CHAPTER 10

Olfaction

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Introduction

The sense of smell has been sorely neglected by the neuropsychological community, despite its importance in determining the flavor of foods and beverages and in protecting the organism from environmental hazards such as fire, leaking gas, spoiled food and polluted air. Thus, a perusal of widely used contemporary neuropsychology textbooks finds that olfaction receives either extremely scant attention (e.g., Heilman and Valenstein, 1979) or is not mentioned at all (e.g., Beaumont, 1983). Typical is the sole reference to olfaction (p. 48) in Lezak's (1983) monograph, 'Another prominent mass lying within each of the cerebral hemispheres is the amygdala, which has direct connections with the primitive centers involving the sense of smell.'

There are several reasons for this neglect: first, olfactory dysfunction, compared to dysfunction of vision, hearing, balance or tactile sensation, is less obvious and rarely influences such everyday activities as locomotion and social interaction; second, as alluded to in Lezak's quotation, this sensory system is assumed by many to be 'primitive' and not of great concern to humans; third, until recently, easy-to-use quantitative tests of olfactory function have not been generally available; and fourth, the benefits derived from olfactory sensation are typically taken for granted. Indeed, it is often only after smell loss or distortion has occurred that its importance becomes evident.

The present chapter challenges the assumption that the sense of smell is of little clinical importance to man and presents evidence that disorders of this sense are not only debilitating to the patient, but may reflect the early stages of a number of degenerative neurological disorders. To acquaint the non-specialist with fundamental aspects of this complex sense, a brief discussion of the anatomy and function of the peripheral and central olfactory pathways is first presented, followed by an analysis of the olfactory deficits observed in the elderly and in some common age-related disorders.

Basic anatomy and physiology

Olfactory epithelium and olfactory bulb

Air-borne odorant molecules, drawn into the nose during inhalation, penetrate the highest recesses of the nasal chambers, pass through a thin (< 50 μm) layer of mucus, and bind to cilia of bipolar receptor cells located on a 2 – 4 cm² patch of specialized epithelium (Fig. 1). This epithelium contains approximately 6 million of these receptor cells (which collectively constitute Cranial Nerve I), along with a complement of microvillar and supporting cells. The bipolar receptor cells are unique neural elements, as they periodically reconstitute themselves (Graziadei and Monti-Graziadei, 1978; Hinds et al., 1984). The number of cilia per cell ranges from 10 to 30 (Moran et al., 1982). Unlike
the cilia of the respiratory epithelium, mature olfactory cilia lack the biochemical machinery necessary for intrinsic motility and are comparatively long (i.e., often > 30 μm). The mucus of the olfactory region is largely derived from the sustentacular cells and the acinar cells of Bowman's glands (Getchell et al., 1984).

The unmyelinated axons of the receptor cells collect into small fasciculi at the base of the epithelium and enter the brain cavity through the foramina of the cribriform plate. These fasciculi then terminate within the olfactory bulbs in spherical masses of neuropile termed glomeruli, where they divide into bundles of 25 to 100 axons and synapse with dendrites of second-order neurons (Fig. 2). Convergence of the order of 1000 to 1 occurs between the receptor cells and the second-order cells. The axons of the largest second-order cells (mitral and tufted cells) comprise the medial and lateral olfactory tracts and have primary projections to the basal medial regions of the cerebral cortex, including the prepyriform cortex, the entorhinal cortex and the periamygdaloid region. Some projections terminate in the anterior olfactory nucleus, from which connections are made to the opposite olfactory bulb through the anterior commissure.

Much of the neural activity within the olfactory bulb involves complex local feedback circuits. Glomeruli contain, in addition to processes from receptor, mitral and tufted cells, projections from short-range horizontal neurons which interconnect neighboring glomeruli and presumably contribute to the enhancement of contrast among adjacent channels. Furthermore, axonal collaterals from mitral and tufted cells synapse with granule cells (the most numerous cell type in the olfactory bulb) which send, in turn, inhibitory output back to the bulbar regions containing the primary and secondary dendrites of the mitral and tufted cells.

