Age and Neuropsychologic Function in Schizophrenia: A Decline in Executive Abilities beyond That Observed in Healthy Volunteers

Robert Fucetola, Larry J. Seidman, William S. Kremen, Stephen V. Faraone, Jill M. Goldstein, and Ming T. Tsuang

Background: Kraepelin originally conceptualized schizophrenia as a degenerative brain disorder. It remains unclear whether the illness is characterized by a static encephalopathy or a deterioration of brain function, or periods of each condition. Assessments of cognitive function, as measured by neuropsychologic assessment, can provide additional insight into this question. Few studies of patients with schizophrenia have investigated the effect of aging on executive functions, in an extensive neuropsychologic battery across a wide age range, compared to healthy volunteers.

Methods: We examined the interaction of aging and neuropsychologic function in schizophrenia through a cross-sectional study in patients (n = 87) and healthy control subjects (n = 94). Subjects were divided into three age groups (20–35, 36–49, and 50–75), and performance on an extensive neuropsychologic battery was evaluated.

Results: Compared to control subjects, patients with schizophrenia demonstrated similar age-related declines across most neuropsychologic functions, with the exception of abstraction ability, in which significant evidence of a more accelerated decline was observed.

Conclusions: These results are consistent with previous reports indicating similar age effects on most aspects of cognition in patients with schizophrenia and healthy adults, but they support the hypothesis that a degenerative process may result in a more accelerated decline of some executive functions in older age in schizophrenia. Biol Psychiatry 2000;48:137–146 © 2000 Society of Biological Psychiatry

Key Words: Schizophrenia, neuropsychology, executive functions, age, deterioration

Introduction

A central question in schizophrenia is whether the disorder is developmental, degenerative, or both. From the earliest descriptions of schizophrenia by Kraepelin (1919), the disorder has generally been considered a deteriorating illness; however, there is limited research confirming the long-held contention that deterioration occurs beyond that found in the first few years of illness (i.e., “dementia praecox”). Moreover, much recent evidence supports the hypothesis (e.g., Murray and Lewis 1987; Seidman 1990; Weinberger 1987) that patients with schizophrenia have primary neurodevelopmental etiologies, usually involving obstetric complications, genetic factors, or both. The presence of neurodevelopmental abnormality, however, does not negate the possibility of subsequent deterioration.

In this study we evaluate whether neuropsychologic deficits, prominent early in the disorder (Hoff et al 1992; Saykin et al 1994), decline further during the illness. Neuropsychologic impairments associated with schizophrenia involve a broad range of functions and appear to be present in most schizophrenic patients (Kremen et al 1999; Levin et al 1989; Palmer et al 1997; Randolph et al 1993; Seidman et al 1992). Impairments in sustained and selective attention, executive functions (i.e., abstract reasoning, planning, and cognitive flexibility), working memory, motor and psychomotor functions, declarative memory, and olfaction have been documented in schizophrenia. In reviews of the literature, Heaton and Drexler (1988), Seidman (1985), and Goldberg and Seidman (1991) noted little evidence indicating decline in neuropsychologic functioning over time; however, Seidman (1983), based on the few studies then available, summarized the evidence suggesting that if there was a deterioration, the brain system involved was the frontal-executive network. Other
investigators have suggested that olfaction and executive function, both of which are associated with frontal networks, may deteriorate more rapidly with age in schizophrenia (Moberg et al 1997; Sullivan et al 1994). Complicating this view of the relationship of aging and schizophrenia is the possibility that age at disease onset or illness duration may have independent and/or interactive effects on neuropsychiatric status.

