Global intellectual impairment does not accelerate with age in patients with schizophrenia
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Global Intellectual Impairment Does Not Accelerate With Age in Patients With Schizophrenia: A Cross-Sectional Analysis

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Abstract

Neuropsychological studies show impairment in intellectual functions in schizophrenia patients. It is still unclear, however, whether intelligence scores decline progressively during the illness as compared to healthy subjects' scores. Longitudinal studies conducted so far have been restricted to relatively short time spans. The aim of this study is to investigate whether changes in intelligence scores accelerate with age in schizophrenia patients. In a cross-sectional design, performance of four subtests of the Wechsler Adult Intelligence Scale (WAIS) was analyzed in 112 schizophrenia patients and compared to that of 70 healthy subjects, across an age span of 40 years (16–56 years). A linear regression analysis was performed. A main effect on the total ratio score of the four tests was demonstrated between the two groups. No main effect of age and no interaction effect of age with group for the total ratio score were found. The results confirm that there is global intellectual impairment in schizophrenia patients at the onset of illness but no age-accelerated decline and are consistent with the neurodevelopmental hypothesis of schizophrenia.

Keywords: Schizophrenia, neuropsychology, IQ, stability, age.

decline in schizophrenia patients had relatively short time spans, while most age-controlled cohort or cross-sectional studies did not use a design with healthy comparison subjects.

The present cross-sectional investigation compares schizophrenia patients ($n = 112$) with healthy subjects ($n = 70$) across an age span of 40 years (16–56 years). Its aim is to investigate whether age-accelerated changes in intelligence scores are present in schizophrenia. To that end, we performed a linear regression analysis using non-age-corrected raw scores of four subtests of the Dutch version of the Wechsler Adult Intelligence Scale (WAIS).

Methods

Subjects. One hundred and twelve schizophrenia patients or schizophreniform disorder and 70 healthy comparison subjects from the Utrecht Schizophrenia Project participated after written informed consent was obtained. Patients were recruited from various outpatient and inpatient clinics, with treatment setting being unrelated to age; the correlation of outcome (defined by the square-root-transformed ratio of the cumulative months of hospitalization and the cumulative months of illness since first symptoms) with age was not significant ($r = -0.12$, $p = $ nonsignificant [$ns$]).

All subjects were between 16 and 56 years of age. Subjects with a major medical or neurological illness—including head trauma in the past, hypertension, cardiac disease, diabetes mellitus, cerebrovascular disease, epilepsy, migraine, endocrine disorders, or drug or alcohol dependence—were excluded. No patient entered neuropsychological assessment in an episode of severe psychosis.

The presence or absence of psychopathology was established in all subjects using the Comprehensive Assessment of Symptoms and History (Andreasen et al. 1992) and assessed by two independent raters. Diagnostic consensus was achieved in the presence of a psychiatrist. All patients met DSM-IV (American Psychiatric Association 1994) diagnoses of schizophrenia ($n = 110$) or schizophreniform disorder ($n = 2$); those with a schizophreniform disorder met the criteria for diagnosis of schizophrenia after 1 year of illness; and all healthy comparison subjects met Research Diagnostic Criteria of “never mentally ill” (Spitzer et al. 1978).

Age at first symptoms was defined as the first time patients had been seeking medical or psychological help for their psychotic symptoms. Subjects' own education is expressed in years of completed education, and parents' socioeconomic status is expressed as the highest completed level of education (in years) by one parent. Table 1 contains demographic data.

Intelligence Scores. Four subtests of the Dutch version of the WAIS (Stinissen et al. 1970)—Comprehension, Vocabulary, Block Design, and Picture Arrangement—were administered. Raw scores were used to reflect a more reliable effect of change because there is no correction for increasing age. Five ratio scores were calculated, one for each subtest separately and a total ratio score for the four subtests. The ratio scores of the subtests of the patient group and the healthy comparison group were calculated by computing the raw scores divided by the maximum score of the subtest and multiplied by 100, as follows: subtest ratio = (raw score subtest/maximum score subtest) $\times$ 100. The maximum scores for the subtests are Comprehension 28, Vocabulary 60, Block Design 26, and Picture Arrangement 20. The total ratio score was derived by adding the four subtest ratio scores divided by four, as follows: total ratio score = (ratio score Comprehension + ratio score Vocabulary + ratio score Block Design + ratio score Picture Arrangement)/4. For interpretation of the results, an estimated full-scale IQ was calculated using the mean raw scores for both groups on each subtest. The mean raw group score was transformed into the corresponding C-score of the WAIS for each subtest. The full-scale score was derived by adding the four C-scores of the four subtests divided by 4 and multiplied by 11, as follows: full-scale score = (C-score of four subtests/4) $\times$ 11. Table 2 provides detailed information on WAIS performance for the four age groups within each set of subjects.