![Cellular Organization of the Vertebrate Olfactory Epithelium](image)

**Fig. 1.** The cellular organization of the vertebrate olfactory epithelium. From Warwick R, Williams PL: *Gray's Anatomy*. Philadelphia: Saunders, 1973. Used with permission.
bypassing the granule cells. This latter arrangement appears to provide a means for spreading excitation at very low levels of stimulation when the inhibitory feedback system lacks too little input to be activated (MacLeod, 1971).

It is important to note that the olfactory bulb also contains many efferent (i.e., centrifugal) projections from higher brain regions which somehow modulate or alter the incoming signals (Heimer, 1968; Powell and Cowan, 1963). For example, projections are present (mainly to granule cells) from sectors of the olfactory cortex, the nucleus of the horizontal limb of the diagonal band, the locus coerules, the dorsal raphe nucleus and regions of the hypothalamus. Furthermore, fibers from the pars externa of the anterior olfactory nucleus project through the anterior commissure in a well-organized topographic manner to the contralateral bulb, possibly providing coordination between related parts of the olfactory bulbs on the two sides (Schonfeld and Macrides, 1984).

Central connections and projections

The olfactory tract flattens posteriorly and divides into two fiber bundles termed the lateral and medial striae. The medial stria becomes continuous with the subcallosal area and the paraterminal gyrus. Some of these fibers reach the olfactory tubercle and the anterior perforated substance. The fibers of the lateral olfactory tract pass along the lateral edge of the external olfactory peduncle and spread over the whole prepiriform lobe, including the periamygdaloid complex, making ipsilateral connections with the anterior olfactory nucleus, the olfactory tubercle, the prepiriform cortex, the periamygdaloid cortex, the lateral entorhinal cortex and the corticomedia amygdaloid nuclei — structures which are collectively termed the ‘olfactory cortex’ (Price, 1987). In man, the periamygdaloid and the prepiriform regions are found in barely visible gyri near the uncus (the semilunaris and ambiens gyri, respectively). The entorhinal area (Brodmann’s area 28) is comparatively large in humans, occupying a significant
portion of the anterior hippocampal gyrus (Brodal, 1981). This region is the origin of a major afferent input into the hippocampus.

The olfactory bulb fibers terminate in the most superficial of the layers of the olfactory cortex (layer Ia; Price, 1973), whose thickness decreases progressively as a function of distance from the lateral olfactory tract (reflecting, in part, decreases in the number of olfactory bulb axons which are present; Price, 1987). There appears to be no well-defined topographic organization in these projections, in that small areas of the bulb can project to large areas of the olfactory cortex and small areas of the cortex can receive fibers from large areas of the olfactory bulb (Haberly and Price, 1977). However, mitral and tufted cells are differentially represented in the olfactory cortex, with mitral cells projecting to all parts of the olfactory cortex and tufted cells projecting mainly to the anterior part of the olfactory cortex near the lateral olfactory tract (i.e., the lateral olfactory tubercle; Haberly and Price, 1977).

The different components of the olfactory cortex are connected in a broad and overlapping manner via an associational fiber system which has a well-defined laminar pattern of termination in the deep part of cortical layer I (layer Ib) and deeper cortical layers (primarily layer III) (Price, 1987). Some degree of topographical organization is apparent at this level, in that associative areas near the lateral olfactory tract evidence the heaviest projections to cortical areas near the tract, whereas such regions lateral or caudal to the tract project most heavily to caudal, medial or lateral cortical areas. Other corticocortical projections are also found in smaller areas of the olfactory cortex, including ones from the nucleus of the lateral olfactory tract, the anterior cortical amygdaloid nucleus and the periamygdaloid cortex. With the exception of the anterior cortical nucleus projections (which end throughout layer I), most of these projections terminate in cortical layer II below the association fiber system (Price, 1987).

Numerous brain regions receive projections from the olfactory cortex, including the orbital neocortex, the dorsomedial and submedial thalamic nuclei, the lateral hypothalamus, the amygdala and the hippocampus (Price, 1987). It is noteworthy that the hypothalamus receives not only fibers from the olfactory cortex, but also projections from the olfactory bulb. These projections, along with those between the hypothalamus and the corticomedial amygdaloid nuclei, are of significance to a number of activities, since these brain regions play important roles in the modulation or initiation of eating, reproduction and emotional behaviors.