The neurodegenerative hypothesis has been tested using neuropsychologic, neuroimaging, and electrophysiological techniques. Although this paper will focus on evidence from neuropsychology, it is notable that some longitudinal reports have indicated that frontal lobe volume reductions occur early in the course of the illness and may progress over time (Gur et al 1998). In addition, progressive ventricular enlargement has been documented among subsets of chronic patients (e.g., DeLisi et al 1997), though not consistently. Neuropsychologic studies indicate that there may be at least a subset of patients who demonstrate premature brain degeneration and accelerated cognitive decline (Buchsbaum and Hazlett 1997); however, evidence suggests that a substantial portion of patients do not decline beyond an initial deterioration of cognitive function that apparently occurs during the first 5 years of illness (Bilder et al 1992; Heaton and Drexler 1988).

Several longitudinal studies have observed no overall decline in global cognitive functioning over 8 month to 5-year periods (Harvey et al 1990, 1995; Sweeney et al 1991; Waddington et al 1990). In a recent review of 15 longitudinal studies of neuropsychologic function in schizophrenia, Rund (1998) concluded that cognitive deficits are relatively stable over the course of the illness; however, the conclusions reached are limited by the variable ages, phases of illness, and length of follow-up periods used in these studies. In contrast to most longitudinal reports, Harvey et al (1999) recently demonstrated that a significant subset of chronically institutionalized, older patients with schizophrenia exhibited detectable declines in cognitive and functional status over a longer 30-month study period in old age.

The majority of cross-sectional studies of age-related neuropsychologic change also find little evidence of decline (Chen et al 1996; Goldberg et al 1993; Hyde et al 1994; Kremen 1990; Mockler et al 1997), though not all concur (Bilder et al 1992; Davidson et al 1995). Davidson et al (1995) found a slight decline with increasing age on mental status examination scores in a sample of very ill schizophrenia patients (ages 25–95) with low mental status scores overall, compared to control subjects (mean Mini-Mental Status score was 9.6); however, age-related differences in patients with schizophrenia may disappear when the effects of normal aging are accounted for (Heaton et al 1994). Chen et al (1996) studied a large group of patients aged 16 to 65 and found similar age-related effects on neuropsychologic performance in comparison to healthy control subjects when looking at patients with varying disease durations. Mockler et al (1997) found no evidence of deterioration in intelligence or memory functioning with age in schizophrenic patients (at least to age 69). Finally, Hyde et al (1994) studied five cohorts of patients using neuropsychologic measures of naming, verbal learning and fluency, as well as a global dementia rating scale and a mental status examination, and found no evidence of decline across age groups. As with the Mockler et al (1997) report mentioned above, however, a control group was not included. In sum, most, but not all, of the cross-sectional reports are consistent with the longitudinal studies indicating that little if any deterioration occurs with advanced age in most patient with schizophrenia, beyond that which would be expected with normal aging. It is important to note, however, that most reports indicating no decline with old age in schizophrenia studied relatively young elderly patients (younger than age 70).

Several methodological issues have limited the interpretation of previous studies of neuropsychologic decline in schizophrenia. Longitudinal studies suffer from short follow-up periods, variable follow-up intervals, and a limited range of instruments. Cross-sectional studies in particular have been limited by the absence of appropriate age-matched control groups. Moreover, few studies have considered the possible confound of age of onset. Finally, the selection of neurocognitive functions measured may have an influence on the identification of an age-related effect in schizophrenia. There is some evidence that a younger age of onset and longer disease duration are associated with greater impairment in executive functioning (i.e., abstraction/cognitive flexibility) (Albus et al 1996; Sullivan et al 1994). For example, Sweeney et al (1992) compared young first-episode and young patients with multiple episodes on neuropsychologic measures and found greater impairment in patients with multiple episodes on tests of frontal lobe function and verbal memory, suggesting the possibility of progressive decline in these functions with more frequent episodes. Kremen et al (1999) suggested that age of onset is related to neuropsychologic function based on the observation that schizophrenia patients with relatively normal neuropsychologic profiles had a later onset of illness than those with abnormal profiles. Some recent work, however, suggests that age at disease onset and duration of illness may be unrelated to neuropsychologic functioning (Chen et al 1996; Heaton et al 1994), indicating that more research is needed to answer this question.

