Olfactory Identification in Elderly Schizophrenia and Alzheimer’s Disease

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MOBERG, P. J., R. L. DOTY, R. N. MAHR, R. I. MESHOLAM, S. E. ARNOLD, B. I. TURETSKY AND R. E. GUR. Olfactory identification in elderly schizophrenia and Alzheimer’s disease. NEUROBIOI AGING 18(2) 163-167, 1997.—In the present study we assessed olfactory identification ability using the University of Pennsylvania Smell Identification Test (UPSIT) in 16 elderly patients with schizophrenia (ES), 20 patients with a diagnosis of probable Alzheimer’s disease (AD), and 20 healthy elderly controls (EC). Both patient groups exhibited marked deficits in UPSIT performance relative to controls. ES and AD patients with similar levels of general cognitive impairment did not differ on the UPSIT, suggesting that the two disorders may share a common dysfunction in olfactory brain regions. While there have been recent reports of greater olfactory impairment in males, neither patient group exhibited significant gender differences on the UPSIT. © 1997 Elsevier Science Inc.

Olfaction Smell Identification Elderly Schizophrenia Alzheimer’s

SINCE the earliest reports of Ansari and Johnson (2) and Waldton (50), it has become apparent that olfactory dysfunction is present in a number of neurodegenerative disorders including Alzheimer’s disease (AD) (17,44), idiopathic Parkinson’s disease (19,51), Huntington’s chorea (35,37), alcoholic Korsakoff’s syndrome (25,32), Pick’s Disease (39), the Parkinsonian-dementia complex of Guam (15), and amyotrophic lateral sclerosis (42). During the last decade, a number of studies have also documented olfactory dysfunction in young patients with schizophrenia, including deficits in odor identification (22,23,43,45), odor detection threshold sensitivity (21,23,24), and odor memory (10,52). This deficit does not appear to be due to current or prior neuroleptic use, cognitive deficits, smoking history, or severity of clinical symptoms (29,52). Notably, in the case of odor identification, Kopala and colleagues (27,28) have reported that men with schizophrenia evidence greater olfactory impairment than women with schizophrenia. Recently, however, these investigators have noted olfactory loss in male patients, which may be accentuated by menopause (30).

To our knowledge, no evaluation has been made of the specificity of the olfactory deficits seen in schizophrenia patients. Given that recent studies have suggested that AD and elderly schizophrenia (ES) patients exhibit some similarities in pathologic involvement of cortical brain regions associated with olfactory processing (5,6,12), the present study sought to determine whether the olfactory dysfunction of ES is equivalent to, or differs from, that observed in AD. Given these similarities, we hypothesized that ES patients would exhibit a pattern of olfactory dysfunction similar to that seen in AD. In addition, based on prior reports of gender differences in olfactory identification in patients with schizophrenia, we hypothesized that male ES patients would evidence greater olfactory deficits relative to females.

METHOD

Subjects

Sixteen elderly patients who met DSM-III-R (1) criteria for schizophrenia (ES), 20 patients with a NINCDS-ADRDA (34) diagnosis of probable Alzheimer’s disease (AD), and 20 healthy elderly controls (EC) were recruited from the Mental Health Clinical Research Center (MHCRC) on Schizophrenia at the University of Pennsylvania, and the Alzheimer Disease Center (ADCC) at the University of Pennsylvania. Elderly controls were recruited from local senior centers, places of worship, and newspaper advertisements. All subjects were examined for medical and neurological status. For all groups, exclusion criteria included: 1) history of psychiatric disorder (other than schizophrenia for ES patients); 2) history of neurologic disorder (including tardive dyskinesia); 3) history of head trauma with loss of consciousness; 4) substance abuse (according to DSM-III-R criteria, assessed by history from patient and family and review of records); 5) medical conditions that may alter cerebral functioning (assessed by examination and routine laboratory tests), including

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Assessment of Olfactory Identification

Olfactory identification performance was assessed using the University of Pennsylvania Smell Identification Test (UPSIT) (16,18). The UPSIT is a standardized, four-alternative, forced-choice test of olfactory identification comprised of four booklets containing 10 odorants apiece, 1 odorant per page. The stimuli are embedded in "scratch and sniff" microcapsules fixed and positioned on strips at the bottom of each page. A multiple-choice question with four response alternatives for each item is located above each odorant strip. The specific stimuli, basis for their selection, as well as the reliability and sensitivity of this test have been described in detail elsewhere (16,18).