**Influence of aging on smell function**

In addition to smoking and gender, age has been shown to be significantly correlated with the ability to smell. Indeed, when the relative influences of a number of subject variables are examined statistically, age invariably accounts for the greatest proportion of variance (e.g., Doty et al., 1984). However, it is not known to what extent such sensory changes represent aging processes, per se, or alterations in the sensory system brought about by factors correlated with age (e.g., cumulative viral insults, repeated exposures to air pollutants, etc.). Whatever their basis, age-related alterations are found in a variety of olfactory tasks, as indicated below.

**Odor identification**

It is now well established that, on average, older people have difficulty in identifying or recognizing odorants (e.g., Murphy, 1985; Schemper et al., 1981; Schiffman, 1977). As the result of the development of an easy-to-use quantitative microencapsulated test of olfactory function (the University of Pennsylvania Smell Identification Test or UPSIT (commercially termed the Smell Identification Test™, Sensonics, Inc., Haddonfield, NJ)), the odor-identification ability of thousands of subjects has now been evaluated and the function relating olfactory identification performance to age has been established (Doty et al.,
In general, (a) peak performance occurs during the third to fifth decades of life and markedly declines after the seventh decade, (b) smokers perform worse than nonsmokers, and (c) men perform worse than women, particularly in the later years (Fig. 3). More than half the subjects between the ages of 65 and 80 years show considerable impairment, whereas more than three-quarters of those over the age of 80 years do so. The poor scores in the older age range are unlikely to be due to losses in memory, per se, since (a) the memory load on the UPSIT probably does not exceed the span of immediate attention and (b) UPSIT scores of elderly subjects do not significantly correlate with scores on the Wechsler Memory Scale (Doty et al., 1984a). Interestingly, the sex difference appears to occur in a number of cultural groups and is probably universal (Doty et al., 1985).

**Odor detection**

As in the case of odor identification, impairment in the ability to detect low concentrations of odorants is generally found in the later years and may well be a primary basis for the marked decrease in the ability to identify odors (e.g., Chalke et al., 1958; Fordyce, 1961; Kimbrell and Furtchgott, 1963; Murphy, 1983; Schiffman et al., 1976; Venstrom and Amoore, 1968). Although the data are limited, the decline in olfactory sensitivity appears to follow a function similar to that observed for odor identification, as shown in Fig. 4 for the rose-like odorant phenyl ethyl alcohol, and is composed of both linear and quadratic components (Deems and Doty, 1987). Note that the sensitivity decreases at an earlier age in men than in women.

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Fig. 3. University of Pennsylvania Smell Identification Test (UPSIT) scores as a function of age in a large heterogeneous group of subjects. Numbers by data points indicate sample sizes. From Doty et al.: Smell identification ability: changes with age. Science: 226, 1441 – 1443, 1984. Used with permission.


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**Suprathreshold odor intensity perception**

Suprathreshold odor intensity perception is also altered in elderly compared to young subjects. Stevens et al. (1982), for example, asked 20 young (18 to 25 yrs) and 20 elderly (65 to 83 yrs) subjects to provide intensity magnitude estimates for concentrations of isoamyl butyrate (a relatively non-irritating odorant) and carbon dioxide (a trigeminal stimulus with minimal or no odor qualities), as well as to a low-pitched noise. The estimates of noise (presented in the same test session as the odorants) allowed for the normalization of the subjects’ scales of measurement (under the assumption that subjects perceive the auditory stimulus in a similar manner; see Stevens and Marks, 1980). These investigators found that the standardized magnitude estimation functions of the young and the old for each odorant were nearly parallel. However, the function of the older subjects for both odorants was displaced downward (i.e., with a lower y-intercept), suggesting that older people have a proportional loss of smell function across a broad range of stimulus concentrations. A similar finding was reported by Stevens and Cain (1985), with sodium chloride as the non-olfactory matching stimulus and iso-amyl butyrate, benzaldehyde, d-limonene, pyridine, ethanol, iso-amyl alcohol as odorants.