The present study addressed these questions through a cross-sectional examination of age-related changes in
neuropsychologic functioning among a large sample of patients with schizophrenia and healthy control subjects. An extensive battery of neuropsychologic tests was utilized to permit the assessment of a wide range of neurocognitive functions, including assessment of executive functions. We hypothesized that similar age-related reductions in cognitive performance would be detected in patients and control subjects based on earlier cross-sectional work, but that if age-related declines were present, they would be detected on measures of executive function. We also examined the impact of age of onset on the relationship between age and neuropsychologic function.

**Methods and Materials**

**Subjects**

All participants (87 patients with schizophrenia, 94 healthy control subjects) gave informed consent and were paid for their participation in this study. Patients were recruited from three Boston-area public hospitals specializing in the treatment of chronic mental illness. Inclusion criteria for patients were a diagnosis of schizophrenia according to the DSM-III-R (American Psychiatric Association 1987), age between 18 and 75, English as the primary language, and a minimum of 8 years of formal education. Exclusion criteria included neurologic disease or damage, current substance abuse (within the past 6 months), history of head injury with loss of consciousness greater than 5 minutes or with documented neurocognitive sequelae, mental retardation, and medical illnesses associated with significant cognitive dysfunction.

The mean number of hospitalizations was 7.8 (SD = 5.2), with a mean lifetime length of hospitalization of 72.6 (SD = 72.0) months. The mean age at first hospitalization was 24.0 (SD = 6.4) years. At the time of testing, 66% of the patients were outpatients (n = 57) and 34% were inpatients (n = 30). Patients were generally tested while on antipsychotic medications (mean dosage in chlorpromazine equivalents = 634.8; SD = 589.4), and while clinically stable (see Table 1 for demographics). Fifty-one of the patients with schizophrenia (59%) were taking anticholinergic medication. SANS and SAPS (Scales for the Assessment of Negative and Positive Symptoms; Andreasen and Olsen 1982) global scores were grouped into the three factors typically found when these scores have been factor-analyzed: Negative Symptoms, Positive Symptoms (“Reality Distortion”), and Disorganization factors (Toomey et al 1997). Schizophrenia patients for whom clinical data was available (n = 56) had a mean Negative Symptom score of 1.81 ± 0.6, a Disorganization score of 1.38 ± 1.0.

Healthy control subjects (n = 94) were recruited through advertisements placed in the community and from among the nonprofessional hospital staffs. With the exception of presence of current psychopathology or family history of psychosis, selection criteria were the same as for patients. In place of a diagnostic interview, a short form of the Minnesota Multiphasic Personality Inventory (MMPI-168; Vincent et al 1984) was used to screen control subjects for current psychopathology. Further details about ascertainment of control subjects are provided in previous reports (Faraone et al 1995; Kremen et al 1996).

Control subjects were similar to patients in age, ethnicity, single word reading ability (Wide Range Achievement Test—Revised), and parental socioeconomic status. As can be seen in Table 1, control subjects had more years of education and higher IQ estimates (based on age-scaled Vocabulary and Block Design scores; Brooker and Cyr 1986) than patients, as expected; however, the performance of the control subjects on estimated IQ and reading ability were solidly in the average range. Moreover, the six groups were matched on reading ability, which we and others have argued is an appropriate way to match schizophrenia patients and control subjects (cf., Kremen et al 1996). The patient group overall was composed of significantly more men and fewer women than the control group. Subjects were divided into three age groups: “young” (age 20–35: 23 schizophrenics, 39 control subjects); “middle” (age 36–49: 38 schizophrenics, 27

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**Table 1. Demographic Characteristics of Patients with Schizophrenia and Control Subjects by Age Group (Mean and SD)**

