Studies of Olfactory Dysfunction in Major Neurological Disorders

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ABSTRACT

Decreased ability to smell results from a number of medical conditions, ranging from simple congestion of the nose to serious neurological disturbances. In this chapter I provide an overview of the olfactory dysfunctions present in several major neurological disorders and discuss current theories as to their cause. In some disorders, such as Alzheimer's disease and idiopathic Parkinson's disease, hyposmia or anosmia is widespread and present early in the disease process. In others, such as amyotrophic lateral sclerosis, essential tremor, multiple sclerosis, multiple system atrophy, progressive supranuclear palsy, and schizophrenia, such dysfunction, when present at all, is much more sporadic. Given the differences in olfactory test scores among some closely related neurological disorders, standardized olfactory testing may be of considerable value in their early differential diagnosis, as well as in better understanding etiologic factors.

KEYWORDS
Alzheimer's disease; aging; amyotrophic lateral sclerosis; anosmia; differential diagnosis; dysosmia; epilepsy; essential tremor; head trauma; multiple sclerosis; multiple system atrophy; olfaction; Parkinson's Disease; Parkinsonism; progressive supranuclear palsy; pseudohypoparathyroidism; Schizophrenia.

INTRODUCTION

Wide-spread application of standardized olfactory tests, such as the University of Pennsylvania Smell Identification Test (UPSIT), has now made it possible to accurately evaluate and compare the relative degree of olfactory dysfunction in a wide range of diseases. As a result of the use of such tests, we now know that the olfactory dysfunction of patients with early-stage Alzheimer's disease (AD), idiopathic Parkinson's disease (PD), and the parkinsonism-dementia complex of Guam (PDCG) is marked and, for all practical purposes, equivalent in magnitude. We also know that the olfactory dysfunction of patients with amyotrophic lateral sclerosis

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(ALS), essential tremor (ET), multiple sclerosis (MS), progressive supranuclear palsy (PSP), and schizophrenia (SZ) is either non-existent, comparatively sporadic, or of lesser average magnitude than that seen in AD, PD, or PDCG.

In this chapter I discuss the olfactory dysfunction found in a number of neurological diseases and discuss current theories of such loss. In some instances, neuroimaging or neuropathological studies are reviewed which shed light on the underlying physiological processes involved in the dysfunction.

OLFACTORY DYSFUNCTION IN SPECIFIC NEUROLOGICAL DISORDERS

Because most of the available research on olfaction in neurological disorders comes from studies of Alzheimer's disease and idiopathic Parkinson's disease, these two disorders are discussed first, followed alphabetically by other neurological disorders for which olfactory testing has been performed.

Alzheimer's Disease

Olfactory dysfunction is present in nearly all patients with AD and is observed using tests of odor identification, detection, discrimination, and memory (see Doty, 1991, for review). Although aspects of the AD-related olfactory alterations may be related to age, early stage AD patients with mild dementia consistently score much more poorly on olfactory tests than do age-matched controls (e.g., Doty et al., 1987). Despite the fact that the magnitude of the olfactory dysfunction is weakly related (rs typically < 0.40) to the severity of the dementia (Knupfer and Spiegel, 1986; Moberg et al., 1987; Murphy et al., 1990; Serby et al., 1991a; Waldton, 1974), difficulties in interpreting test results from other than the most mild AD patients make such observations enigmatic.

Even though the basis for the olfactory loss of AD is unknown, several non-mutually exclusive hypotheses have been proposed to explain such loss, each with numerous variants and applications to both inherited and non-inherited forms of the disease. The first, termed the "olfactory vector hypothesis," proposes, in its most general form, that the loss in smell ability reflects damage to the olfactory system caused by movement of environmental viruses or toxins from the nasal cavity into the brain via the olfactory fila (e.g., Doty, 1991; Ferreyra-Moyano and Barragan, 1989; Roberts, 1986). Potential support for this hypothesis includes (i) a large animal literature demonstrating that intranasally-instilled viruses and toxins can enter the brain via active transport mechanisms of the olfactory nerves and can induce damage in olfactory-related structures (see Stroop, 1995, for review), (ii) studies which suggest that histopathological changes occur within the olfactory epithelium of patients with Alzheimer's disease (e.g., Jafek et al., 1992), and (iii) observations that the neuritic plaques and neurofibrillary tangles of AD are found preferentially in limbic brain regions which receive fibers directly from the olfactory bulb, including the anterior olfactory nucleus, the uncus, and the medial amygdaloid nuclei (Pearson et al., 1985). The second, somewhat more orthodox, hypothesis, termed the "secondary degeneration hypothesis," postulates that the olfactory loss is due to retrograde degeneration within the olfactory system proper (including the formation of plaques and tangles). One variant of this hypothesis postulates that limbic structures are
particularly prone to damage from the AD process. Potential support for the secondary degeneration hypothesis includes (i) the finding, in AD patients, of an inverse correlation between UPSIT scores and metabolic activity in the anterior portion of the medial temporal cortex (as measured by positron emission tomography) (Buchsbaum et al., 1989), (ii) an association between decreased UPSIT scores and the number of hippocampal lesions in AD patients (Serby et al., 1992b), and (iii) the discovery that rats recently made experimentally anosmic do not evidence learning deficits, unlike rats whose experimental anosmia was induced at an earlier time (Kurtz et al., 1989).