Statistical Analysis. Data were examined for outliers and extreme values and normality of the distribution. There were no outliers. The analysis showed that the data were normally distributed. Multiple linear regression of total ratio score and the ratio scores for the four subtests was performed with group (schizophrenia patients and healthy comparison subjects) as the predictor variable, and with age and parental highest education as covariates. To evaluate the interaction with age, a similar linear regression was performed, adding the interaction between age and schizophrenia patients as predictor variable. To evaluate whether age of onset and years of illness influenced the findings, a post hoc analysis was added in the patient group.

The SPSS 8.0 statistical package for Windows (SPSS 1997) was used for these analyses, with a 2-tailed alpha level of 0.05.

Results

Table 3 contains intelligence scores and changes of diagnosis, age, and interaction of diagnosis with age.
Table 1. Demographic data for schizophrenia patients and healthy comparison subjects

<table>
<thead>
<tr>
<th></th>
<th>Schizophrenia patients (n = 112)</th>
<th>Healthy comparison subjects (n = 70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female, n</td>
<td>75/37</td>
<td>54/16</td>
</tr>
<tr>
<td>Age (yrs), mean ± SD</td>
<td>31.6 ± 10.2</td>
<td>31.4 ± 10.7</td>
</tr>
<tr>
<td>Age range (yrs)</td>
<td>16–56</td>
<td>16–56</td>
</tr>
<tr>
<td>Right-handed/left-handed/ambidextrous, n</td>
<td>96/14/2</td>
<td>59/9/2</td>
</tr>
<tr>
<td>Completed education (yrs), mean ± SD</td>
<td>11.3 ± 3.01</td>
<td>12.3 ± 2.7</td>
</tr>
<tr>
<td>Parental highest education (yrs), mean ± SD</td>
<td>11.7 ± 3.3</td>
<td>12.3 ± 2.9</td>
</tr>
<tr>
<td>Age at first symptoms (yrs), mean ± SD</td>
<td>20.0 ± 5.0</td>
<td></td>
</tr>
<tr>
<td>Illness duration (yrs), median (range)</td>
<td>8.2 (0.1–36.0)</td>
<td></td>
</tr>
<tr>
<td>Ratio score, mean ± SD²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score for subtests</td>
<td>58.64 ± 17.13</td>
<td>72.08 ± 11.21</td>
</tr>
<tr>
<td>Comprehension</td>
<td>58.04 ± 19.12</td>
<td>71.58 ± 13.98</td>
</tr>
<tr>
<td>Vocabulary</td>
<td>54.29 ± 20.92</td>
<td>65.12 ± 15.48</td>
</tr>
<tr>
<td>Block Design</td>
<td>62.60 ± 26.30</td>
<td>77.20 ± 20.51</td>
</tr>
<tr>
<td>Picture Arrangement</td>
<td>59.64 ± 22.61</td>
<td>74.43 ± 16.36</td>
</tr>
</tbody>
</table>

*Note.*—SD = standard deviation.

¹ Indicates the *p* < 0.05 significance level of comparison between the schizophrenia patients and the healthy comparison subjects on the demographic variables by chi-square analysis.

² Values are mean scores expressed as ratio scores.

**Effects of Diagnosis.** The total ratio score for the four subtests of the WAIS was significantly lower (mean difference = −12.86, standard error [SE] = 2.27; *p* < 0.0001) in the schizophrenia patients as compared to the healthy comparison subjects. The ratio scores for all four subtests were significantly lower in the schizophrenia patients as compared to the healthy comparison subjects: Comprehension (mean difference = −12.92, SE = 2.59; *p* < 0.0001), Vocabulary (mean difference = −9.83, SE = 2.73; *p* < 0.0001), Block Design (mean difference = −14.26, SE = 3.69; *p* < 0.0001), and Picture Arrangement (mean difference = −14.43, SE = 2.98; *p* < 0.0001).