<table>
<thead>
<tr>
<th></th>
<th>Young (n = 23)</th>
<th>Middle (n = 38)</th>
<th>Older (n = 26)</th>
<th>Young (n = 39)</th>
<th>Middle (n = 27)</th>
<th>Older (n = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>30.0 (3.6)</td>
<td>41.1 (4.2)</td>
<td>58.3 (5.6)</td>
<td>28.5 (4.4)</td>
<td>41.3 (3.8)</td>
<td>62.5 (7.2)</td>
</tr>
<tr>
<td>Education (years)</td>
<td>11.9 (2.3)</td>
<td>12.3 (2.0)</td>
<td>11.8 (2.8)</td>
<td>13.7 (2.2)</td>
<td>14.1 (2.2)</td>
<td>12.6 (2.9)</td>
</tr>
<tr>
<td>Estimated IQ</td>
<td>97.9 (16.4)</td>
<td>96.5 (13.1)</td>
<td>94.2 (14.9)</td>
<td>102.8 (12.8)</td>
<td>108.0 (12.9)</td>
<td>110.9 (15.8)</td>
</tr>
<tr>
<td>Parental SES</td>
<td>3.1 (1.1)</td>
<td>3.4 (1.1)</td>
<td>3.5 (1.1)</td>
<td>3.0 (1.2)</td>
<td>3.4 (0.8)</td>
<td>3.6 (1.1)</td>
</tr>
<tr>
<td>WRAT-R Reading</td>
<td>95.3 (19.3)</td>
<td>100.5 (16.1)</td>
<td>101.6 (15.4)</td>
<td>97.4 (12.1)</td>
<td>106.8 (10.0)</td>
<td>103.3 (16.2)</td>
</tr>
<tr>
<td>Women</td>
<td>5 22</td>
<td>10 26</td>
<td>4 15</td>
<td>24 62</td>
<td>15 56</td>
<td>12 43</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>20 87</td>
<td>30 79</td>
<td>22 85</td>
<td>36 95</td>
<td>25 93</td>
<td>21 78</td>
</tr>
</tbody>
</table>

Significant group differences were found for gender [Pearson $\chi^2(5) = 23.22, p < .001]. Within each diagnostic group, participants were not significantly different on education and IQ. All six groups were not significantly different on parental socioeconomic status (SES), ethnicity, and WRAT-R Reading score. WRAT-R, Wide Range Achievement Test—Revised.
Table 2. Neuropsychologic Battery of Tests Grouped by Function

<table>
<thead>
<tr>
<th>Function</th>
<th>Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abstraction</td>
<td>Wisconsin Card Sorting Test (WCST); number of categories and perseverative responses</td>
</tr>
<tr>
<td>Verbal memory</td>
<td>Logical Memory I and II and Percent Retention (&quot;Savings&quot;) Score (WMS-R)</td>
</tr>
<tr>
<td>Verbal skills</td>
<td>WAIS-R Vocabulary, WRAT-R Reading and Spelling scores</td>
</tr>
<tr>
<td>Visual skills</td>
<td>WAIS-R Block Design, Benton Judgment of Line Orientation Test, Hooper Visual Organization Test; total score</td>
</tr>
<tr>
<td>Executive motor skills</td>
<td>Luria Graphic Sequences (alternating open square/triangle)</td>
</tr>
<tr>
<td>Perceptual motor skills</td>
<td>Manual Position Sequencing Task (palm-fist-side); total number of qualitative errors</td>
</tr>
<tr>
<td>Trail Making Test (A &amp; B) and WAIS-R Digit Symbol</td>
<td>Sustained attention</td>
</tr>
<tr>
<td>Stroop and Auditory Continuous Performance Test</td>
<td>Dichotic Listening Test and Auditory Continuous Performance Test</td>
</tr>
<tr>
<td>Mental control</td>
<td>WAIS-R Digit Span and WRAT-R Arithmetic</td>
</tr>
</tbody>
</table>


dichotic listening measure was the total digits apprehended (regardless of which ear the subject identified s/he heard the digits) in both ears over 48 trials (cf. Seidman et al 1993) rather than the 24 trials used to study relatives of schizophrenic patients (Faraone et al 1995). Each trial consisted of strings of three digits presented simultaneously to each ear (Kimura 1967) at an equal intensity (80 dB). Percent retention of verbal memory passages was delayed recall divided by immediate recall × 100 (described in Seidman et al 1998). The Wisconsin Card Sort (WCST) was the original 128 card, noncomputerized version used in all of our studies (Heaton 1981; Koren et al 1998).

