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Clinical Studies of Olfaction

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Introduction

Disorders of the senses of taste and smell are not uncommon, occurring in over three million adults in the United States alone. Olfactory dysfunction occurs in about half of the population between the ages of 65 and 80 years and in about three-quarters of those 80 years of age and older (Figure 1). Although rarely appreciated, taste and smell disorders have significant consequences for the patient, including (i) impaired quality of life; (ii) increased health or safety risks from spoiled foods and dangerous vapors (e.g. leaking natural gas); (iii) compromised vocational abilities; and (iv) altered food choices and consumption patterns that can adversely impact health or worsen underlying illnesses (e.g. decreased body weight, impaired immunity, overuse of salt in hypertension or sugar in diabetes mellitus).

A major focus of our Center over the last 25 years has been on the development of reliable, valid and easy-to-use tests for evaluating the senses of taste and smell. Quantitative testing is needed to (i) determine what specific cranial nerves are affected; (ii) accurately assess function (patient subjective reports can be misleading); (iii) communicate valid information to patients regarding the level of dysfunction and whether it is normal for their age and sex; (iv) monitor disease progression; (v) determine treatment efficacy; (vi) provide objective information regarding worker's compensation and other insurance or legal claims; (vii) detect early signs of tumors and neurological disorders that may not be discerned otherwise; (viii) maximize efficacy of intervention or treatment; (ix) detect malingering; and (x) provide state-of-the-art medical surveillance and care. Most of the olfactory tests we have developed, including tests of odor detection, identification and memory, are commercially available and some, such as the University of Pennsylvania Smell Identification Test (UPSIT), have been translated into multiple languages and administered to hundreds of thousands of persons. Among the findings of our Center is the close relationship between a test's length (e.g. number of items) and its reliability, a key index of its sensitivity (Figure 2).

Disorders associated with olfactory loss

Although there are numerous diseases, disorders, drugs and interventions that can adversely influence smell function, nearly two-thirds of chronic anosmia or hyposmia cases (i.e. those which are presumably permanent) are due to prior upper respiratory infections, head trauma and nasal and paranasal sinus disease (Deems *et al.*, 1991). Fewer instances of olfactory dysfunction are associated with iatrogenic interventions (e.g. septoplasty, rhinoplasty, turbinectomy, radiation therapy, medications), intranasal neoplasms (e.g. inverting papilloma, hemangioma and esthesioneuroblastoma), intracranial tumors or lesions (e.g. Foster Kennedy syndrome, olfactory groove meningiomas, frontal lobe gliomas, epilepsy-related lesions), neurodegenerative diseases, toxic agents, psychiatric disorders and endocrine and metabolic disorders.

Common colds or influenzas seem to be the most frequent disorders associated with permanent smell loss in the adult human (Deems *et al.*, 1991). Rhinosinusitis and head trauma are the next most common disorders associated with such loss. In the case of head trauma, blows to the back of the head are more likely to cause greater olfactory loss than blows to the front of the head (Doty *et al.*, 1997). The prevalence of olfactory dysfunction in patients with head trauma is usually 15% or less and the dysfunction is roughly proportional to the severity of the injury (Levin *et al.*, 1985; Deems *et al.*, 1991). Of 268 head trauma patients complaining of smell loss who were evaluated at our center, 66.8% had anosmia and 20.5% hyposmia. Of the 66 patients who were retested over intervals ranging from 1 month to 13 years, only three, none of who initially

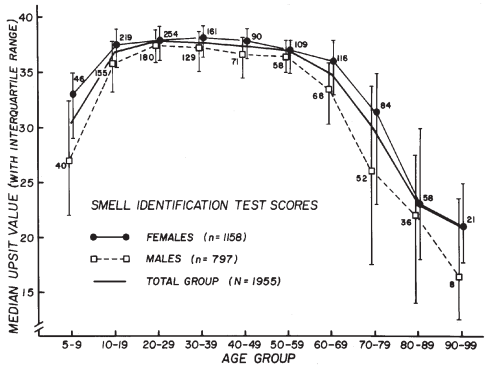

Figure 1 Scores on the University of Pennsylvania Smell Identification Test as a function of age in a large heterogeneous group of 'normal' subjects. Numbers by data points indicate sample sizes. From Doty *et al.* (1984).

