of each page, just below a four-alternative multiple choice question. For a given item, the patient releases an odor by scratching the microencapsulated pad with a pencil tip, smells the pad, and indicates the odor quality from four alternatives. Even if no smell is perceived, a response is required (i.e., the test is

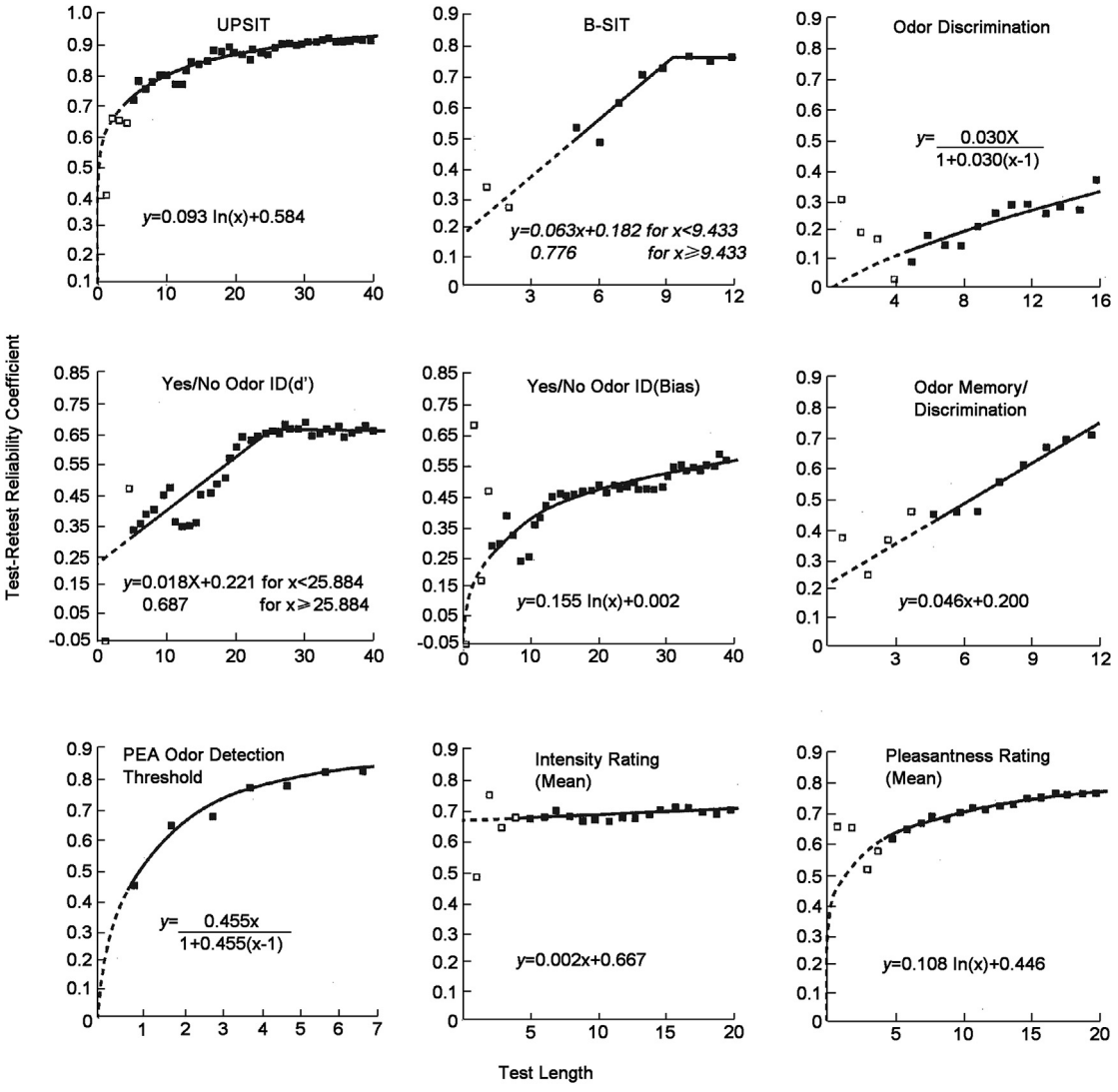

Fig. 1 Relationship of reliability to cumulative test length for test measures amenable to such an evaluation. Best fit formulae are indicated. Modified from Doty et al. (1995). Copyright© 1995 Oxford University Press.