Data Analysis

First, raw test scores on each test in Table 5 were transformed to Z scores (mean = 0; SD = 1). Standardization of these individual raw scores (to a mean of zero and a standard deviation of 1) was completed using the control mean and the pooled standard deviation within all groups (i.e., root mean square error). Second, composite function scores were created by averaging Z scores within each theoretical domain.

Pearson product-moment correlations were used first to examine the association between age and each of the eight function scores in each group (schizophrenia patients and control subjects). We used Fisher’s r-to-Z transformation to test for between-group differences for each set of correlations. To determine whether age at first hospitalization influenced age-related changes in neuropsychologic performance, partial correlations between age and the eight function scores were also calculated (controlling for age at first hospitalization). The groups were each subdivided into three roughly equal size subgroups, in part, because performance patterns in some subgroups could be obscured by using simple correlations. Multivariate analysis of covariance (MANCOVA) was then used with diagnosis (patients, control subjects) and age group (young, middle-aged, older) as the between-group factors, and the eight neuropsychologic composite function scores as the dependent variables.

Gender was included as a covariate because of the significant difference in the gender distribution between patients and control subjects. This was followed by within-group contrasts on each function.

Results

Correlations of Age with Neuropsychologic Function Scores

Zero-order Pearson correlations of age with each of the eight function scores for each group are shown in Table 3. Among patients with schizophrenia, increasing age was associated with significantly decreased performance on Abstraction, Visual Skills, and Perceptual Motor Skills functions. Among control subjects, increasing age was also associated with decreased performance on the Abstraction, Visual Skills, and Perceptual Motor Skills functions, as well as on the Memory, Executive Motor, and Sustained Attention functions. No group differences were
observed in correlations between age and function scores with the exception of the Verbal Memory function in which control subjects exhibited a significantly stronger association.

Indicators of disease severity may obscure interpretation of age-related declines, because differences along such variables may reflect cohort effects (i.e., an older age at first hospitalization may reflect a less severe illness and/or limited access to psychiatric resources; Kremen 1990). Indeed, age was positively correlated with age at first hospitalization in our sample of schizophrenics \((r = .43, p < .0001)\), indicating that our oldest patients (ages 50–75) were older at their first hospitalization compared to middle and younger patients. Furthermore, significant correlations were found between age at first hospitalization and the Verbal Skills, Executive Motor Skills, Mental Control, and Sustained Attention function scores in the patients (all \(p < .02\)). We calculated partial correlations between age and each of the eight function scores controlling for age at first hospitalization among the schizophrenics to see if the zero-order correlations discussed above remained significant. Results indicated that the negative correlations between age and Abstraction, Visual Skills, and Perceptual Motor Skills remained significant (and were stronger) when the effects of age at first hospitalization were controlled \((r = -.47, r = -.38, \text{and} \ r = -.50, \text{respectively})\). There were no significant associations between the three symptom dimensions (derived from the SANS and SAPS), age, and the eight neuropsychologic functions in the patients with schizophrenia (all \(rs < .21, \text{all} \ p < .20\)).