**Effects of Age.** There was no main effect for age on the total ratio score for the four subtests of the WAIS (unstandardized regression coefficient [B] = −0.029 per year, SE = 0.11; *ns*). Effects of age were found on the ratio score of the subtest Picture Arrangement, which significantly decreased with age (B = −0.56 per year, SE = 0.15; *p* < 0.0001) and on the ratio score of the subtest Vocabulary, which significantly increased with age (B = 0.47 per year, SE = 0.13; *p* < 0.001). The ratio scores of the subtests Comprehension (B = 0.23 per year, SE = 0.13; *ns*) and Block Design (B = −0.26 per year, SE = 0.18; *ns*) did not show age effects.

**Effects of Parental Highest Education.** Main effects of parental education were found on the total ratio score for the four subtests (B = 1.09 per year of education, SE = 0.37; *p* < 0.003) and for the subtests Comprehension (B = 1.27 per year of education, SE = 0.42; *p* < 0.003) and Vocabulary (B = 2.07 per year of education, SE = 0.44; *p* < 0.0001). The ratio scores of these three variables increased with higher parental education. No effects of parental education were found on the subtests Block Design (B = 0.55 per year of education, SE = 0.60; *ns*) and Picture Arrangement (B = 0.48 per year of education, SE = 0.49; *ns*).

**Effects of Diagnosis With Age.** No interaction effect of age with group (schizophrenia patients and healthy comparison subjects) was found on the total ratio score for the four subtests (B = −0.11 per year, SE = 0.21; *ns*). Interaction effects were also not found on the ratio scores on any of the four subtests: Comprehension (B = −0.25 per year, SE = 0.25; *ns*), Vocabulary (B = 0.08 per year, SE = 0.26; *ns*), Block Design (B = 0.05 per year, SE = 0.35; *ns*), and Picture Arrangement (B = −0.34 per year, SE = 0.28; *ns*).

**Effects of Age of Onset and Years of Illness.** No effects of age of onset (B = 0.20 per year of age of onset, SE = 0.33; *ns*) and years of illness (B = −0.29 per year of illness, SE = 0.31; *ns*) were found on the total ratio score for the four subtests in the patient group.

Figure 1 presents the main result from the linear regression procedure on the total ratio score for the four subtests of the WAIS.
Table 2. Distribution of age for schizophrenia patients and healthy comparison subjects; raw scores of the four subtests and the total ratio score of the four subtests of the Dutch WAIS

<table>
<thead>
<tr>
<th></th>
<th>Schizophrenia Patients (n = 112)</th>
<th>Healthy Comparisons (n = 70)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>16–25 yrs (n = 37)</td>
<td>26–35 yrs (n = 41)</td>
</tr>
<tr>
<td>Raw scores, Comprehension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>15.4 ± 5.1</td>
<td>17.5 ± 5.2</td>
</tr>
<tr>
<td>Raw scores, Vocabulary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>28.2 ± 13.1</td>
<td>34.9 ± 12.4</td>
</tr>
<tr>
<td>Range</td>
<td>3–58</td>
<td>11–54</td>
</tr>
<tr>
<td>Raw scores, Block Design</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>16.3 ± 7.2</td>
<td>16.7 ± 6.5</td>
</tr>
<tr>
<td>Range</td>
<td>4–26</td>
<td>6–26</td>
</tr>
<tr>
<td>Raw scores, Picture Arrangement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>12.9 ± 3.9</td>
<td>12.1 ± 4.9</td>
</tr>
<tr>
<td>Total ratio, score of 4 subtests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>57.3 ± 17.3</td>
<td>61.4 ± 16.4</td>
</tr>
<tr>
<td>Range</td>
<td>22.9–91.6</td>
<td>26.1–89.4</td>
</tr>
</tbody>
</table>

Note.—SD = standard deviation; WAIS = Wechsler Adult Intelligence Scale.

1 Comprehension maximum raw score 28, Vocabulary maximum raw score 60, Block Design maximum score 26, Picture Arrangement maximum raw score 20.

