Influence of Age and Age-Related Diseases on Olfactory Function

RICHARD L. DOTY

Smell and Taste Center
Department of Otorhinolaryngology and Human Communication
and
Department of Physiology
School of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania 19104

INTRODUCTION

Major changes in the ability to smell occur as a function of aging and a number of age-related neurologic degenerative disorders. Although such changes are less obvious than the changes that may occur in vision, hearing, balance, or tactile sensation (which can dramatically influence such everyday activities as locomotion and social interaction), they are of considerable consequence to the people who experience them and are commonly irreversible. In addition to adversely altering the flavor of foods and beverages, loss or distortion of smell function increases the chance of accidental poisoning from toxic fumes and spoiled foodstuffs. Thus, it is not surprising that a disproportionate number of elderly persons succumb to accidental gas poisonings each year.1

Age-related alterations in smell function are observed in tests of odor identification, discrimination, threshold detection, suprathreshold intensity perception, and perceived pleasantness.2-4 Unfortunately, it is not known to what degree such alterations represent aging processes per se or changes in the olfactory system brought about by factors correlated with age (for example, cumulative viral insults or repeated exposures to air pollutants).

The relationship between age and scores on a standardized 40-odorant test of smell function (the University of Pennsylvania Smell Identification Test or UP-SIT) is presented in FIGURE 1.5 In general, 1) peak performance occurs in the third through fifth decades of life and markedly declines after the seventh decade, 2) nonsmokers outperform smokers, and 3) women outperform men, particularly during the later years. More than half of the subjects between the ages of 65 and 80 years, and more than three-quarters of those over the age of 80 years, evidence major impairment on this test. Interestingly, the sex difference appears to occur in a number of cultural groups and is probably universal.6

Decrement in the perception of odors presented to the receptors from inside the oral cavity (as during chewing and swallowing) have also been reported in the elderly.7-8 Because the intensity of such retronasally perceived odor is influenced by mouth movements occurring normally during deglutition,9 some age-related alterations in retronasal odor perception may be due to alterations of pressure/

* This work was supported by Grant NS 16365 from the National Institute of Neurological and Communicative Disorders and Stroke.
flow relations within the nasopharynx resulting from changes in such behaviors as
the speed and amount of chewing or swallowing.

COMMON CAUSES OF SMELL LOSS IN THE ELDERLY

Upper Respiratory Viral Infections

Upper respiratory infections are probably the most common basis for decreased smell perception in persons 50 or more years of age. 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, and that metaplasia occurs from respiratory epithelium, along with the formation of scar tissue. The scar tissue appears to block the transit of olfactory receptor cell axons through the cribriform plate to the olfactory bulb.

Head Trauma

Of the variety of head injuries that can influence olfactory function in both young and elderly persons, those involving the rapid acceleration and/or deceler-
ation of the brain are most commonly associated with smell loss. For example, coup and contrecoup contusions, in which the brain is momentarily but significantly displaced, 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 persons (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 similar in young and old accident victims. It is of interest to note that from 5% to 10% of major head injury cases evidence olfactory dysfunction, although this statistic has yet to be calculated separately for young and old cases (for reviews, see Costanzo and Becker* and Sumner†).

Calcification of the Cribriform Plate

In addition to insults from viruses, toxic fumes, or head injuries, smell loss may occur in some elderly persons as the result of apposition of bone around the cribriform plate openings through which the olfactory neurons pass. Such calcification results in the degeneration of the primary olfactory neurons. The degree to which this occurs has not received much scientific study, although examination of cadaver skulls suggests it is probably not an uncommon occurrence.

AGE-RELATED NEUROLOGIC DISEASES ASSOCIATED WITH SMELL DYSFUNCTION

Alzheimer’s Disease

Alzheimer’s disease (AD) is associated with significant impairments in both the ability to identify and to detect odorants. In addition, patients with this disease evidence a marked impairment in odor recognition memory, with those with less severe dementia (scores ≥24 on the Mini-Mental State Exam (MMSE))25 scoring better than those with more severe dementia (<24 on the MMSE).26 Data that illustrate the odor identification and detection deficits of AD are presented in Figure 2. To measure identification, the UPSIT was administered to 25 patients who satisfied stringent criteria for the clinical diagnosis of probable AD and who scored above 35 on the Picture Identification Test (PIT), a test identical in content and format to the UPSIT except that pictures rather than odors are presented. To measure detection, a single staircase forced-choice odor detection threshold test using the rose-like odorant phenyl ethyl alcohol (PEA) was administered to 15 AD patients and matched controls. Although some overlap appears between the AD and the control subject data, very few AD patients performed better than their individually matched controls.