### Multivariate Analysis of Age Effects on Neuropsychologic Function Scores

Figure 1 plots the neuropsychologic profiles of the patients with schizophrenia (graph on the left) and control subjects (graph on the right) according to age group (young, middle, and older). Schizophrenic patients scored lower than control subjects across all neuropsychologic functions except the Verbal Function \(F(1,161) = 21.63, p < .0001\). This main effect can be seen in Figure 1 (the profiles for all patient groups lie below the mean of zero). A significant multivariate age group × diagnosis interaction was also detected \(F(2,161) = 1.86, p = .02\); however, the only significant univariate age group × diagnosis interaction was on Abstraction \(F(2,161) = 3.29, p = .040; \text{see Figure 1}\), in which the oldest patients had significantly worse deficits in functioning. This two-way interaction remained significant when neuroleptic dose was controlled statistically \((p = .042)\), and when patients on anticholinergic medications were excluded from the analysis \((p = .037)\). The magnitude of difference

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**Table 3. Pearson Correlations of Age and Neuropsychologic Function Scores by Group**

<table>
<thead>
<tr>
<th>Function</th>
<th>Schizophrenia</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abstraction</td>
<td>−0.31&lt;sup&gt;b&lt;/sup&gt;</td>
<td>−0.32&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Verbal memory</td>
<td>−0.13</td>
<td>−0.47&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Verbal skills</td>
<td>0.08</td>
<td>0.05</td>
</tr>
<tr>
<td>Visual skills</td>
<td>−0.32&lt;sup&gt;b&lt;/sup&gt;</td>
<td>−0.30&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Executive motor skills</td>
<td>−0.01</td>
<td>−0.24&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Perceptual motor skills</td>
<td>−0.39&lt;sup&gt;b&lt;/sup&gt;</td>
<td>−0.53&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mental control</td>
<td>−0.05</td>
<td>−0.08</td>
</tr>
<tr>
<td>Sustained attention</td>
<td>−0.01</td>
<td>−0.29&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> \(p < .05\).

<sup>b</sup> \(p < .005\).

<sup>c</sup> A significant difference was found between groups on correlations of Verbal Memory and age \((r = -2.51, p < .05)\).
Table 4. Performance on Abstraction Function by Age Group (Mean Z score + SD): WCST and VVT Variables

<table>
<thead>
<tr>
<th>Group</th>
<th>WCST-Categories</th>
<th>WCST-PR</th>
<th>VVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Young (n = 23)</td>
<td>−0.70 ± 1.290</td>
<td>−0.64 ± 1.320</td>
<td>−1.33 ± 1.410</td>
</tr>
<tr>
<td>Middle (n = 38)</td>
<td>−1.33 ± 1.170</td>
<td>−1.15 ± 1.320</td>
<td>−1.25 ± 1.080</td>
</tr>
<tr>
<td>Older (n = 26)</td>
<td>−1.84 ± 0.860</td>
<td>−1.93 ± 1.450</td>
<td>−1.79 ± 1.330</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Young (n = 39)</td>
<td>0.17 ± 0.570</td>
<td>0.10 ± 0.240</td>
<td>0.04 ± 0.610</td>
</tr>
<tr>
<td>Middle (n = 27)</td>
<td>0.03 ± 0.610</td>
<td>0.00 ± 0.380</td>
<td>0.12 ± 0.530</td>
</tr>
<tr>
<td>Older (n = 28)</td>
<td>−0.26 ± 0.960</td>
<td>−0.13 ± 0.500</td>
<td>0.18 ± 0.680</td>
</tr>
</tbody>
</table>

WCST-PR is number of perseverative responses on the Wisconsin Card Sorting Test task. All three variables are scored in the same direction (minus is worse performance).

*aSignificant differences were found between young and older patients with schizophrenia on WCST categories (t[36] = 3.49, p = .001) and perseverations (t[45] = −3.17, p = .003), but not VVT score. Middle-aged patients differed from older patients on WCST perseverations only (t[48] = −2.15, p = .037).

