Neuropsychological Decline in Schizophrenia From the Premorbid to the Postonset Period: Evidence From a Population-Representative Longitudinal Study

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Objective: Despite the widespread belief that neuropsychological decline is a cardinal feature of the progression from the premorbid stage to the chronic form of schizophrenia, few longitudinal studies have examined change in neuropsychological functioning from before to after illness onset. The authors examined whether neuropsychological decline is unique to schizophrenia, whether it is generalized or confined to particular mental functions, and whether individuals with schizophrenia also have cognitive problems in everyday life.

Method: Participants were members of a representative cohort of 1,037 individuals born in Dunedin, New Zealand, in 1972 and 1973 and followed prospectively to age 38, with 95% retention. Assessment of IQ and specific neuropsychological functions was conducted at ages 7, 9, 11, and 13, and again at age 38. Informants also reported on any cognitive problems at age 38.

Results: Individuals with schizophrenia exhibited declines in IQ and in a range of mental functions, particularly those tapping processing speed, learning, executive function, and motor function. There was little evidence of decline in verbal abilities or delayed memory, however, and the developmental progression of deficits in schizophrenia differed across mental functions. Processing speed deficits increased gradually from childhood to beyond the early teen years, whereas verbal deficits emerged early but remained static thereafter. Neuropsychological decline was specific to schizophrenia, as no evidence of decline was apparent among individuals with persistent depression, children with mild cognitive impairment, individuals matched on childhood risk factors for schizophrenia, and psychiatrically healthy individuals. Informants also noticed more cognitive problems in individuals with schizophrenia.

Conclusions: There is substantial neuropsychological decline in schizophrenia from the premorbid to the postonset period, but the extent and developmental progression of decline varies across mental functions. Findings suggest that different pathophysiological mechanisms may underlie deficits in different mental functions.

(Am J Psychiatry 2014; 171:91–101)

Neuropsychological impairment is a core feature of schizophrenia (1), and understanding the nature and course of neuropsychological functioning in schizophrenia may have important pathophysiological implications. It is widely believed that individuals diagnosed with schizophrenia experience neuropsychological decline from the premorbid to the postonset period, but relatively few studies have examined change in neuropsychological functioning from before to after the onset of schizophrenia. In this study, we provide a rigorous test of neuropsychological changes in schizophrenia using a battery of tests administered during childhood (ages 7, 9, 11, and 13) and adulthood (age 38) as part of an ongoing population-representative longitudinal study.

There is clear evidence of mild neuropsychological deficits among children who later develop schizophrenia (2). Neuropsychological deficits are even more pronounced among adults diagnosed with schizophrenia. For example, meta-analyses show an average premorbid 8-point IQ deficit (SD=0.50) among individuals who later develop schizophrenia (3) but a 14- to 21-point IQ deficit (SD=0.90–1.40) among first-episode and chronic schizophrenia patients (1, 4, 5). These findings suggest that individuals with schizophrenia experience a relative decline in neuropsychological functioning over time from before to after illness onset, with stabilization in neuropsychological functioning thereafter (6, 7), or at least until older adulthood (8–10).

In line with cross-sectional evidence, the few longitudinal studies that have addressed neuropsychological changes in schizophrenia from before to after illness onset have consistently shown evidence of neuropsychological decline (Table 1). However, these studies suffer from various limitations. First, the majority of the studies are based on clinical samples, which may not be representative of the full

This article is featured in this month's AJP Audio and is discussed in an Editorial by Dr. Dickinson (p. 9)

TABLE 1. Characteristics of Studies Assessing Neuropsychological Decline From Before to After the Onset of Schizophrenia[a]

Study	N (Cases)	Baseline Age or Age Range (Years)	Follow-Up Age or Age Range (Years)	Comparison Group	Same Test Across Time	Neuropsychological Tests	Finding
Kremen et al. (11)	10	5 or 9	Late 30s	Yes	Yes	Peabody Picture Vocabulary Test	Relative decline
Seidman et al. (12)	26	7	35	Yes	Yes	Two IQ subtests	Decline
Caspi et al. (13)	44	16–17	20s	Yes	Yes	Army Induction Tests	Decline
Schwartzman and Douglas (14)	50	20s	30s	Yes	Yes	Army Induction Tests	Decline
Bilder et al. (15)	39	17	20s	Yes	No	Scholastic Aptitude Test, IQ	Decline
Gochman et al. (16)	18	Childhood	Adolescence, adulthood	No	Yes	IQ	Decline
Russell et al. (17)	34	8–25	17–59	No	Yes	IQ	No decline
Lubin et al. (18)	159	18	18–51	No	Yes	Army Induction Tests	Decline
Sheitman et al. (19)	27	9–17	18–60	No	No	Various IQ tests	Decline
Rappaport and Webb (20)	10	Adolescence	15–28	No	Yes, no[b]	Various IQ tests	Decline
Albee et al. (21)	112	Childhood	Adulthood	No	No	Various IQ tests	No decline