2 The total ratio score of 4 subtests was derived as follows: (ratio score Comprehension + ratio score Vocabulary + ratio score Block Design + ratio score Picture Arrangement)/4. A ratio subtest score was calculated as follows: (raw score subtest maximum score subtest) x 100.
### Table 3. Intelligence scores and changes of diagnosis, age, and interaction of diagnosis \( \times \) age in 112 schizophrenia patients as compared to 70 healthy comparison subjects

<table>
<thead>
<tr>
<th></th>
<th>Effects of Diagnosis</th>
<th>Effects of Age</th>
<th>Effects of Diagnosis ( \times ) Age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( B \pm SE )</td>
<td>( t (df = 178), p )</td>
<td>( B \pm SE )</td>
</tr>
<tr>
<td>Total ratio score</td>
<td>-12.86 ± 2.27**</td>
<td>-5.68, &lt;0.0001</td>
<td>-0.029 ± 0.11</td>
</tr>
<tr>
<td>Ratio score, Comprehension</td>
<td>-12.92 ± 2.59**</td>
<td>-4.98, &lt;0.0001</td>
<td>0.23 ± 0.13</td>
</tr>
<tr>
<td>Ratio score, Vocabulary</td>
<td>-9.83 ± 2.73**</td>
<td>-3.60, &lt;0.0001</td>
<td>0.47 ± 0.13*</td>
</tr>
<tr>
<td>Ratio score, Block Design</td>
<td>-14.26 ± 3.69**</td>
<td>-3.87, &lt;0.0001</td>
<td>-0.26 ± 0.18</td>
</tr>
<tr>
<td>Ratio score, Picture Arrangement</td>
<td>-14.43 ± 2.98**</td>
<td>-4.84, &lt;0.0001</td>
<td>-0.56 ± 0.15**</td>
</tr>
</tbody>
</table>

Note. — \( B \) = the unstandardized regression coefficient; SE = standard error.

1 Difference in intelligence scores in schizophrenia patients as compared to healthy comparison subjects expressed as unstandardized regression coefficients \( B \pm SE \), corrected for age and parental highest education.
2 Difference in regression slopes in unstandardized (raw) regression coefficients \( B \pm SE \) for age, corrected for parental highest education.
3 The regression slopes in unstandardized (raw) regression coefficients \( B \pm SE \) for schizophrenia with age after adding this predictor variable to the regression, corrected for age and parental highest education.

\* \( p \leq 0.001 \); ** \( p \leq 0.0001 \)

### Figure 1. Age-related variation in total ratio scores in schizophrenia patients versus comparison subjects
Discussion

This cross-sectional study compared intellectual functioning, expressed as WAIS scores, in 112 schizophrenia patients with that of 70 healthy subjects, across an age span of 40 years (range 16–56 years). The main finding is that schizophrenia patients demonstrated an overall decrease in intelligence scores independent of age but did not show an age-accelerated change in intelligence scores as compared to the healthy comparison subjects. Moreover, we found a small but significant decrease with age on the subtest Picture Arrangement and a small increase on the subtest Vocabulary for both groups.

The global intellectual deficit in schizophrenia patients is in line with earlier reports (Aylward et al. 1984; Heaton et al. 1994; Mockler et al. 1997). The fact that no age-accelerated decrease is found in intelligence scores in the patient group as compared to the healthy subjects suggests that intellectual functioning—albeit diminished from the onset of illness—does not decrease further in schizophrenia patients over time.

Several other neuropsychological studies also failed to find intellectual or cognitive decline in schizophrenia patients over the course of illness. However, most longitudinal studies evaluated a time span of less than 8 years and did not include healthy comparison subjects (Sweeney et al. 1991; see Rund 1998), while the cross-sectional studies spanning longer age ranges (18–69 years) did not compare schizophrenia subjects with healthy subjects (Hyde et al. 1994; Mockler et al. 1997). Our approach has the advantage that we included a matched healthy comparison group with the same range of 40 years (16–56 years) as in the schizophrenia patients.