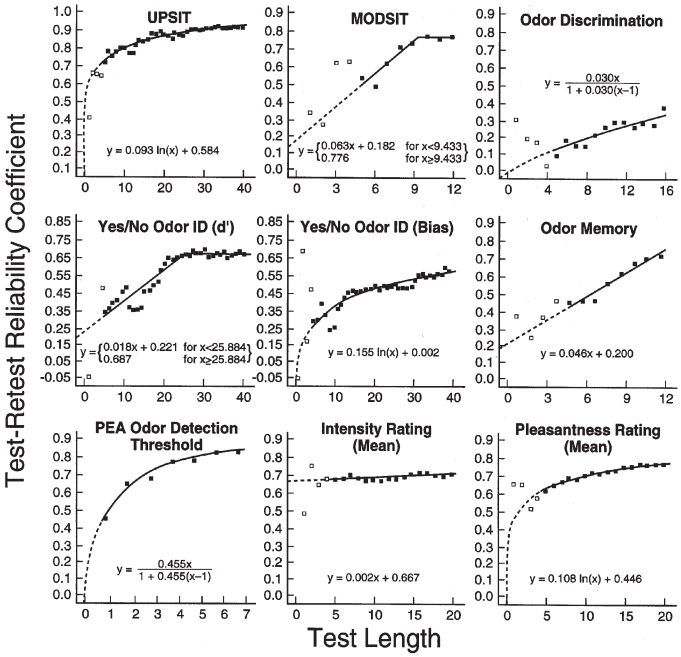

Figure 2 Relationship between reliability and olfactory test length of nine norminally distinct olfactory test measures. Note that in all cases reliability is clearly correlated with test length. From Doty *et al.* (1995).

had anosmia, regained normal olfactory function. Dysosmia prevalence decreased from 41.1 to 15.4% over post-trauma periods averaging several years (Doty *et al.*, 1997).

It is now well established that smell loss is associated with a number of neurodegenerative diseases (for recent reviews, see Mesholam *et al.*, 1998; Doty, 2003; Hawkes, 2003). In the case of Parkinson's disease (PD), the prevalence of such loss is greater than that of tremor and, by a number of accounts, essentially equivalent to that of the other cardinal signs of the disease (Hawkes *et al.*, 1999). Medications commonly used to mitigate PD symptoms (e.g. L-dopa, dopamine agonists, anticholinergic compounds) have no influence on the smell deficit, which is as severe in non-medicated or never-medicated patients as in those who are medicated (Quinn *et al.*, 1987; Doty *et al.*, 1992b; Roth *et al.*, 1998). In PD, Alzheimer's disease (AD) and the Parkinsonism-dementia complex of Guam (PDCG), severe bilateral loss, but rarely total anosmia, appears in the earliest disease stages (Doty *et al.*, 1987; Hawkes *et al.*, 1997, 1999; Bacon *et al.*, 1998; Graves *et al.*, 1999; Devanand *et al.*, 2000; Royall *et al.*, 2002; Schiffman *et al.*, 2002; Swan and Carmelli, 2002). This is in contrast to diffuse Lewy body disease (DLBD) and dementia with Lewy bodies (DLB), where anosmia is the norm, as well as to progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyrine-induced Parkinsonism (MPTP-P), where smell function is normal or only marginally altered (Doty *et al.*, 1992a, 1993; Wenning *et al.*, 1995). Moderate loss of olfactory function is most commonly present in Huntington disease (HD) and multiple system atrophy (Wenning *et al.*, 1995; Bylsma *et al.*, 1997; Moberg and Doty, 1997). This heterogeneity of dysfunction among diseases makes it possible to use olfactory tests as an aid in differential diagnosis [e.g. in distinguishing PD from PSP (Hawkes, 2003) and AD from dementia (McCaffrey *et al.*, 2000)] and provides a comparative means for better understanding the pathophysiological substrate responsible for the underlying olfactory anomalies.

Smell testing has also been found useful in predicting the onset of AD and PD. In one study, for example, the 12-item version of the UPSIT was administered to 1604 non-demented community-dwelling senior citizens 65 years of age or older (Graves *et al.*, 1999). Over a subsequent 2 year time period, the olfactory test scores were a better predictor of cognitive decline than scores on a global cognitive test. Anosmics who had at least one APOE-4 allele had 4.9 times the risk of having cognitive decline than normosmics not having this allele. This contrasts with the 1.23 times greater risk for cognitive decline in normosmics with at least one such APOE allele. When the data were stratified by sex, women who were anosmic and possessed at least one APOE-4 allele had an odds ratio of 9.71, compared to an odds ratio of 1.90 for women who were normosmic and possessed at least one allele. The corresponding odds ratios for men were 3.18 and 0.67, respectively. In a recent study, tests of odor detection, identification and discrimination were administered to 250 relatives of PD patients (~84% children, ~16% siblings, one parent; Berendse, 2001). In the 25 hyposmic relatives and in 23 normosmics sampled from this group, nigrostriatal dopaminergic function was assessed using single photon emission computer tomography (SPECT) with [^{125}I]β-CIT as a dopamine transporter ligand. An abnormal reduction in striatal dopamine transporter binding was present in 4 of the 25 (16%) hyposmic relatives, two of whom subsequently developed clinical parkinsonism, and in none of the 23 normosmic relatives. This implies that the olfactory dysfunction likely occurs before the development of classical motor signs.