The UPSIT was administered individually by experienced clinical neuropsychologists, who released the microencapsulated stimuli, placed them under each patient's nares, and recorded the answer following the patient's response. All analyses were performed on log-transformed data to correct for skewness \([\log_{10}(41-\text{UPSIT})]\). This transformation reverses the UPSIT score polarity in that higher scores represent greater impairment.

After the UPSIT was administered, all controls, AD patients, and 10 of the ES patients were given the Picture Identification Test (PIT), a test analogous to the UPSIT except that line drawings related to the quality of the odorant are presented instead of odorant labels (49). This test was designed to screen for individuals with cognitive deficits that may confound UPSIT score. Most subjects scored 40/40 on this test and none scored below 37/40.

RESULTS

Analysis of variance (ANOVA) with diagnosis and gender as grouping factors was used to examine differences in UPSIT scores. Overall, both patient groups demonstrated a marked deficit in olfactory identification performance relative to controls, \(F(2, 53) = 70.8, p \leq 0.001\). No interaction between diagnosis and gender was observed, \(F(2, 53) = 0.53, p = \text{NS}\), nor was a main effect seen for gender, \(F(2, 53) = 1.72, p = \text{NS}\). As can be seen in Fig. 1, ES patients did not differ significantly from AD patients with regard to UPSIT performance, \(t(34) = -0.37, p = \text{NS}\).

To further evaluate any potential gender differences in olfactory identification in both patient groups, subjects were classified as either microsmic (reduced olfactory ability) or anosmic (loss of olfactory ability) based on raw UPSIT score using age and gender cutoffs from the UPSIT normative tables (14). As can be

![FIG. 1. Comparison of raw UPSIT scores for elderly controls (EC), elderly schizophrenia (ES), and Alzheimer's disease (AD) groups (mean ± SEM).](image)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>EC</th>
<th>ES</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raw UPSIT Score</td>
<td>35</td>
<td>30</td>
<td>25</td>
</tr>
</tbody>
</table>

Table 1 presents demographic information of ES, AD and EC groups. The three groups did not differ with regard to age, \(F(2, 53) = 2.28, p = \text{NS}\), education, \(F(2, 53) = 0.53, p = \text{NS}\), gender, \(\chi^2(2) = 0.76, p = \text{NS}\), ethnic background, \(\chi^2(2) = 0.15, p = \text{NS}\), or smoking history, \(\chi^2(4) = 8.8, p = \text{NS}\). As expected, Mini-Mental State Examination (MMSE) scores for both ES and AD groups were significantly poorer relative to controls, \(F(2, 53) = 30.08, p \leq 0.001\). However, ES and AD patients did not differ from each other on the MMSE, \(t(34) = -0.21, p = \text{NS}\), falling in the mildly–moderately demented range of cognitive functioning.

A recent study by de Leon and colleagues (13) has indicated that the MMSE may be less reliable in patients with schizophrenia. To assure comparability of general cognitive impairment, clinical dementia ratings (CDR) (8) were also obtained in both groups. These ratings indicated similar levels of dementia, \(\chi^2(2) = 0.23, p = \text{NS}\), with patients in both groups generally falling within the mild to moderate dementia classification (CDR-1 or CDR-2).

Performance on the MMSE was not significantly correlated with UPSIT scores in either ES or AD groups (\(r = -0.17, p = \text{NS}\), and \(r = -0.29, p = \text{NS}\), respectively).