[a] Studies are ordered by methodology and date, with the most methodologically rigorous and recent studies listed first. The first two studies (11, 12) used epidemiological samples; all the others used clinical samples.
[b] The same test was used across time within participants, but not between participants.

population of individuals with schizophrenia (22). Second, the age at baseline assessment varies considerably, with many studies assessing neuropsychological functioning for the first time in adolescence or adulthood, when prodromal symptoms (and altered neuropsychological functioning) tend to be present (23–25). Thus, these studies may underestimate the magnitude of the decline in functioning. Third, only five of the studies included a comparison group, which is needed to provide a rigorous test of change in functioning. Fourth, many of these studies employed different neuropsychological tests across time, making it difficult to ascertain true change in functioning. Fifth, these studies focused exclusively on IQ (or IQ proxies). Since different neural systems underlie performance on different neuropsychological tests, other important mental functions, such as memory and executive function, should be examined as well. Sixth, none of the studies examined whether, in addition to poor IQ test performance, individuals with schizophrenia experience cognitive problems in their daily life.

In a previous report of our population-representative cohort followed prospectively from birth, we showed that children who later developed schizophrenia had IQ deficits, and we mapped changes in the specific mental functions that constitute the IQ across four measurement occasions from ages 7 to 13 years (26). Now that this cohort has been followed to age 38 and undergone additional neuropsychological testing, we examined change in IQ, as well as more specific neuropsychological functions, from before (ages 7–13) to after (age 38) the onset of schizophrenia using the same measures across time. In the present study, we tested four hypotheses. First, we tested the "IQ decline" hypothesis to determine whether individuals with schizophrenia experience a decline in IQ from before to after illness onset. We compared the group of individuals with schizophrenia to a psychiatrically healthy group to allow for an accurate interpretation of test-retest performance. Second, we tested the "generalized decline" hypothesis to determine whether decline is apparent broadly across different neuropsychological domains: verbal IQ, performance IQ, learning and memory, processing speed, executive function, and motor function. Third, we tested the "specificity" hypothesis to address whether neuropsychological decline is specific to schizophrenia. We compared neuropsychological decline in schizophrenia to decline in three other groups: a persistent depression group, a mild cognitive impairment group, and a group at risk for schizophrenia. We evaluated neuropsychological decline in individuals with persistent depression to test whether decline is common to other psychiatric disorders. Depression is characterized by neuropsychological impairment (27, 28), but it is not clear whether there is neuropsychological decline from before to after illness onset. We evaluated neuropsychological decline in children with mild cognitive impairment because they, like children with schizophrenia, exhibit cognitive difficulties early in life. However, unlike in schizophrenia, these children do not develop a psychotic condition. We also evaluated neuropsychological decline in "at-risk" individuals who did not develop schizophrenia but who matched those who did on key childhood risk factors (low IQ, family history of psychotic illness, low socioeconomic status). Fourth, we queried third-party informants to test the "everyday cognition" hypothesis that individuals with schizophrenia experience cognitive problems in daily life.

Method

Participants

Participants are members of the Dunedin Multidisciplinary Health and Development Study, a longitudinal investigation of

the health and behavior of a complete birth cohort of consecutive births between April 1, 1972, and March 31, 1973, in Dunedin, New Zealand. The cohort of 1,037 children (91% of eligible births; 52% boys) was constituted at age 3 years. Cohort families represent the full range of socioeconomic status in the general population of New Zealand's South Island and are primarily of white European ancestry. Follow-up assessments were conducted at ages 5, 7, 9, 11, 13, 15, 18, 21, 26, 32, and, most recently, 38 years, when 95% of the 1,007 living study members underwent assessment in the period 2010–2012.

The study protocol was approved by the institutional ethical review boards of the participating universities, and study members gave informed consent before participating.