Age-related decrements in suprathreshold smell perception have also been reported for odorants presented to the olfactory receptors from inside the oral cavity, as during chewing and swallowing (retronasal olfaction) (Stevens and Cain, 1986). Since the intensity of retronasally perceived odor is largely dependent upon mouth movements (such as those which occur normally during deglutition; cf. Burdach and Doty, 1987), some age-related alterations in retronasal odor perception may be caused by alterations of pressure/flow relationships within the nasopharynx which result from changes in such behaviors as the speed and amount of chewing and swallowing.

**Odor discrimination**

The ability to distinguish qualitatively between odorants is impaired in many elderly people, as exemplified by multidimensional scaling studies (which represent relative perceptual differences among stimuli as distances in spatial coordinates). Thus, Schiffman and Pasternak (1979) had sixteen 19 – 25-year-olds and sixteen 72 – 78-year-olds rate 91 pairs of 14 commercial food flavors on a 5-inch ‘same-different’ rating scale. The multidimensional scaling procedure yielded a two-dimensional solution in which two main clusters emerged (simulated fruit flavors and simulated meat flavors). Analysis of the spaces of individual subjects suggested that some of the elderly subjects could not discriminate between many of the odorants, since a number of stimuli normally

![Image](image-url)

**Fig. 4.** Mean log phenyl ethyl alcohol detection threshold values as a function of age (decade) and gender in non-smoking men and women. Numbers by data points indicate sample sizes. From Deems and Doty: Age-related changes in the phenyl ethyl alcohol odor detection threshold. *Trans. PA Acad. Ophthalmol. Otolaryngol.* 39, 646 – 650, 1987. Used with permission.
found in disparate sectors of the multidimensional space were located near one another.

**Odor hedonicity**

Odors are frequently described using hedonic descriptors (e.g., 'good', 'bad', 'pleasant', 'unpleasant'; cf. Harper et al., 1968; Schiffman, 1974). When the similarity judgements of subjects are subjected to multidimensional scaling analysis, the primary dimension observed in the multidimensional space appears to be one of pleasantness/unpleasantness (Schiffman, 1974). Although the basis of this phenomenon is unknown, it presumably reflects the hedonic role that odors play in the monitoring of foodstuffs, the avoidance of polluted environments, and, at least in the case of most non-human mammals, sexual behavior (cf. Doty, 1974, 1986). Although alterations in the perceived pleasantness of an odor can be theoretically independent of alterations in its perceived intensity, there is often an association between these two dimensions. For instance, certain odorants judged pleasant at low concentrations are judged even more pleasant at high concentrations, and some odorants judged unpleasant at low concentrations are typically judged more unpleasant at high concentrations. However, a given individual’s basic odor preference can be idiosyncratic, and strict monotonicity is rarely the rule. For example, subjects who dislike low concentrations of the odor of licorice (anethole) report it to be even more unpleasant at higher concentrations, whereas subjects who like this odor find it more pleasant at higher concentrations (Doty, 1975).

If an odorant is perceived as less intense by an elderly person than by a younger one, then its perceived pleasantness or unpleasantness would also be expected to be correspondingly altered, depending upon the form of the intensity/pleasantness relationship for the odorant in question. It is therefore not surprising that Murphy (1983) found that increases in menthol concentration produced much larger increments in estimates of odor pleasantness by young than by elderly subjects. Similarly, the observations by Springer and Dietzmann (see Engen, 1977) that diesel fumes are less offensive to older than to younger persons conceivably reflects age-related decreased nasal chemosensitivity.

**Medical problems and diseases commonly affecting smell function in middle to late life**

**Upper respiratory viral infections**

Upper respiratory infections are probably the most common basis for permanent decreased smell perception in people of 50 or more years of age (Deems et al., 1989). Whether this reflects some age-related lack of resistance to viral insult or simply a culmination of repeated insults to the olfactory epithelium (or both) is unknown. Autopsy and biopsy studies indicate that the integrity of the olfactory epithelium decreases with age, metaplasia occurs from respiratory epithelium, and scar tissue blocks the transit of olfactory receptor cell axons through the cribriform plate of the olfactory bulb (Douek et al., 1975; Nakashima et al., 1984).