*bSignificant differences were found between younger and older controls on WCST categories (t[41] = 2.13, p = .039) and perseverations (t[37] = −2.26, p = .030), but not VVT score.

between the youngest and the oldest age groups was approximately 1.0 SD in patients, versus 0.4 SD in control subjects. This was accounted for by lower performance on the WCST rather than by conceptual impairment on the Visual Verbal Test (VVT; Feldman and Drasgow 1981) (see Table 4 and discussion below). Although visual inspection of the profile levels in Figure 1 suggests strong age-related declines in Perceptual Motor Skills (particularly in the oldest schizophrenics), statistical differences in the magnitude of age-related decline were not found between patients and control subjects. For descriptive purposes only, mean scores (including age-scaled scores for Wechsler Adult Intelligence Scale—Revised and Wide Range Achievement Test—Revised scores) on all neuropsychologic measures, for each age sub-group, are presented in Table 5.

### Discussion

In this cross-sectional investigation of the effects of aging on neuropsychologic function in patients with schizophrenia, similar patterns of age effects on neuropsychologic functions were observed in patients and healthy control subjects, with the exception of significantly greater age-related declines in abstraction functions among the patients, observed when the patients and control subjects were subdivided into three age groups ("young," "middle," "older"). The decline in abstraction is consistent with some previous cross-sectional and longitudinal studies using electrophysiologic and neuropsychologic measures (O’Donnell et al 1995; Sullivan et al 1994).

Correlational analyses revealed similarly significant age-related declines on most functions in patients and in...
control subjects, with the exception of the Verbal Memory function, in which control subjects demonstrated a stronger association with age than patients. The significant correlations between age and the Executive Motor, Verbal Memory, and Sustained Attention functions found in control subjects were not observed for patients perhaps because deficits in these areas occurred early in the disease process (i.e., earlier onset of cognitive deficit), though this hypothesis is speculative and needs empirical support. The significant association between age and the Abstraction function was not attenuated when the effects of age at first hospitalization (a possible confound and indicator of disease severity) was controlled. Differences between the groups could not be attributed to any gender differences as this was controlled in the analyses.

Multivariate analyses confirmed that although patients with schizophrenia performed at lower levels than control subjects on all functions (except the Verbal function), the magnitude of age-related declines on most functions was similar in both groups. This was consistent with most other studies demonstrating that neuropsychologic functions do not decline significantly in most patients after the early years of the illness, but are vulnerable to the same effects of normal aging as those of healthy adults (Goldberg et al 1993; Harvey et al 1995; Hyde et al 1994; Rund 1998; Seidman 1983; Weinberger 1987). Recently, Goldstein et al (1998) reported similar correlations between age and a global index of cognitive functioning among mildly impaired patients with schizophrenia, patients with progressive dementias and control subjects; however, consistent with our results, a more severely impaired subset of schizophrenia patients showed no significant associations between age and the impairment index, indicating early and substantial cognitive loss in some patients which may be nonprogressive.

Consistent with speculations by Seidman (1983), we found evidence of significantly greater decline in executive functions (in the Abstraction function) among the patients with schizophrenia, when the groups were subdivided into three roughly equal size age groups. The greater decline in Abstraction in patients with schizophrenia than in control subjects, in the MANCOVA as compared to the correlational analyses, reflects functioning in different age defined subgroups of patients obscured by simple correlations within the entire group. The magnitude of the difference between diagnostic groups was approximately 0.6 SD. Furthermore, this finding could not be accounted for by antipsychotic medication dose (in chlorpromazine equivalents), anticholinergic medication, or the later age at first hospitalization of our oldest group of patients. Clinical symptoms as measured by the SANS and SAPS were not significantly correlated with age or any of the eight neuropsychologic function scores, indicating that positive and negative symptomatology could not account for the age-related decline found in our sample.