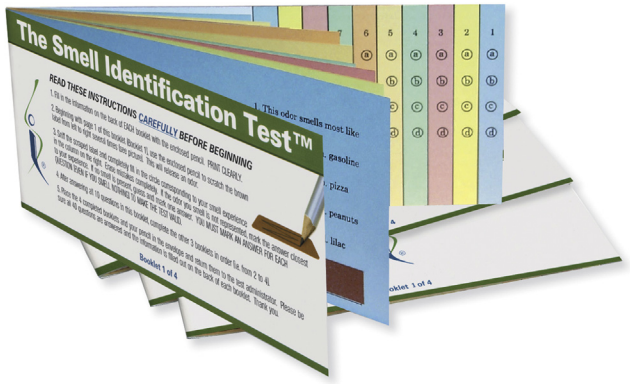

Fig. 2 The University of Pennsylvania Smell Identification Test. This 40-odorant self-administered test consists of four 10-page booklets. Each page contains a different "scratch and sniff" scented strip and an associated multiple choice question. The stimuli are released using a pencil tip.
Photo courtesy of Sensonics International, Haddon Hts., NJ 08035, USA. Copyright© 2000 Sensonics International.

forced-choice). An answer column for each item is located on the back of the test booklet, and the subject's total correct score out of the 40 items is determined. This score is then compared to a normative database from nearly 4000 normal individuals, providing an indication of the level of absolute smell function (i.e., normosmia, mild hyposmia, moderate hyposmia, severe hyposmia, total anosmia) and a percentile rank for each age and gender group. Malingering is detected on the basis of improbable responses.

The UPSIT was the impetus for a massive smell function survey sent to nearly 11 million subscribers of the National Geographic Magazine in 1986.[10] The UPSIT and its shorter versions [e.g., the 4-item Pocket Smell Test™ (PST) and the 12-item Brief Smell Identification Test™ (B-SIT)] have been administered to nearly a million persons worldwide and are the basis for the smell testing that has been incorporated into the current National Health and Nutrition Examination Survey of the United States (NHANES).[11] This survey periodically assesses the health and nutritional status of the American population. The UPSIT has now been adapted to multiple cultures and is available in languages in addition to English, including Arabic, Afrikan, Chinese (both simplified and classical), Czechoslovakian, Dutch, French, German, Hungarian, Italian, Japanese, Polish, Portuguese, Spanish, Swedish, and Turkish.

Olfactory threshold testing: the single staircase odor detection threshold test

Olfactory threshold tests are analogous to pure-tone auditory threshold tests in that their goal is to detect the lowest amount of stimulus a subject can discern. In the early 1970's, I developed a staircase procedure for assessing smell thresholds based upon a paradigm I had used in vestibular psychophysics at the North American Space Administration's Ames Research Center at Moffett Field, California (NASA).[12] In this staircase test, the concentration of an odorant is increased following trials on which a subject fails to detect the stimulus and decreased following trials where correct detection occurs, and an average of a set of up—down transitions ("reversals") is used to estimate the threshold value.[13] This provides a much more reliable estimate of threshold than procedures in which only a single ascending or descending series of stimuli is employed,[14] and is much less time consuming than procedures that present large numbers of trials at each of a number of concentrations (e.g., the method of constant stimuli).[2] The patient is required to indicate which of two or more stimuli (i.e., an odorant and one or more blanks) seems strongest on a given trial, rather than to simply report the presence or absence of a smell, mitigating the influences of response biases (e.g., the conservatism or liberalism in reporting the presence of an odor under uncertain conditions) on the sensitivity measure. Forced-choice testing is critical for threshold testing, as it controls for a subject's response bias or criterion for responding, i.e., liberalism or conservatism in reporting the presence of a stimulus independent of the subject's actual sensory sensitivity. The response criterion is confounded with the measure of sensitivity when forced-choice procedures are not employed, as discussed in detail elsewhere.[2]