**Nasal sinus disease**

Nasal sinus disease, including allergic rhinitis, polyposis, bacterial rhinitis, and sinusitis, can lead to decreased olfactory function in elderly persons. Although it is generally believed that the severity of allergic nasal symptoms decreases with aging, the frequency of nasal polyposis reportedly increases with advancing years (Settipane and Chaffee, 1977). Unlike most age-related olfactory disorders, however, those which are a direct result of nasal sinus disease have a reasonable prognosis, since restoration of a patent airway through pharmacological or surgical intervention is possible in some cases and can enhance access of odorants to the receptors.

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Head trauma

Of the variety of head injuries that can influence olfactory function, those which involve rapid acceleration/deceleration of the brain are most commonly associated with smell loss. For example, coup and contrecoup contusions, in which the brain is significantly displaced for a moment within the confines of the skull, can result in the shearing or tearing of the olfactory filaments at the level of the cribriform plate. Contusions or bruises of the frontal or temporal cortices, as well as ischemia, can also result in injury to regions associated with olfactory perception. Although the frequency of head injury is higher in younger than in older people (presumably as a result of greater participation in active sports and more carelessness or inexperience in vehicle operation and other activities), the magnitude of the olfactory dysfunction appears to be equivalent in young and old accident victims (Deems et al., 1989). It is of interest to note that from 50% to 100% of serious head injury cases show olfactory dysfunction, although this statistic has yet to be calculated separately for young and old cases (for reviews, see Costanzo and Becker, 1986, and Sumner, 1976).

Alzheimer's disease

A number of well-controlled studies have noted olfactory dysfunction in patients with Alzheimer's disease (AD). In the case of odor identification, uniformity of findings exists; namely, all such studies note that the ability to identify odors is greatly impaired in this disease (Doty et al., 1987; Koss et al., 1987; Knupfer and Spiegel, 1986; Rezek, 1987; Serby et al., 1985; Warner et al., 1986). In the case of threshold-level olfactory sensitivity, all reports but one (Koss et al., 1987) indicate decreased odor sensitivity for at least some odorants (e.g., Doty et al., 1987; Knupfer and Spiegel, 1986; Murphy and Nerison, 1987; Rezek, 1987; Schiffman, personal communication). Close inspection of the data of the one exception (Koss et al., 1987) reveals, however, that of the 8 probable and 2 possible AD patients tested, one was anosmic and two evidenced threshold values within the hyposmic range. Thus, even the data of this study suggest that AD is associated with an olfactory sensitivity deficit.

A recent report suggests that AD patients show marked impairment on an odor recognition memory task, but not on a suprathreshold odor discrimination task (although the data from the latter task are not presented; Moberg et al., 1987). The deficit on the odor memory task was more marked than deficits on analogous visual and verbal recognition memory tests. Unfortunately, the olfactory, visual and verbal tasks were not equated for initial familiarity or difficulty, making the cross-modal comparisons problematic. Not surprisingly, there was a tendency for patients with less severe dementia (scores ≥ 24 on the Mini-
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1. Uncus, and the medial group of amygdaloid nuclei—all receive fibers directly from the olfactory bulb. These observations at least raise the possibility that the olfactory pathway is the site of initial involvement of the disease (p. 4534). Such findings gain even more significance in the context of theories that some dementia-related diseases may be related to environmental toxins or viruses (cf. Esiri, 1982), and evidence that (a) the olfactory system can be a major conduit of materials from the nasal cavity into the central nervous system (Shipley, 1985; Stroop et al., 1984; Tomlinson and Esiri, 1983; Monath et al., 1983) and (b) inoculation of rodents with some viruses results in necrosis of the olfactory neuroepithelium, the olfactory bulbs and tracts, and the prepyriform cortex (e.g., Goto et al., 1977; Reinacher et al., 1983).