Parkinson's Disease

Traditionally, idiopathic Parkinson's disease (PD) has been considered a motor system disease, with a diagnosis based upon the presence of a set or subset of cardinal motoric signs (e.g., rigidity, bradykinesia, tremor and postural reflex disturbance). James Parkinson (1817), in his classic monograph on shaking palsy, defined this disorder as "Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the senses and intellects being uninjured".

We now know that sensory deficits are observed in PD, with olfactory deficits occurring early in the disease process. Indeed, the proportion of early-stage PD patients with olfactory dysfunction appears to rival the proportion of early-stage PD patients exhibiting any one of the cardinal signs of PD (i.e., tremor, rigidity, bradykinesia, or gait disturbance). For example, Doty, Deems and Stellar (1988) found that 73 of 81 patients studied (90%) had odor identification test scores lower than their matched normal controls; 29 of 38 patients studied (76%) had higher olfactory thresholds than matched controls. The PD-related loss is bilateral (Doty et al., 1992b), present in early hemiparkinsonism (Doty et al., 1988; Doty et al., 1992b), stable over time (Doty et al., 1988) and unrelated to disease stage (Doty et al., 1988; Quinn et al., 1987; Ward et al., 1983), degree of motoric dysfunction (Doty et al., 1989; Ward et al., 1983), or the use of antiparkinson medications (Doty et al., 1988; Quinn et al., 1987; Ward et al., 1983). Recently, Hawkes and Shephard (1992) have demonstrated that PD patients evidence altered olfactory evoked potentials relative to normal subjects, in addition to decreased scores on the UPSIT.

It has been suggested that subtle variations may exist among some subtypes of PD when large numbers of PD subjects are evaluated (Stern et al., 1994). For example, 80 patients with "benign PD" [where the disease has been confined to Hoehn and Yahr (1967) Stages I or II for at least 4 years] were found to evidence a lower average UPSIT score (mean = 22.51) than 29 patients with "malignant PD" (Hoehn and Yahr Stage III) (mean = 17.38). Twenty-two patients with chronic hemiparkinsonism (unilateral signs for 4 or more years) evidenced, on average, a lower UPSIT score than 96 patients with bilateral parkinsonism [respective means: 24.36 and 20.42]. In general, the more malignant subtype of PD, the greater the olfactory dysfunction.

The basis for the olfactory deficit of PD is unknown. Interestingly, this deficit appears to be indistinguishable from that of AD (Doty et al., 1991), suggesting the possibility that these two disorders may share a common neuropathologic substrate. As with AD, both olfactory vector and degenerative hypotheses could explain the dysfunction. Tangential support for the olfactory vector hypothesis comes from evidence that (i) certain viruses (e.g., encephalitis
lethargica; see Eadie et al., 1965; von Economo, 1931) have been epidemiologically associated
with PD, (ii) a number of viruses, including ones associated with encephalitis, enter the central
nervous system via the primary olfactory neurons (for review, see Stroop, 1995), and (iii)
patients whose parkinsonism is due to intravenous injection of the proneurotoxin 1-methyl-4-
phenyl-1,2,3,6-tetrahydropyridine (MPTP) have relatively normal smell ability (Doty et al.,
1992a).

Amyotrophic Lateral Sclerosis

Unlike AD, amyotrophic lateral sclerosis reflects widespread denervation of upper and lower
motor neurons (Kuncl et al., 1992). Operationally, "widespread denervation" is considered
denervation in two or more muscles innervated by two or more roots in at least three anatomic
regions (Lambert, 1969). As is the case with AD, clinical diagnosis of ALS is one of exclusion
and little racial or geographic variation has been found in the incidence of ALS within or
among countries (Kurtzke, 1982). Unlike AD, no meaningful changes in primary sensory
systems, aside from those mediated via the afflicted peripheral nerves, have been reported for
this disorder.