The aforementioned olfactory deficits are presumably related to structural alterations that have been recently described in the olfactory pathways of patients with AD, although cause-and-effect relations have yet to be determined. There is now evidence that neurofibrillary tangles and neuritic plaques are very concentrated within limbic structures associated with olfactory function. Pearson et al. summarize the olfactory involvement as follows: “The invariable finding of severe and even maximal involvement of the olfactory regions in Alzheimer’s
disease is in striking contrast to the minimal pathology in the visual and sensori-
motor areas of the neocortex and cannot be without significance. In the olfactory
system, the sites that are affected—the anterior olfactory nucleus, the uncus, and
the medial group of amygdaloid nuclei—all receive fibers directly from the olfac-
tory bulb. These observations at least raise the possibility that the olfactory
pathway is the site of initial involvement of the disease. Such findings gain even
more significance within the context of 1) theories that some dementia-related
diseases may be related to environmental toxins or viruses; 2) evidence that
the olfactory system can be a major conduit of materials from the nasal cavity into
the central nervous system; and 3) evidence that the inoculation of rodents
with some viruses results in necrosis of the olfactory neuroepithelium, the olfac-
tory bulbs and tracts, and the prepyriform cortex.

**Parkinson's Disease**

It now well established that many patients with Parkinson's disease (PD) have
a number of sensory and cognitive deficits, in addition to their motoric distur-
bances (for a recent general review of nonolfactory cognitive aspects of parkin-
sonism, see Growden and Corkin). Relatively recent data suggest that such
deficits include difficulties in detecting, recognizing, and identifying odorants.

Anasari and Johnson were the first to demonstrate olfactory dysfunction in PD patients. These workers found the amyl acetate detection thresholds of 22 PD patients to be significantly higher than those of 37 controls. This PD-related decrease in sensitivity to amyl acetate was subsequently confirmed by Ward et al. and by Quinn et al.
In an extensive study of PD-related olfactory dysfunction, Ward et al.\textsuperscript{41} not only demonstrated threshold deficits, but also deficits in the ability to perceive odorants at suprathreshold levels. For example, these authors had PD patients attempt to select, from a set of three test tubes, the one that contained a neat concentration of phenyl ethyl methyl ethyl carbinol. This task was repeated three times, and each subject was given a score ranging from 0 to 3 (that is, no correct responses to correct responses on all three trials). The mean score of the 28 PD patients was 1.5 (SEM = 0.2), whereas the mean score of the 30 controls was 2.7 (SEM = 0.1), suggesting that PD is associated with a suprathreshold discrimination deficit. Ward et al.\textsuperscript{41} also presented evidence based upon the testing of identical twins that the olfactory dysfunction is probably not inherited.

To more fully examine the nature of the olfactory problems associated with PD, we recently administered the UPSIT and PIT to 93 PD patients who had symptoms ranging in duration from 3 months to 55 years.\textsuperscript{43} Clinical ratings of 11 neurologic symptoms were obtained at the time of testing. Because 12 of the PD patients failed to achieve a score of 35 or higher on the PIT, the final study group consisted of 81 patients and their matched controls. Twenty of these patients had previously undergone ventrolateral thalamic surgery for treatment of severe tremor. The number of patients at each of the Hoehn and Yahr\textsuperscript{44} stages were as follows: I: 22; II: 21; III: 25; IV: 11; and V: 2. In addition, 38 patients and 38 controls were administered the PEA odor detection threshold test, and odor identification was retested in 24 patients after intervals ranging from 5 months to 3 years.

As can be seen in Figure 3, the PD patients evidenced marked decrements in both odor identification and detection ability. No relationship was present between the magnitude of the olfactory test scores and the time since the onset of symptoms in months (Figs. 4 & 5), and no significant longitudinal changes were observed. These findings suggest that the olfactory deficit of PD is relatively stable across the time periods explored in this study.

Because the PD test scores were remarkably similar to those observed in our AD study,\textsuperscript{19} we statistically compared the olfactory test scores of the PD patients to those of the AD patients. To achieve this assessment, we first matched each
AD patient to a PD patient on the basis of ethnic background, age, 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. Surprisingly, no significant difference between the UPSIT test scores of the PD and AD patients was found, although the PIT covariate was highly significant, indicating—even within the PIT range from 35 to 40—that 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 alpha level.

In a subsequent study, a factor analysis was performed on data obtained from 53 patients to whom a number of cognitive and perceptual motor tests, in addition to the PIT, had been administered. Included in the test battery was the Randt memory test, a number cancellation test, a reaction time test, a finger tapping test, and selected verbal and performance subscales of the Wechsler Adult Intelli-

![Figure 4](image1.png)

**FIGURE 4.** UPSIT scores of PD patients ($N = 81$) as a function of disease duration. From Doty et al., with permission.