2. Parkinson’s disease

Although it was generally believed until the 1960s that Parkinson’s disease was associated with dysfunction limited to motor symptoms (Proctor et al., 1964), it is now clear that most patients with this disease have a number of sensory and cognitive deficits, including difficulty in detecting, recognizing and identifying odorants (for a general review of non-olfactory cognitive aspects of parkinsonism, see Growden and Corkin, 1986).

The first study to demonstrate olfactory dysfunction in parkinsonism was that of Anasari and Johnson (1975). This study found amyl acetate detection thresholds of 22 PD patients to be significantly higher than the thresholds of 37 controls. This decrease in sensitivity to amyl acetate was confirmed by Ward et al. (1983) and Quinn et al. (1987).

In an extensive study, Ward et al. (1983) demonstrated suprathreshold olfactory deficits in PD patients, in addition to threshold deficits. For example, 28 PD patients were required to select, from a set of three test tubes, the one which contained a neat concentration of phenyl ethyl methyl ethyl carbinol. This task was repeated three times and a score ranging from 0 to 3 (i.e., no correct
responses to correct responses on all three trials) was assigned to each subject. The mean score of the PD patients was 1.5 (SEM = 0.2), whereas that of controls was 2.7 (SEM = 0.1). These workers also tested identical twins and found no evidence that the olfactory alterations are inherited.

Recently we administered the UPSIT and PIT to 93 parkinsonians who had symptoms ranging in duration from 3 months to 55 years (Doty et al., 1988). Ratings of 11 neurological symptoms (3 bilateral) were obtained at the time of testing. Since 12 of the patients scored below 35 on the PIT, the study group was reduced to 81 patients and their matched controls. The number of patients at each of the Hoehn and Yahr (1967) stages were as follows: I = 22; II = 21; III = 25; IV = 11, and V = 2. Of this group, 38 patients and 38 controls were also administered the PEA odor-detection threshold test, and odor identification was retested in 24 patients after intervals ranging from 5 months to three years.

The data of this study revealed that the PD patients had a marked decrement in the ability both to identify and to detect odorants (Fig. 6). The olfactory deficit appeared to be relatively stable, since (a) no statistically meaningful relationship was present between the olfactory test scores and the time since the onset of symptoms (Figs. 7 and 8) and (b) longitudinal changes did not occur in the test scores.

Since the PD test scores were similar to those of the AD patients tested earlier (Doty et al., 1987), we statistically compared the olfactory test scores of these two groups of patients. To achieve this assessment, we first matched each AD patient to a PD patient on the basis of ethnic background, age, and illness duration. The scores of the AD patients were then compared with the scores of the PD patients, and the results were analyzed statistically. The comparison revealed that the PD patients had significantly lower olfactory test scores than the AD patients.

The data from this study provide evidence that olfactory dysfunction is a widespread phenomenon in Parkinson's disease and is not related to underlying neurologic signs or disease stage. The findings also suggest that olfactory dysfunction is a stable feature of the disease, independent of the duration of symptoms.

Fig. 6. (A) University of Pennsylvania Smell Identification Test (UPSIT) scores of Parkinson's disease patients and matched normal controls. (B) Phenyl ethyl alcohol (PEA) odor-detection threshold values of PD patients and matched normal controls. From Doty et al.: Olfactory dysfunction in Parkinson's disease: a general deficit unrelated to neurologic signs, disease stage, or disease duration. *Neurology*: 38, 1237–1244, 1988. Used with permission.

Fig. 7. University of Pennsylvania Smell Identification Test (UPSIT) scores of Parkinson's disease patients as a function of disease duration. From Doty et al.: Olfactory dysfunction in Parkinson's disease: a general deficit unrelated to neurologic signs, disease stage, or disease duration. *Neurology*: 38, 1237–1244, 1988. Used with permission.

Fig. 8. Phenyl ethyl alcohol (PEA) odor-detection threshold values of Parkinson's disease patients as a function of disease duration. From Doty et al.: Olfactory dysfunction in Parkinson's disease: a general deficit unrelated to neurologic signs, disease stage, or disease duration. *Neurology*: 38, 1237–1244, 1988. Used with permission.
gender and smoking habits, and then subjected the UPSIT and PEA threshold scores to separate analyses of covariance with disease type as a factor and PIT score as a covariate (Doty et al., 1988). The covariate was important because many of the PIT scores of the AD patients fell below those of the PD patients within the 35 to 40 PIT score range, making it impossible to directly match all of the subjects on this cognitive variable.