A modern example of an olfactory test system utilizing the single staircase paradigm is physically comprised of a series of "snap and sniff" wands that allow for rapid presentation of concentration series of various odorants (Fig. 3).[15] Liquids, per se, are not present in the wands, as the odorants are embedded in an absorbent material exposed to the air when the collar on the outside of the wand is moved forward. This reliable test provides a standardized means for assessing sensitivity to such stimuli as amyl (pentyl) acetate, n-butanol, and phenyl ethyl alcohol (PEA), the latter being preferred. PEA is an odorant with a rose-like smell at higher concentrations and little or no intranasal trigeminal nerve (Cranial Nerve V) reactivity.[16] In this test, concentrations of PEA ranging from −9.00 to −2.00 $\log_{10}$ units in half-log steps are presented, with comparisons being made on each trial with a blank stimulus. While most threshold tests require considerable time to administer in order to obtain reliable results, this test can obtain a reliable threshold in 10—12 min.

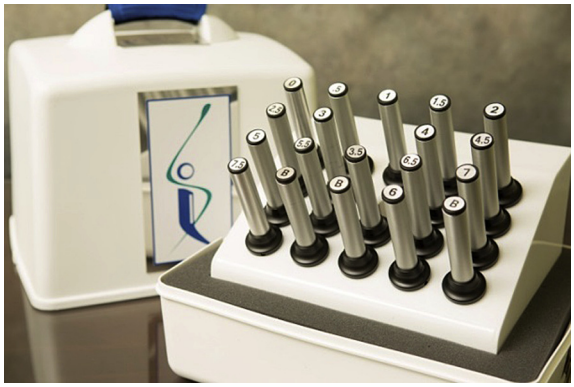

Fig. 3 The Snap and Sniff® Threshold Test. This modern test allows for rapid and reliable determinations of detection thresholds. Concentrations of phenyl ethyl alcohol, ranging from 10^{-2} to 10^{-9} log vol/vol in half-log concentration steps are commonly employed, along with blanks for forced-choice testing.
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Findings from the application of quantitative olfactory tests

The majority of major discoveries involving human olfactory function in the modern era have been made using the UPSIT. Among the non-clinical basic discoveries that have resulted from the administration of this test are the following: (a) women, on average, have a better sense of smell than men, and this superiority is noticeable as early as four years of age, increases in the later years of life, and is culture independent,[17,18] (b) there is a substantial genetic influence on the ability to identify odors,[19] although environmental factors likely overcome this influence later in life,[20] (c) major loss of olfactory function occurs after the age of 65 years, with over half of those between 65 and 80 years of age, and over three-quarters of those 80 years of age and older, having such loss,[17] (d) the decrement in olfactory function associated with smoking is present in past smokers and recovery to pre-smoking levels, while possible, can take years, depending upon the duration and amount of past smoking,[21] and (e) olfactory function is compromised in urban residents and in workers in some industries, including the paper and chemical manufacturing industries.[22–26]