Assessment of Olfactory Identification

TABLE 1

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>EC</th>
<th>ES</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>77.9 (6.5)</td>
<td>73.9 (9.4)</td>
<td>72.5 (6.4)</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>4/12</td>
<td>4/16</td>
<td>6/14</td>
</tr>
<tr>
<td>Ethnic background</td>
<td>16 Caucasian</td>
<td>18 Caucasian</td>
<td>20 Caucasian</td>
</tr>
<tr>
<td>Education (years)</td>
<td>10.6 (1.8)</td>
<td>10.5 (1.3)</td>
<td>10.1 (1.5)</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>2</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Previously smoked</td>
<td>11</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Current smoker</td>
<td>3</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>MMSE (raw score)</td>
<td>19.1 (6.6)</td>
<td>19.5 (5.5)</td>
<td>29.8 (0.5)*</td>
</tr>
<tr>
<td>UPSIT (raw score)</td>
<td>18.6 (7.8)</td>
<td>18.4 (5.6)</td>
<td>36.5 (2.5)*</td>
</tr>
<tr>
<td>PIT (raw score)</td>
<td>38.3 (0.9)</td>
<td>38.7 (0.8)</td>
<td>39.5 (0.6)*</td>
</tr>
</tbody>
</table>

Mean ± SD.

* \(p \leq 0.001\).

cardiac, endocrine, renal, and pulmonary disease; 6) age less than 65 years; 7) upper respiratory infection; or 8) other conditions known to affect olfactory functioning (e.g., common cold, blocked nasal passages, etc.). Controls were also screened for neuropsychiatric history in first degree relatives. Written informed consent was obtained for all subjects prior to participation.

Clinical characteristics of the ES group included age at onset (mean ± SD: 72.7 ± 6.0) and duration of illness (50.3 ± 10.0 years). All ES patients were on neuroleptics at the time of testing. None of the AD patients were taking any psychoactive medications at the time of assessment nor did they show any symptoms of psychiatric disturbance (e.g., depression, psychosis).

Table 1 presents demographic information of ES, AD and EC groups. The three groups did not differ with regard to age, \(F(2, 53) = 2.28, p = \text{NS}\), education, \(F(2, 53) = 0.53, p = \text{NS}\), gender, \(\chi^2(2) = 0.76, p = \text{NS}\), ethnic background, \(\chi^2(2) = 0.15, p = \text{NS}\), or smoking history, \(\chi^2(4) = 8.8, p = \text{NS}\). As expected, Mini-Mental State Examination (MMSE) scores for both ES and AD groups were significantly poorer relative to controls, \(F(2, 53) = 30.08, p \leq 0.001\). However, ES and AD patients did not differ from each other on the MMSE, \(t(34) = -0.21, p = \text{NS}\), falling in the mildly–moderately demented range of cognitive functioning. A recent study by de Leon and colleagues (13) has indicated that the MMSE may be less reliable in patients with schizophrenia. To assure comparability of general cognitive impairment, clinical dementia ratings (CDR) (8) were also obtained in both groups. These ratings indicated similar levels of dementia, \(\chi^2(2) = 0.23, p = \text{NS}\), with patients in both groups generally falling within the mild to moderate dementia classification (CDR-1 or CDR-2).

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TABLE 2
NUMBER OF ELDERLY SCHIZOPHRENIA (ES) AND ALZHEIMER'S DISEASE (AD) PATIENTS FALLING IN UPSIT IMPAIRMENT CATEGORIES* BY GENDER

<table>
<thead>
<tr>
<th>Group</th>
<th>Normosmic</th>
<th>Microsmic</th>
<th>Anosmic</th>
</tr>
</thead>
<tbody>
<tr>
<td>ES</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>0</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>AD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Females</td>
<td>0</td>
<td>8</td>
<td>8</td>
</tr>
</tbody>
</table>

* Based on raw UPSIT score.

seen in Table 2, no ES or AD patient fell in the normosmic (normal olfactory ability) range with regard to UPSIT scores. While there does appear to be a trend toward poorer UPSIT performance by males in both patient groups, ES and AD males and females did not differ significantly, $X^2(1) = 0.76, p = NS$, and $X^2(1) = 3.33, p = NS$, respectively.