![Figure 5](image2.png)

**FIGURE 5.** PEA odor detection threshold values of PD patients ($N = 38$) as a function of disease duration. From Doty et al., with permission.
gence Scale-Revised (WAIS-R).\textsuperscript{41} The WAIS-R Information, Digit Span, Vocabulary, and Similarities subtests were combined into a single verbal score (WAIS-Verbal), and the Picture Completion, Block Design, and Digit Symbol subtests were combined into a single performance score (WAIS-Performance). Similarly, the Randt General Information, Five Items, Paired Words, Short Story, and Picture Recognition modules were combined into a Randt Memory Score.

Six easily interpretable factors were extracted that accounted for 73.6\% of the total variance and are shown (along with factor names given to them) in TABLE I.

### TABLE I. Varimax-Rotated Factor Matrix for Olfactory, Neuropsychological, and Motor Measurement Variables

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Randt memory</td>
<td>.880</td>
<td>-.077</td>
<td>-.157</td>
<td>.024</td>
<td>-.086</td>
<td>.225</td>
</tr>
<tr>
<td>WAIS-performance</td>
<td>.810</td>
<td>-.204</td>
<td>-.147</td>
<td>-.088</td>
<td>.001</td>
<td>-.108</td>
</tr>
<tr>
<td>WAIS-verbal</td>
<td>.780</td>
<td>-.165</td>
<td>-.039</td>
<td>-.078</td>
<td>-.052</td>
<td>-.132</td>
</tr>
<tr>
<td>PIT</td>
<td>.763</td>
<td>-.191</td>
<td>-.158</td>
<td>-.141</td>
<td>.014</td>
<td>.161</td>
</tr>
<tr>
<td>Cancellation</td>
<td>.753</td>
<td>-.045</td>
<td>-.368</td>
<td>-.246</td>
<td>.108</td>
<td>-.027</td>
</tr>
<tr>
<td>Bradykinesia</td>
<td>-.827</td>
<td>.433</td>
<td>.355</td>
<td>.400</td>
<td>.309</td>
<td>.184</td>
</tr>
<tr>
<td>Rigidity (L)</td>
<td>.050</td>
<td>.883</td>
<td>-.062</td>
<td>.066</td>
<td>-.018</td>
<td>.097</td>
</tr>
<tr>
<td>Rigidity (R)</td>
<td>-.074</td>
<td>.858</td>
<td>.014</td>
<td>.086</td>
<td>.050</td>
<td>-.017</td>
</tr>
<tr>
<td>Altern Move (L)</td>
<td>-.392</td>
<td>.799</td>
<td>.186</td>
<td>.033</td>
<td>-.025</td>
<td>-.022</td>
</tr>
<tr>
<td>Altern Move (R)</td>
<td>-.378</td>
<td>.748</td>
<td>.222</td>
<td>-.057</td>
<td>.041</td>
<td>-.026</td>
</tr>
<tr>
<td>Masking</td>
<td>-.499</td>
<td>.564</td>
<td>.407</td>
<td>.221</td>
<td>.186</td>
<td>-.210</td>
</tr>
<tr>
<td>Reaction time (R)</td>
<td>-.298</td>
<td>.491</td>
<td>-.022</td>
<td>.437</td>
<td>.265</td>
<td>-.395</td>
</tr>
<tr>
<td>Speech</td>
<td>.064</td>
<td>-.021</td>
<td>.839</td>
<td>.059</td>
<td>.040</td>
<td>-.212</td>
</tr>
<tr>
<td>Disease duration</td>
<td>.036</td>
<td>.114</td>
<td>.789</td>
<td>.135</td>
<td>-.097</td>
<td>.140</td>
</tr>
<tr>
<td>Voice</td>
<td>-.313</td>
<td>.035</td>
<td>.786</td>
<td>-.043</td>
<td>-.053</td>
<td>-.019</td>
</tr>
<tr>
<td>Thalamic surgery</td>
<td>.022</td>
<td>.012</td>
<td>.682</td>
<td>-.092</td>
<td>.193</td>
<td>.159</td>
</tr>
<tr>
<td>Balance, gait, turning</td>
<td>-.425</td>
<td>.342</td>
<td>.639</td>
<td>.160</td>
<td>.227</td>
<td>.121</td>
</tr>
<tr>
<td>Disease stage</td>
<td>-.426</td>
<td>.458</td>
<td>.601</td>
<td>.201</td>
<td>.233</td>
<td>.201</td>
</tr>
<tr>
<td>Swallowing</td>
<td>-.010</td>
<td>.001</td>
<td>.523</td>
<td>.232</td>
<td>-.454</td>
<td>-.004</td>
</tr>
<tr>
<td>Tapping (L)</td>
<td>.041</td>
<td>-.068</td>
<td>-.075</td>
<td>-.870</td>
<td>.097</td>
<td>-.089</td>
</tr>
<tr>
<td>Tapping (R)</td>
<td>.189</td>
<td>-.101</td>
<td>-.132</td>
<td>-.818</td>
<td>.133</td>
<td>.001</td>
</tr>
<tr>
<td>Reaction time (L)</td>
<td>-.294</td>
<td>.409</td>
<td>-.109</td>
<td>.546</td>
<td>.271</td>
<td>-.314</td>
</tr>
<tr>
<td>Smell threshold</td>
<td>.142</td>
<td>.091</td>
<td>.102</td>
<td>.056</td>
<td>.888</td>
<td>-.152</td>
</tr>
<tr>
<td>UPSIT</td>
<td>.344</td>
<td>-.028</td>
<td>.024</td>
<td>.205</td>
<td>-.617</td>
<td>.202</td>
</tr>
<tr>
<td>Tremor (L)</td>
<td>.050</td>
<td>-.104</td>
<td>.167</td>
<td>.082</td>
<td>-.042</td>
<td>.828</td>
</tr>
<tr>
<td>Tremor (R)</td>
<td>-.079</td>
<td>.205</td>
<td>-.057</td>
<td>-.050</td>
<td>.219</td>
<td>.581</td>
</tr>
</tbody>
</table>