Recently, Sajjadian et al. (1993) administered the UPSIT bilaterally to 17 female and 20 male,
and unilaterally to 7 male and 7 female, ALS patients. Age-, gender-, smoking-habit-, and race-
matched controls were also tested. Significantly lower average UPSIT scores were found for
the ALS patients than for the controls. Of the 37 ALS patients, 28 (i.e., 75.7%) had
UPSIT scores below those of matched controls, although, on average, the degree of dysfunc-
tion was not as great as that seen earlier in patients with Alzheimer's disease, idiopathic
Parkinson's disease, and the PD-dementia complex of Guam. Only 4 (11%) of the ALS patients
had UPSIT scores indicative of total or near total anosmia (i.e., < 17). The UPSIT scores of
the ALS and control subjects decreased as a function of age. No sex differences or laterality in
the ALS-related test scores were observed, although several statistically-significant
correlations between UPSIT scores and neurophysiological measures of peripheral nerve con-
ductance were present. Taken together, these data indicate that ALS, which has been
traditionally considered a motor neuron disease, is associated with discernible deficits in
chemosensory function which appear to be correlated, in some instances, with electrophysio-
logical indices of peripheral nerve function.

Essential Tremor

Essential tremor (ET) is a tremor of unknown origin which is frequently progressive and
exaggerated by action and emotional tension. Some, but not all, studies have suggested that
ET is associated with PD (see Cleeves et al., 1988; Geraghty et al., 1985). Recently,
Busenbark et al. (1992) administered the UPSIT to 16 patients with ET, 16 patients with PD,
and 16 normal controls. The test scores of the ET patients did not differ significantly from
those of the controls, unlike the test scores of the PD patients, which were significantly lower
(respective UPSIT means: 37.2, 36.3 and 27.4). These findings suggest that ET and PD differ
in regards to olfactory function and that olfactory testing maybe of value in the differential
diagnosis of these two conditions.
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Multiple Sclerosis

Estimates of the prevalence of olfactory dysfunction in patients with multiple sclerosis (MS) vary widely. Several studies report no olfactory deficits in MS patients, including the study by Anasari (1976), which evaluated odor detection thresholds for amyl acetate and nitrobenzene in 40 patients, and the study by Kesslack et al. (1988), which examined odor identification ability in 14 MS patients using the UPSIT and a match-to-sample test. In contrast are studies which have noted olfactory dysfunction in some proportion of MS patients. Doty et al. (1984), for example, found 23% of 31 MS patients evidenced olfactory dysfunction using the UPSIT. Hawkes et al. (1995) found 15% of 72 MS patients scored, on the UPSIT, outside the 95% confidence limits of 96 control subjects. The latter authors also demonstrated that, in comparison to controls, 47 MS patients evidenced increased evoked potential latencies to the odorant H2S.

Since the primary olfactory neurons are unmyelinated and little myelin is found in the olfactory bulbs and tracts, it has been generally assumed that the olfactory system is spared from damage in MS (see, for example, Lumsden, 1970). However, the more recent studies noted above suggest this is not the case, and we have recently found an association between neuropathological markers and the degree of olfactory dysfunction. Thus, using magnetic resonance imaging (MRI), we found, in five patients that we examined, an inverse correlation between UPSIT scores obtained for the left nasal chamber and the number of plaques within the basal left frontal and left temporal lobe regions of the brain (r = -0.98, p < 0.01) (Doty et al., unpublished data). A similar correlation was not found for UPSIT scores obtained for the right nasal chamber and analogous plaque counts for the right side of the brain (r = -0.35, ns). A larger study is currently being planned to establish whether this left/right difference is reliably present and, if so, if it occurs for tests other than those of odor identification.

Multiple System Atrophy

Multiple system atrophy (MSA) describes a tetrad of four entities previously considered as distinct and separate: striatonigral degeneration, Shy-Drager syndrome, olivopontocerebellar atrophy (PCA), and parkinsonism-amyotrophy syndrome (Fahn, 1992). Common to these disorders is lack of response to levodopa, vocal cord paralysis, rapid progression, dysautonomia, ataxia, pyramidal signs, and amyotrophy.

Wenning et al. (1993) administered the UPSIT to 23 patients with clinically probable MSA, 23 patients with PD, and 23 normal control subjects. The patients with MSA evidenced UPSIT scores which, on average, were higher than those of the PD patients and lower than those of the normal subjects (respective median UPSIT values: 27, 19 and 32). Interestingly, within the MSA group, significant negative correlations were observed between UPSIT scores and various measures of disability, including the Hoehn and Yahr scale (r = -0.64, p = 0.001), the Modified Schwab and England Activities of Daily Living Scale (MSEADL; r = -0.72, p = 0.001), and the motor examination and activities of daily living sections of the United Parkinson's Disease Rating Scale (UPDRS; respective r's = -0.74 and -0.60; p's = 0.001 and 0.01).

