Objective: The authors examined the relationship between deficits in olfactory identification and duration of illness in young and elderly patients with schizophrenia.

Method: Olfactory identification performance of 38 patients with schizophrenia and 40 normal subjects was compared by using the University of Pennsylvania Smell Identification Test.

Results: The schizophrenic patients demonstrated olfactory deficits relative to the comparison group, and the elderly schizophrenic patients displayed a greater magnitude of olfactory deficit than the younger patients. Independent of normal aging effects and cognitive deficit, patients with schizophrenia showed a strong relationship between olfactory identification scores and duration of illness, which suggests that olfactory abilities decline progressively over the course of the disorder.

Conclusions: In contrast to other neuropsychological measures that have been reported to be stable over the course of illness, olfactory identification abilities deteriorate steadily in patients with schizophrenia, even for those with relatively recent onset.

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Cross-sectional and longitudinal studies that have investigated age-related differences in cognitive performance in patients with schizophrenia have noted either no differences or a very slow and gradual progression (1, 2). Deficits in neuropsychological functioning have been interpreted as being consistent with a neurodevelopmental process rather than a neurodegenerative model of illness. Deficits in odor identification, odor detection threshold sensitivity, and odor memory have been described in young patients with schizophrenia (3, 4). Neuroleptic use, smoking, cognitive deficits, and illness severity all appear unrelated to this abnormality (5). Olfactory processing is mediated by limbic neuroanatomical structures that have been implicated in the pathophysiology of schizophrenia, particularly the prefrontal cortex, ventromedial temporal lobe, basal forebrain, and diencephalon (6). Olfactory deficits in patients with schizophrenia may reflect disturbances of cortical or subcortical brain regions untapped by traditional neuropsychological measures. No study has yet examined the effect of aging or duration of illness on olfactory function in patients with schizophrenia.

METHOD

Thirty-eight patients who met DSM-III-R criteria for schizophrenia and 40 healthy volunteers were recruited by the Mental Health Clinical Research Center on Schizophrenia at the University of Pennsylvania. All subjects underwent a medical and psychiatric evaluation that included a physical examination and the administration of standardized clinical scales. Exclusion criteria included history of psychiatric disorder (other than schizophrenia), neurologic disorder, head trauma, loss of consciousness, substance abuse, or the presence of one of the following: a medical condition that could alter cerebral functioning, an upper respiratory infection, or a condition that could affect olfactory functioning (e.g., common cold). Normal subjects were screened for psychiatric history in first-degree relatives. Written informed consent was obtained from all subjects.

Of the younger patients with schizophrenia (age range=18-50 years, N=20), 10 were neuroleptic-naive, and 10 were taking neuroleptics. All elderly patients (age range=66-88, N=18) were taking neuroleptic medication. The schizophrenic patients did not differ from the comparison subjects in age (schizophrenic group: mean=50.6 years, SD=25.5; comparison group: mean=49.6 years, SD=24.6), gender composition (schizophrenic group: 18 men and 20 women; comparison group: 18 men and 22 women), race (84% [N=32] of the schizophrenic patients and 73% [N=29] of the comparison subjects were Caucasian), or smoking history (schizophrenic group: 18 nonsmokers, 13 past smokers, and seven current smokers; comparison group: 23 nonsmokers, 11 past smokers, and six current smokers).

Olfactory identification was assessed with the University of Pennsylvania Smell Identification Test (7), a forced-choice test with

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RESULTS

Scores on the University of Pennsylvania Smell Identification Test for the schizophrenic patients differed from those of the comparison group and indicated significant olfactory identification deficits ($F=37.3$, $df=1$, 74, $p<0.001$). There was no observed main effect for gender or diagnosis-by-gender interaction (all $p$ values $>0.40$). In the younger schizophrenic patients, scores of those who were neuroleptic-naive did not differ from scores of those who were medicated, which suggests minimal medication effects ($p=0.88$). Analysis of covariance between younger and elderly schizophrenic patients for performance on the University of Pennsylvania Smell Identification Test, with age and gender as the covariates, revealed that the elderly patients demonstrated greater olfactory deficit than the younger patients ($F=13.5$, $df=1$, 34, $p<0.001$).

A significant correlation was seen between scores on the University of Pennsylvania Smell Identification Test and duration of illness, which was defined as the length of time since the onset of psychotic symptoms in context of functional decline ($r=-0.88$, $df=36$, $p<0.001$). Poorer scores were associated with longer duration of schizophrenia. To ensure that this relationship was not confounded by normal age and gender effects, we adjusted the University of Pennsylvania Smell Identification Test values to account for these influences by using regression coefficients that were computed from the normal comparison group. Results indicated that even when variance attributable to normal age and gender effects was removed, the relationship with duration of illness remained ($r=-0.92$, $df=36$, $p<0.001$) (figure 1).

To assess the impact of general cognitive deficits on performance, partial correlations were calculated between scores on the University of Pennsylvania Smell Identification Test and duration of illness with Mini-Mental State scores held constant. Analysis of residuals revealed that controlling the effect of generalized cognitive impairment did not diminish the correlation between scores on the University of Pennsylvania Smell Identification Test and duration of illness ($r=-0.92$, $df=34$, $p<0.001$). Similarly, patients did not score below impairment cutoffs on the Picture Identification Test, which indicated that they had the cognitive skills to visually identify the test items but could not identify the odor.

DISCUSSION

This is the first study to demonstrate that elderly patients with schizophrenia have an olfactory identification deficit relative to age-matched comparison subjects and that the magnitude of this deficit is greater than that seen in younger schizophrenic patients. While longitudinal assessment of individual patients is the ideal method to demonstrate decline over the lifespan, this is rarely possible for human studies. However, these cross-sectional data strongly suggest that in patients with schizophrenia, olfactory identification performance decreases over the course of the illness until the very late stages of life. Indeed, there seemed to be a coupling between performance on the University of Pennsylvania Smell Identification Test and duration of illness that was independent of normal aging and gender effects. The tightness of this coupling permits prediction of illness duration from olfactory performance and raises the possibility that olfactory structures are altered by slow neurodegenerative processes in schizophrenia. Two caveats must be noted. First, the elderly patients had been taking neuroleptic medication for many years. While effects of long-term neuroleptic treatment on olfaction are not fully understood, published empirical data that concerned the effects of medication on University of Pennsylvania Smell Identification Test performance in several neurological disorders have been uniformly negative. For schizophrenia specifically no study has noted differences among neuroleptic-naive, neuroleptic-withdrawn, and currently medicated patients on olfactory test performance (4, 5). Second, fewer elderly male than female subjects were available for study, which perhaps militates against further elucidation of sex differences in test performance.

Recent neuropathological studies of younger and elderly schizophrenic patients have described a variety of cytoarchitectural abnormalities in brain regions associated with olfactory functioning (6, 10). A postmortem study that examined astrocytosis (pathology thought to result from postmaturational CNS injury) in elderly schizophrenic patients found modest increases in astro-
cytosis in hippocampal and orbitofrontal cortices, regions known to be involved in olfaction (11). To our knowledge, no specific neuropathological investigation of primary or unimodal olfactory structures in schizophrenia has been conducted. We hypothesize, however, that it would reveal pathological changes in olfactory brain regions. On the basis of these data, such investigation is clearly warranted.

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