**Note:** Loadings $>$0.50 are in boldface for emphasis (R: right; L: left). See text for details.

From Doty et al.,\textsuperscript{45} with permission.

Of particular interest in the present context is that the olfactory test scores loaded strongly on a separate factor (factor 5) that received no strong loadings from any of the other measures. Interestingly, no other factors received strong loadings from the smell tests. The reader is referred to the original paper for a discussion of the details and interpretation of this analysis.\textsuperscript{45}

The findings of the aforementioned study suggest that the olfactory dysfunction of PD is relatively independent of cognitive and motor symptoms. Further exploration of our data has shown no clear-cut pattern of smell loss to the various
DOTY: INFLUENCE OF AGE AND AGE-RELATED DISEASES

items on the UPSIT for either the AD or PD patients, implying that the odor identification problem is probably a general one. Interestingly, of 25 PD patients asked to answer whether or not some type of odorant was noticed after sniffing each odor item of the UPSIT, only seven responded negatively to any odorant of the test. Of these seven, only three responded negatively to more than one odorant, and the number of odorants responded to by even these three patients was small (two, three, and six 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**

Huntington's disease (HD) serves as a classic example of gene action with autosomal-dominant transmission in middle to late life. Recently, HD patients have been shown to have a marked deficit in an odor recognition memory task. Interestingly, such dysfunction was seen in patients who had been affected early on with minimal chorea or cognitive deficits and who had apparently normal verbal and visual recognition memory scores. The early HD and late HD patients reportedly performed normally on a three-stage odor discrimination task, although data for this latter task were not presented. This pioneering study is important from a theoretical perspective, in that it indicates that a largely genetically determined dementia-related disorder is accompanied by smell dysfunction at the time of its phenotypic expression.

**SUMMARY**

It is clear from this review that olfactory function is markedly altered in old age and in a number of age-related diseases. The deficits appear to be rather general and detectable by several types of olfactory tests. Considerable interindividual variability exists, however, and the physiologic bases of these changes are not clear. In many healthy elderly persons, 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.

Several reviews have appeared suggesting that the olfactory system may be a center of primary involvement in AD. Of particular interest is the hypothesis that environmental agents (related etiologically to the disease process) pass into the central nervous system via the highly active transport mechanisms of the olfactory receptors. This latter notion, although attractive, must be viewed conservatively, as it is possible that the olfactory pathways are simply selectively vulnerable to destruction by various disease processes. This may explain why Huntington's chorea and multiinfarct dementia, in addition to AD and PD, are associated with alterations in smell function.

Although it is tempting to assume, as have authors such as Koss et al., 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 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 utility 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 may occur in some central brain disorders.11-13

It is apparent from the studies reviewed in this chapter that considerable progress has been made during the last decade in elucidating the nature and prevalence of olfactory disturbances in elderly patients, as well as in patients with dementia-related diseases. Progress in the future will be facilitated by the development and administration of a broad range of standardized olfactory tests, along with concurrent and detailed neuropsychological testing and postmortem neurochemical and structural studies of the olfactory pathways. It is important that the olfactory system of patients with other dementia-related diseases (for example, Down’s syndrome and Pick’s disease) be studied to allow for comparisons across a broad range of brain disorders. A major challenge for the next decade will be to determine the pathophysiological bases of these sensory alterations and whether they can be reversed, halted, or altered by therapeutic intervention.14

ACKNOWLEDGMENTS

I am grateful to Ms. Carrie Krasnow for her comments on a previous version of the manuscript.

REFERENCES

DOTY: INFLUENCE OF AGE AND AGE-RELATED DISEASES

... taste disorders: A study of 750 patients from the University of Pennsylvania Smell and Taste Research Center. Submitted for publication.