DISCUSSION

The results of this study indicate that ES patients exhibit significant impairment in olfactory identification, and that this deficit is of a similar magnitude to that seen in AD. This similarity in degree of dysfunction is noteworthy. Clearly, the pathophysiological processes that give rise to AD and schizophrenia are distinct. It is possible that some of the psychophysical similarities between schizophrenia and AD that we observed may be due to common neuroanatomical substrates being affected in each of the diseases. Indeed, recent neuropathological investigations of schizophrenia have noted similarities in the topographical distribution of aberrant cytoarchitecture, neuronal morphology, and modest astrocytosis observed in schizophrenia with the topographical distribution of neurofibrillary tangles in AD (3-6). For example, the entorhinal cortex has been highlighted as a particular focus of abnormality in both diseases. In AD, it is the first and most heavily involved with neurofibrillary tangles anywhere in the brain (9,38). In schizophrenia, the entorhinal cortex exhibits cytoarchitectural disarray, smaller neurons, and abnormal expression of microtubule associated proteins (7). While the entorhinal cortex is not exclusively an olfactory region, it does receive a large direct olfactory input from the olfactory bulb via the lateral olfactory tract (46,48), and abnormalities in this region are likely to disrupt olfactory functioning (40,47). This notion is consistent with recent MRI volumetric studies, which find a significant correlation between entorhinal-hippocampal volume and deficits on the UPSIT (26). Beyond the entorhinal cortex, there are other brain regions that have been invoked as abnormal in schizophrenia and are vulnerable to accumulation of neurofibrillary tangles in AD, and which play a role in olfactory functioning (20). In particular, these include orbitofrontal cortex, basal forebrain, and the amygdaloid complex.

Several caveats must be noted with respect to our findings. First, our population of ES patients were chronically hospitalized, and thus reflect the most severe form of the disorder. We are currently recruiting an outpatient schizophrenia cohort for further studies in this area. Second, the current sample of ES patients had been on neuroleptic medication over the course of many years. While the effects of long-term neuroleptics on olfaction are unknown, published empirical data concerning medication effects in several major neurological disorders on the UPSIT has been uniformly negative. Specifically, in the literature on olfactory function in schizophrenia, no study has noted differences between neuroleptic-naive, neuroleptic withdrawn, and currently medicated patients on a variety of olfactory tests (29,52). Similarly, medication effects on UPSIT performance in AD have not been observed (26), suggesting that the olfactory deficit seen in AD and ES is independent of neuroleptic or anticholinergic medications. Third, the majority of patients in this study were Caucasian, and the results may not be generalizable to other ethnic groups. Last, few male subjects were available for study, perhaps militating against the elucidation of sex differences in UPSIT performance.

The pattern of deficits among AD and ES may also implicate dysfunction in the mesolimbic dopamine system, which is closely related to olfactory processing in both humans and animals. In future studies, examination of mesocorticolimbic pathways may prove fruitful in further explicating the nature of the olfactory dysfunction in both disorders. For example, it is significant that in contrast to AD and schizophrenia, MPTP-induced Parkinsonism and progressive supranuclear palsy are associated with relatively normal olfactory identification, but also with a relative sparing of the mesocorticolimbic dopamine pathways (11,41).

Postmortem studies in AD have shown pathologic changes in the olfactory neuroepithelium, and disproportionate numbers of neuritic plaques and neurofibrillary tangles in olfactory bulbs and tract, the olfactory cortex, the periamygdaloid nuclei, the hippocampus, the ventral striatum, and regions of ventral cortex receiving projections from olfactory-related structures (15,33). To our knowledge, no specific neuropathological investigation of olfactory structures in ES has been published as of this date. Based upon the presence of significant olfactory deficits in both young and elderly schizophrenia patients, such neuropathological investigations are clearly warranted.

While the current data indicate that these two disorders do not differ with regard to UPSIT performance, the relationship of duration of illness to olfactory function in both ES and AD patients merits consideration. In a recent study by our group (36), we observed that young and elderly schizophrenia patients show a strong inverse relationship between UPSIT performance and duration of illness (independent of normal aging and gender effects). These findings are suggestive of duration-linked changes in olfactory identification over the course of illness in schizophrenia. Similar relationships between stage of dementia and olfactory function have been reported in AD (31,50), suggesting that both disorders may exhibit progressive deterioration of olfactory abilities over the course of illness. In light of differences in age of onset between schizophrenia and AD, examination of the rate of decline in olfactory performance may yield important information about the onset and progression of olfactory dysfunction in these two disease states. Future studies examining olfactory identification in nonneurodegenerative disorders such as multifarct dementia will be important to document the specificity of olfactory deficits as well to as probe their relationship to generalized cognitive impairment.

ACKNOWLEDGEMENTS

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