Causes of chemosensory loss

Most cases of chemosensory dysfunction reflect damage to the olfactory, rather than the taste, system. The latter system is less vulnerable to head trauma and regional insults than the olfactory system, reflecting, to some degree, redundancy of taste bud innervation (i.e. involvement of the paired CN VII, IX and X nerves). The most common taste aberrations arise from systemic causes, such as side effects of antilipid, antibiotic and antifungal medications.

Olfactory dysfunction can be attributed to one of three causes: (i) conductive or transport impairments from obstruction of the nasal passages (e.g. by chronic nasal inflammation, polyposis, etc.); (ii) sensorineural impairment from damage to the olfactory neuroepithelium (e.g. by viruses, airborne toxins, etc.); or (iii) central olfactory impairment from damage to central olfactory structures and/or connections (e.g. tumors, masses impacting on olfactory tract, etc.). In some cases, it is difficult to classify an olfactory disorder into one or another of these classes, as both blockage of airflow to the receptors and damage to the receptors and/or more central elements of the olfactory system can be simultaneously present. In the case of chronic rhinosinusitis, for example, damage to the olfactory membrane in addition to blockage of airflow can occur. Although many cases of olfactory dysfunction due to conductive factors and to well-defined tumors or hematomas are treatable, most olfactory disorders due to sensorineural factors are not.

There is clear histological evidence that upper respiratory infections adversely influence the olfactory neuroepithelium. Thus, on intranasal olfactory biopsy of four patients with anosmia and 11 patients with hyposmia following a viral illness, patients with anosmia were found to have markedly reduced number of receptors and those receptors were abnormal compared to those patients with hyposmia (Jafek *et al.*, 1990). Although spontaneous recovery in these patients is possible to some degree given the propensity of olfactory neurons to regenerate, such recovery, when it occurs, is rarely marked and may take years. Topical and oral steroids have not proven effective for post-viral smell loss.

Theoretically, any inflammatory or obstructive process in the nose can disturb smell function, including allergic rhinitis, rhinosinusitis, nasal polyposis, intranasal tumors and previous nasal surgery. Although medical (e.g. administration of topical or systemic steroids) or surgical (e.g. excision of polyps) treatment can improve olfactory function in some of these cases, return of function to normal levels is not the norm (Doty and Mishra, 2001). In the case of rhinosinusitis, for example, factors other than, or in addition to, nasal airflow blockage are responsible for the loss and chronic inflammation is likely toxic to olfactory neurons. Hence, many cases of rhinosinusitis also have a sensorineural component. The severity of mucosal histopathological changes of patients with chronic rhinosinusitis is positively related to the magnitude of olfactory loss (Kern, 2000). Biopsies from the neuroepithelial region of patients with nasal disease are less likely to yield olfactory related tissue than biopsies from controls (Feron *et al.*, 1998). The same is true for anosmic versus non-anosmic rhinosinusitis patients, the former of whom exhibit a generally more pathological epithelium (e.g. disordered arrangement of cells, more islands of respiratory-like epithelium) (Lee *et al.*, 2000).

Smell disturbance following head trauma usually reflects rapid acceleration/deceleration of the brain (i.e. coup/contrecoup injury). The most common mechanisms include disruption of the sinonasal tract from shearing forces and direct contusion and ischemia to the olfactory bulb and frontal and temporal poles. Although cribriform plate fractures can occur in some cases, they are not a prerequisite for dysfunction. Most head trauma-related loss is perceived soon after the injury, although damage to the olfactory receptors may lead to delayed cell death in some cases and to a delay in the onset of dysfunction.

The weight of the evidence implicates central olfactory structures as the most likely entities that harbor the pathology responsible for the olfactory dysfunction of AD and PD, including the anterior olfactory nucleus and the olfactory bulb (Esiri and Wilcock, 1984; Hyman *et al.*, 1991; Davies *et al.*, 1993; Kovacs *et al.*, 1999; Tsuboi *et al.*, 2003). Although there is considerable evidence that the

pathology of AD begins in olfactory regions within the medial temporal lobe, most notably layer II of the entorhinal cortex (Brouillet *et al.*, 1994; Gomez-Isla *et al.*, 1996), and progresses from there to neocortical regions, there is some evidence that the olfactory bulbs are the first structures to exhibit pathology (Braak and Braak, 1998; Kovacs *et al.*, 2001).

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