Our findings are consistent with the presence and course of intellectual and cognitive deficits reported in chronically ill schizophrenia patients (Rund 1998; Fucetola et al. 2000). Cognitive deficits, although less pronounced, have also been found in patients with first episode schizophrenia, which suggests that the decrease in these functions is indeed present at an early stage of the illness (Bilder et al. 1992; Saykin et al. 1994; Censits et al. 1997; Hoff et al. 1999; Mohamed et al. 1999). Some studies even report lower WAIS IQ scores or lower scores on other intelligence tests before onset of the illness in schizophrenia patients, suggesting that a lower intelligence score is a risk factor or precedes schizophrenia (David et al. 1997; Russell et al. 1997; Kremen et al. 1998; Bedwell et al. 1999; Rabinowitz et al. 2000). Albee et al. (1963) already came to the same conclusion. Moreover, they compared scores of childhood premorbid IQs with scores of the same patients as adults with the diagnosis of schizophrenia, and they found no significant difference between these two periods of assessment. They concluded that intellectual deterioration in schizophrenia patients starts during childhood and is not initiated by the onset of symptoms of psychosis.

A small but significant decrease with age was found in our study on the subtest Picture Arrangement and a small but significant increase on the subtest Vocabulary, irrespective of diagnosis. These effects are consistent with the validated norm scores of the WAIS for the Dutch population (Stinissen et al. 1970). Moreover, the total ratio score and the verbal subtests Vocabulary and Comprehension showed a main effect of parental education, with higher parental education being associated with higher scores. This indicates that intelligence scores are sensitive for this estimate of premorbid functioning. Therefore, we used the parents’ highest level of education as a covariate in our analysis. Moreover, groups were matched for parental education. Parental highest education did not influence the differences between schizophrenia patients and healthy comparison subjects.

Our study was limited in several aspects. First and foremost, the design was not longitudinal but cross-sectional, and therefore the findings are limited in statistical power and potentially confounded by cohort or time of measurement effects (Diggle et al. 1994). Therefore, we analyzed possible confounding factors. The age of onset and illness duration did not influence the findings.

Another limitation in our study is the age range of 16 to 56 years. Two studies comparing schizophrenia patients and healthy subjects used an age range of 16 to 65 years (Chen et al. 1996) and a range of 20 to 75 years (Fucetola et al. 2000). Both studies reported no age-accelerated decline in cognitive functions, with the exception of an accelerated decline in abstract ability in the elderly patients (Fucetola et al. 2000). This last finding is in line with studies on geriatric chronically hospitalized patients in which cognitive and functional decline was demonstrated (Davidson et al. 1995; Harvey et al. 1998, 1999). The mean age of the older schizophrenia patients in the study of Fucetola et al. (2000) was 58.3 years. All subjects in the studies by Harvey et al. (1998, 1999) were geriatric chronically hospitalized patients 65 years of age or older. Also, Davidson et al. (1995) found cognitive decline in an elderly group of institutionalized schizophrenia patients 65 years of age and older. Therefore, according to these studies, a decline is present in the elderly chronically ill patients.

The only study to conclusively demonstrate a progressive deterioration with age in schizophrenia patients (age ranges of 18–50 years and 66–88 years) concerned olfactory identification (Moberg et al. 1997).

A third limitation of our study is the use of four subtests of the (Dutch) version of the WAIS. When a short form version is used, there is a fair chance of overestima-
tion of the scores (Crawford 1992). In a transformation of the total ratio scores found in our study, we calculated an estimated mean full-scale WAIS IQ of 103 for the schizophrenia patients and 118 for the healthy comparison group. Compared to reported WAIS–R full-scale scores in schizophrenia patients, these results suggest a 10 to 15 points higher IQ score for both groups in our study (Iverson et al. 1998; Ryan et al. 1999). However, the strength of our approach is the use of non-age-corrected raw scores for both groups, by which it is possible to achieve a more valid index of deterioration and to compensate for the bias of overestimated IQ scores (Bedwell et al. 1999).

In conclusion, this study found a global deficit in intellectual functioning expressed as lower intelligence scores in schizophrenia patients, irrespective of age. This global deficit in intellectual functioning supports the neurodevelopmental hypothesis of schizophrenia (Murray and Lewis 1987; Weinberger 1987) and is consistent with morphological studies, in which decreased brain volumes and increased ventricular volumes were found in both first episode schizophrenia patients and chronically ill patients (Wright et al. 2000). These decreases in brain tissue in schizophrenia might be associated with decreased global intellectual functioning in patients. However, if progressive morphologic changes exist in schizophrenia, as has been suggested in a few studies (DeLisi et al. 1997; Gur et al. 1998), then these might not be related to the stable pattern of global intellectual functioning seen in schizophrenia patients.

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