No significant difference between the UPSIT test scores of the PD and AD patients was found, although the PIT covariate was highly significant, indicating that — even within the PIT range from 35 to 40 — the AD patients performed more poorly than did the PD patients on the PIT. A similar result was found for the detection threshold data, although the covariate did not reach significance at the 0.05 probability level (probably because of the smaller sample size).

Recently, we performed a factor analysis on data obtained from 53 patients to whom a number of cognitive and perceptual motor tests, in addition to the PIT, had been given (Doty et al., 1989). Included in the test battery was the Randt memory test (Randt et al., 1980), a number cancellation test, a reaction time test, a finger-tapping test, and selected verbal and performance subscales of the Wechsler Adult Intelligence Scale — Revised (WAIS-R; Wechsler, 1981). For this analysis, we combined the WAIS-R Information, Digit Span, Vocabulary and Similarities subtests into a single verbal score ('WAIS-Verbal') and the Picture Completion, Block Design and Digit Symbol subtests into a single performance score ('WAIS-Performance'). Similarly, we combined the Randt General Information, Five Items, Paired Words, Short Story and Picture Recognition modules into a 'Randt Memory Score'.

As seen in Table 1, six easily interpretable factors were extracted which accounted for 73.6% of the total variance. Factor 1 was clearly a cognitive/memory factor, loading most heavily (i.e., loadings > 0.50) with the Randt Memory, PIT, Number Cancellation and WAIS-R Verbal and Performance measures. Interestingly, this factor also had factor loadings > 0.50 from the neurological measures of bradykinesia and masking. Factor 2 was a gross motor factor, having factor loading > 0.50 for the neurological ratings of rigidity, alternating movements and masking, and factor loadings between 0.40 and 0.50 for left and right hand reaction times. Factor 3 appeared to be an oral motor factor, loading heavily on the speech, voice and swallow neurological ratings. Interestingly, this factor also received strong loadings from the variables of (a) disease duration, (b) thalamic surgery and (c) balance, gait and turning. Factor 4 was a fine motor factor, having strong loadings from the left and right hand finger-tapping and reaction time tests. Factor 5 was clearly an olfactory function factor, having meaningful loadings only from the UPSIT and the PEA odor-detection threshold test. Factor 6 proved to be a tremor factor, loading primarily with the neurological ratings of left and right tremor.

The aforementioned findings suggest that the olfactory dysfunction of PD is relatively independent of cognitive and motor symptoms. Further exploration of these data has shown no pattern of smell loss to the various items on the UPSIT for either the Alzheimer's or Parkinson's disease patients, implying that the odor-identification problem is unlikely to be specific to any given set of odorants. Interestingly, of 25 Parkinson's disease patients asked to answer whether or not some type of odor was noticed after sniffing each odorant item of the UPSIT, only seven responded 'no' to any odorant of the test. Of these seven, only three responded 'no' to more than one odorant, and the number of odorants responded to by even these three individuals was small (2, 3 and 6 items, respectively). These observations, along with the fact that only a few of the PD patients evidenced anosmia on the PEA detection threshold test, support the notion that the olfactory disorder of PD is rarely one of total smell loss.

Huntington's disease

The first symptoms of Huntington's disease are
TABLE 1
Varimax-rotated factor matrix for olfactory, neuropsychological and motor measurement variables. Loadings > 0.50 are printed in bold face for emphasis (R = right; L = left). See text for details. From Doty et al.: The olfactory and cognitive deficits of Parkinson's disease are independent. Ann. Neurol.: 25, 166–171, 1989, with permission.

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typically recognized in middle age, and this disease serves as a classic example of gene action late in life, with autosomal dominant transmission (McClearn and Foch, 1985). Recently, Mobert et al. (1987) reported, in a study of 38 HD patients and 38 controls, that HD patients evidence a marked deficit in an odor-recognition memory task and, furthermore, that such dysfunction is present in early-affected patients with minimal chorea or cognitive deficits and with normal verbal and visual recognition memory performance. The early HD and late HD patients reportedly performed normally on a ‘3-stage odor discrimination task’, although data for this latter task were not presented. This pioneering study suggests that a genetically determined dementia-related disorder can be accom-
panied by smell dysfunction at the time of its phenotypic expression.