It is notable that later age at first hospitalization in the older group would tend to reduce the difference. Sullivan et al (1994) reported a relationship between age at first hospitalization and executive functioning in schizophrenic patients which could account for “selective” age-related declines in these functions. In our sample, however, age at first hospitalization was not correlated with the Abstraction function in patients, and the difference in rate of decline in Abstraction between schizophrenic patients and control subjects remained significant after controlling for age at first hospitalization. As seen in Table 4, the age-related decline observed in patients on VVT performance was substantially smaller than on the WCST, and significant differences were not found on the VVT between age groups among patients or control subjects. In contrast, age-group differences were detected on both WCST variables among patients and control subjects (Table 4). Thus, the accelerated decline detected in the Abstraction function among patients appeared to be accounted for largely by performance on the WCST.

Interestingly, in a study of the nonpsychotic relatives of patients with schizophrenia (Faraone et al 1995), performance on the WCST significantly discriminated relatives and control subjects, but the VVT did not. The VVT requires verbal generation of concepts, set-shifting and generation of a second concept, whereas the WCST does not require verbalization of responses. The WCST requires more shifting of set, utilization of feedback and reinforcement, and probably a greater contribution from working memory (Goldman-Rakic 1991). Patients with schizophrenia have shown a significant inverse relationship between WCST performance and dorsolateral prefrontal blood flow, indicating that the WCST may be particularly sensitive to both schizophrenia (Koren et al 1998) and integrity of prefrontal cortex in schizophrenia (Weinberger et al 1986). It is unclear whether frontal networks degenerate at a more accelerated pace than other brain systems in schizophrenia, although this possibility has been raised by some neuroimaging and neuropsychological studies (Gur et al 1998; O’Donnell et al 1995; Siegel et al 1994).

There is some evidence that prefrontal cortical volumes age more rapidly than other regions in healthy humans (Raz et al 1997). If prefrontal regions are more vulnerable to age in healthy persons, they may be even more vulnerable in patients with schizophrenia, providing some structural basis for cognitive decline. This possible association may also be mediated by severity of lifetime functional outcome, as those studies that have demonstrated cognitive decline in older age patients with schizophrenia (Davidson et al 1995) have tended to study very poor outcome patients who may have the most damaged
brains. This interpretation is speculative and awaits direct empirical test.

Strengths of the present study include use of a large group of patients and well-matched control subjects, a comprehensive neuropsychologic battery of tests, including measures of executive functions, and a wide age range of subjects; however, there are several limitations to the study, which merit consideration. First, cross-sectional studies are sensitive to cohort effects that may confound differential effects of age on performance. We found a relationship between age of onset and age in our sample, but controlling for this variable did not diminish age-related declines. Longitudinal studies over longer time periods that utilize comprehensive neuropsychologic batteries would provide definitive data. Second, we did not study the “very” old patients with schizophrenia (older than 75 years of age), and thus it is not clear whether similar effects of aging would be observed in an older group. Third, our patients were recruited from hospitals that specialize in the treatment of chronically psychotic people. Thus, results may not generalize to other subgroups of patients (although about 65% were outpatients). Moreover, our older patient group was not necessarily a more severely impaired subgroup, because their single word oral reading scores (a premorbid matching variable) were actually higher than that of the older control subjects. Thus, despite average premorbid intellectual ability, these patients showed the largest relative decline with age on some executive functions. Finally, although gender was used as a covariate in all analyses, the results may not generalize to female patients with schizophrenia, given the relatively small representation of women in the current sample. Future studies should include larger samples of female patients to address any interaction between cognitive functioning, age and gender (Goldstein et al 1998).

In summary, similar age-related declines on most neuropsychologic functions were observed in patients with schizophrenia and control subjects, indicating that most patients do not show a progressive, widespread “dementia” course later in the illness. We did find evidence, however, of larger patient-control differences in some higher-order executive functions among the older subjects, as reflected in Wisconsin Card Sorting deficits, which may reflect deterioration of frontal system networks in older patients with schizophrenia. The possibility that there is another phase of deterioration in old age in patients with schizophrenia, long after the decline observed in the first few years of illness, is a hypothesis worthy of further study.

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