Clinical applications of the UPSIT have also led to important discoveries. Thus, it is now apparent that about 15% of patients with significant head trauma, particularly cases where marked coup contra coup movement of the brain has occurred, exhibit demonstrable smell loss, often total anosmia,[27] and is typically associated with a reduction in the size of the olfactory bulbs and tracts.[28] Smell loss is now known to be common in schizophrenia and related diseases and, unlike neuropsychological measures, correlates with disease duration, suggesting the presence of a progressive, perhaps neurodegenerative, component of this disease that has previously gone unrecognized.[29] Marked smell dysfunction has now been documented for myasthenia gravis, an autoimmune disorder previously believed to be solely a peripheral disease of the cholinergic motor endplate, suggesting the likelihood of a significant CNS component.[30] Among the more important observations that followed the development of the UPSIT was the discovery that smell loss can be a very early sign — perhaps the earliest sign — of such serious neurological diseases as Alzheimer's disease (AD), Huntington's disease, and idiopathic Parkinson's disease (PD).[31] Indeed, smell testing can be a useful aid in detecting the early pre-clinical period of such diseases when yet-to-be-developed pharmacologic interventions will likely be most effective. Since some neurodegenerative disorders often misdiagnosed as AD or PD exhibit little or no olfactory dysfunction [e.g., major affective disorder and progressive supranuclear palsy (PSP), respectively], olfactory testing can also be employed in differential diagnosis.[32–35] More recently it has been discovered that impaired odor identification, particularly in the anosmic range, is associated with significantly increased mortality in older adults even after controlling for dementia and medical comorbidity.[36]

While nasal surgery or systemic corticosteroid therapy can improve olfactory function in some patients with rhinosinusitis, polyposis, or other forms or elements of nasal disease, this is not true for all patients.[37] In a prospective trial of 111 patients with medically refractive chronic rhinosinusitis,[38] found that endoscopic nasal sinus surgery improved olfactory function primarily for anosmic patients with nasal polyps. Soler, Sauer et al.[39] also present evidence that such surgery was most effective in anosmic patients with polyps.[40] found the degree of olfactory loss, as measured by the UPSIT, in patients with chronic rhinosinusitis to be correlated with the severity of histopathological changes within the olfactory mucosa. Lymphocytes, macrophages, and eosinophils release inflammatory mediators that trigger the activation of enzymes critical to the apoptotic process (e.g., caspase-3). Disease-related damage to the receptor cells of patients with rhinosinusitis was previously found by Feron, Perry et al.[41] Moreover, nasal biopsies from the posterior superior turbinate, posterior medial turbinate, and posterodorsal septum of patients with nasal disease were less likely to contain olfactory neuroepithelium than analogous biopsies from patients with no such disease. Others have similarly noted that olfactory epithelial biopsies of anosmic patients with rhinosinusitis contain less olfactory epithelial tissue than those from non-anosmic rhinosinusitis patients (27% vs 61% positive biopsies, respectively).[42] Although damage within the epithelium was noted in rhinosinusitis patients with normal smell function, such damage was greater in anosmic patients for whom some olfactory epithelium was able to be located. Abnormalities in the arrangement of the epithelial cell types were common in the biopsies from the anosmics and, when identifiably, the olfactory epithelium was typically atrophic and thin, largely being comprised of mainly sustentacular cells and basal cells.

Conclusions

It is relatively easy to quantitatively assess olfactory function in the clinic. In this brief paper I describe the two most practical, valid, and influential procedures for achieving this end, along with a range of clinical findings based upon their application. The development of such olfactory tests has been a milestone in the history of rhinology, leading to the realization that olfactory loss accompanies a much broader array of medical conditions than previously appreciated. For example, it is now apparent that smell loss is among the earliest pre-clinical signs of such common neurodegenerative diseases as Alzheimer's and Parkinson's, with the attendant implications for potentially effective prophylactic or mitigative interventions. The categorization of olfactory tests into "subjective" and "objective" categories is misleading, since so-called subjective tests, when quantifiable, are often more reliable and sensitive than so-called objective tests. Accurate olfactory assessment requires that an olfactory test is both reliable and sensitive. In general, test length correlates with test reliability. With the exception of severe airway blockage, meaningful relationships between airway patency and quantitative measures of olfactory dysfunction are rare. This observation, along with histopathological studies, point to the importance of accurately assessing smell

function in patients before and after medical or surgical interventions.

Disclosure

Dr. Doty is President and Major Shareholder in Sensonics International, a manufacturer and distributor of quantitative tests of taste and smell.

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