Since the pathological changes of MSA are more widespread than those of PD, it is of considerable interest that the olfactory dysfunction associated with MSA is of smaller average magnitude than that seen in PD. The reason for this phenomenon is not clear.
Parkinsonism-Dementia of Guam

Amyotrophic lateral sclerosis, parkinsonism, and dementia accounted for at least 15% of adult deaths among the Chamorro populations of Guam and Rota between 1957 and 1965 (Reed et al., 1966, 1975). An environmental etiology has been considered for this disorder, since genetic or infectious causes have not been established from epidemiologic studies, including case control comparisons and extensive pedigree analyses.

Guamanian Chamorros with signs of parkinsonism have deficits on the UPSIT analogous to those observed among patients with AD and PD (Doty et al., 1991). Thus, we administered the UPSIT to 24 patients with early signs of the PDC of Guam and statistically compared their test scores to those of 24 early-stage AD and 24 early-stage PD patients of similar age and gender from the United States mainland. The UPSIT scores of the three groups did not differ significantly (respective means: 20.54, 18.38, and 20.21).

As in the case of idiopathic PD, the olfactory loss of this disorder is unknown, although there is some evidence that these patients have marked deterioration of cells within the anterior olfactory nucleus (Perl and Doty, unpublished). Since the olfactory deficit of these patients does not differ from those with AD and PD, these disorders may share a common neuropathologic substrate. As with AD and PD, both olfactory vector and degenerative hypotheses could explain the dysfunction.

Progressive Supranuclear Palsy

Progressive supranuclear palsy (PSP), also termed the Steele, Richardson, and Olszewski syndrome, accounts for nearly 5% of patients with parkinsonian signs (Jankovic, 1984). Although PSP is commonly characterized, in its initial presentation, by bradykinesia and rigidity, tremor is rarely present. The most distinguishing features of this disorder are vertical-gaze paresis (Steele et al., 1964) and the slowing of thought processes (Albert et al., 1974). Because PSP shares a number of motor symptoms with PD, it is often misdiagnosed as PD. However, its parkinsonian features are less responsive to anti-PD medications (Jackson, Jankovic and Ford, 1983), and, relative to PD, it is associated with more severe frontal lobe dysfunction (Cambier et al., 1985), more neuronal loss within the basal ganglia and the upper brain stem (Steele et al., 1964), and less damage to the mesolimbic and mesocortical dopamine systems (Ruberg et al., 1985).

Unlike the case of PD, patients with PSP have a relatively normal ability to smell. For example, we recently administered the 40-item University of Pennsylvania Smell Identification Test (UPSIT; Doty et al., 1984) to 21 PSP patients and matched normal controls (Doty et al., 1993); 17 patients were also administered the phenyl ethyl alcohol single staircase forced-choice odor detection threshold test (Doty et al., 1984). Unlike the olfactory test scores of the PD patients, the PSP test scores did not differ significantly from those of the controls, suggesting that olfactory testing may be useful in differential diagnosis. Given the similarly in motor symptoms between PD and PSP, it was surprising to us that PSP is not associated with meaningful olfactory loss. This could reflect several factors. First, from the perspective of the olfactory vector hypothesis, it is possible that PSP differs from PD in not being caused or catalyzed by environmental agents which enter the central nervous system via the olfactory fila. Second, the lack of association between PSP and olfactory dysfunction could reflect relatively intact mesolimbic dopaminergic systems, in contrast to PD. Finally, in relation to the dege-
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neration hypothesis, it is possible that degeneration of limbic regions associated with olfactory processing does not occur to a meaningful degree in this disorder.

Schizophrenia

A number of studies have reported that persons with schizophrenia evidence olfactory dysfunction, although, on average, the degree of dysfunction is comparatively minor compared to what is observed in such disorders as AD and PD. Deficits in odor identification (Houlihan et al., 1994; Hurwitz et al., 1988; Serby et al., 1990), odor detection threshold sensitivity (Geddes et al., 1991), and odor memory (Moberg et al., 1985; Wu et al., 1993) have all been reported. In the case of odor identification, one laboratory has reported that men with schizophrenia evidence greater olfactory impairment than women with schizophrenia (Kopala et al., 1989, 1991, 1995; Kopala and Clark, 1990). Although this suggests the possibility of an X-linked inheritance, other workers have not observed this phenomenon. For example, we recently administered the UPSIT to 13 men and 8 women who met DSM-III-R criteria for schizophrenia (APA, 1987) (Moberg et al., 1995). Although analysis of variance revealed a deficit in the performance of the schizophrenics relative to the controls, the main effects of sex and the interaction of sex by diagnosis were not significant. Nevertheless, there was a trend toward poorer performance in males and, importantly, duration of illness was correlated ($r = 0.60, p < 0.005$) with UPSIT performance.

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