General issues and summary

The studies reviewed in this chapter indicate that the sense of smell is dramatically altered in older age and in a number of age-related diseases. The deficits appear to be widespread and detectable by various olfactory tests, including tests of detection threshold, odor identification and odor memory. However, considerable interindividual variability exists and the physiological basis of these changes is not clear. In many healthy elderly people smell loss appears to occur as a result of one or more causes, including viral insult, cumulated exposure
to toxic fumes, head trauma and calcification of the cribriform plate.

While a number of workers have hypothesized that some environmental factor, such as an airborne virus or metallic element, could be responsible for the olfactory dysfunction of Alzheimer's disease (and perhaps other dementia-related diseases), only circumstantial data are available to support this point. Since the genetically determined dementia-related disorder of Huntington's chorea appears to be predictably associated with alterations in smell function, it is possible that the olfactory system is particularly vulnerable to destruction from a number of degenerative neurological disorders and that environmental agents, per se, need not be the basis for the sensory problem. However, more data are needed before one can rule out the possibility that such agents, either alone or in conjunction with a genetic substrate, play some etiological role even in these disorders.

Although it is tempting to assume, as have authors such as Koss et al. (1987), that alterations in threshold function reflect 'peripheral' olfactory dysfunction and that alterations in odor identification and other more demanding tasks reflect 'central' olfactory dysfunction, there is little empirical support at present for such a simple dichotomy. Despite the fact that a peripheral/central distinction is useful in clinical audiology (where threshold loss is commonly associated with CN VIII pathology), an evaluation of the usefulness of this distinction in olfaction requires further research. The limited data suggest that both identification and detection deficits commonly arise from damage to the olfactory epithelium, even though identification deficits unassociated with detection deficits can occur in central brain disorders (see Eichenbaum et al., 1983; Mair et al., 1986).

There is controversy as to whether the olfactory deficits observed in dementia-related diseases are due to the dementia, per se. Because non-sensory aspects of performance on olfactory tests are probably influenced in a monotonic manner by the degree of dementia, one would expect to find statistically significant negative correlations between ratings of dementia and olfactory test scores, particularly when patients with moderate dementia are included in the subject population (e.g., Jensen and Murphy, 1988). However, it is difficult to untangle the sensory and performance factors in such groups. The fact that considerable olfactory deficits are present in parkinsonian patients with minimal or non-existent dementia (and in AD patients with very mild dementia) suggests that the olfactory dysfunction, per se, is not dependent upon the underlying dementia. This notion is supported by (a) the factor analysis study of Doty et al. (1988b) in which the olfactory test scores loaded strongly on a factor which received no significant loadings from neuropsychological cognitive measures and (b) anecdotal reports from a few AD and PD patients and/or their spouses that alterations in smell sensitivity appeared to have preceded the onset of the motor or cognitive problems. On the other hand, one can envisage instances—particularly in the later stages of the disease processes—where both the olfactory system and cortical regions associated with dementia become progressively coinvolved in a way that makes it impossible to determine the degree to which cognitive and sensory factors contribute to the sensory disturbances.

It is apparent from the studies reviewed in this chapter that significant recent progress has been made in elucidating the nature and prevalence of olfactory disturbances in elderly patients and in patients with dementia-related diseases. Further advances in this area will be facilitated by the administration of a broader range of standardized olfactory tests (including ones of odor memory) to such people, as well as detailed postmortem neurochemical and structural studies of their olfactory pathways. Furthermore, studies of patients with other dementia-related diseases (e.g., Down's syndrome and Pick's disease) will provide a better understanding of the factors which underlie the sensory disorders. A big challenge for the next decade will be to determine the pathophysiological bases of these sensory disturbances and whether...
therapeutic strategems can be developed to reverse, halt or mitigate their progression.

Acknowledgements

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