Schizophrenia

Schizophrenia was assessed at ages 21, 26, 32, and 38. We previously described the schizophrenia cases up to age 32 (26, 29, 30), and here we update this information with data from age 38. DSM criteria for schizophrenia were assessed at each age with the Diagnostic Interview Schedule (DIS) (31, 32). We took several steps to enhance the validity of our research diagnosis. First, we required the presence of hallucinations (not substance use-related) in addition to at least two other positive symptoms. This requirement is stricter than that of DSM-IV, which does not require hallucinations, although requiring them has been shown to reduce overdiagnosis (33). Second, because self-reports can be compromised by poor insight in schizophrenia, we required objective evidence of impairment resulting from psychosis, as reported by informants and as recorded in the study's life-history calendars, which document continuous histories of employment and relationships. Third, in our research, the DIS is administered by experienced clinicians, not lay interviewers. These clinicians record detailed case notes. Our staff also rate observable symptoms manifested in affect, grooming, and speech during the full day that participants spend at our research unit. Fourth, participants bring their medications, which are then classified by a pharmacist. Fifth, informants report study members' positive and negative psychotic symptoms via postal questionnaires. Finally, study members' parents were interviewed about their adult child's psychotic symptoms and treatment as part of the Dunedin Family Health History Study (2003–2005). These data, accumulated in the Dunedin study at ages 21, 26, 32, and 38, were compiled into dossiers reviewed by four clinicians to achieve best-estimate diagnoses with 100% consensus. By age 38, 2% of the cohort (N=20) met criteria for schizophrenia and had, according to the multisource information collected in the dossiers, been hospitalized for schizophrenia (totaling 1,396 days of psychiatric hospitalization, according to official New Zealand administrative record searches) or received prescriptions for antipsychotic medications. An additional 1.7% (N=17) met all criteria for schizophrenia, had hallucinations, and suffered significant life impairment but had not, to our knowledge, been treated specifically for psychotic illness. Together, these two groups constituted a total of 37 cases of diagnosed schizophrenia in the cohort. Of these 37 individuals, four died before the age-38 neuropsychological assessment and two declined to participate, leaving an effective group size of 31 for this study.

Of the 31 individuals in the schizophrenia group, the majority (N=17; 55%) had received treatment specifically for psychotic illness. Of those who, to our knowledge, had not received treatment specifically for psychotic illness, nearly all reported receiving treatment for another mental health problem (Table 2). The two groups appeared similar on a variety of correlates, including adult IQ, personality functioning, substance dependence, and even receipt of government benefits, suggesting that the groups are comparably impaired. The notable exception was that those who had not received treatment for psychotic illness were from families with lower socioeconomic status.

The cohort's 3.7% prevalence rate of schizophrenia is high and should be understood in the context of three methodological aspects of our study. First, our birth cohort, with a 95% participation rate, allows us to count psychotic individuals overlooked by previous surveys because individuals with psychotic disorders often decline to participate in surveys or die prematurely (34), and surveys often exclude homeless or institutionalized individuals with psychosis. Second, our cohort members are all from one city in the South Island of New Zealand. It is possible, given geographical variation in rates of schizophrenia (35–37), that the prevalence is somewhat elevated there. No data exist to compare prevalence rates of schizophrenia in New Zealand to rates in other countries, but the high prevalence of suicide in New Zealand could be consistent with an elevated prevalence of severe mental health conditions (38). Third, our research diagnoses did not make fine-grained distinctions among psychotic disorders (e.g., schizophrenia versus schizoaffective disorder). Thus, the cohort members diagnosed with schizophrenia here might not be considered by all clinicians to have schizophrenia. We note, however, that over half of those we diagnosed were confirmed by receipt of treatment. Moreover, etiological mechanisms appear to be similar across the continuum of psychosis (39).

Persistent Depression

Depression was assessed by DSM criteria at ages 18, 21, 26, 32, and 38 using the DIS. Cohort members who were diagnosed with depression on two or more occasions between ages 18 and 38 were classified into the persistent depression group. We focused on persistent depression in an effort to make this group more comparable to the schizophrenia group in terms of chronicity and severity of illness. Neuropsychological data were incomplete for six of the 191 cohort members in the persistent depression group, leaving an effective group size of 185.

Mild Cognitive Impairment

Individuals with a childhood IQ (averaged across ages 7–13) in the range of 80–89 were considered to have mild cognitive impairment (N=120).

Neuropsychological Functioning

We assessed neuropsychological functioning using tests of IQ, learning and memory, processing speed, executive function, and motor function. Full-scale IQ can be thought of as an omnibus measure of general intellectual ability, because it captures overall ability across differentiable components of intellectual functioning (i.e., verbal IQ and performance IQ). Verbal and performance IQ can be further "unpacked" to make finer-grained distinctions in ability. Learning and memory, processing speed, executive function, and motor function represent even more basic mental functions.

IQ was assessed in childhood at ages 7, 9, 11 and 13 (before the onset of schizophrenia) and again in adulthood at age 38. We report a comparison of scores on the WISC-R (40) and the WAIS-IV (41). Full-scale, verbal, and performance IQ were standardized to population norms with a mean of 100 and a standard deviation of 15; subtest scaled scores were standardized to population norms with a mean of 10 and a standard deviation of 3. Learning and memory, processing speed, executive function, and motor function were each assessed at ages 13 and 38 using, respectively, the Rey Auditory Verbal Learning Test (42), the Trail Making Test (43), and the Grooved Pegboard Test (42). (For details about each test, see

TABLE 2. Comparison of Cohort Members Diagnosed With Schizophrenia Who Had or Had Not Received Treatment for Psychotic Illness

Measure (Age at Assessment)	Treated for Psychosis (N=17)		Not Treated for Psychosis (N=14)		Cohort Norm (N[a]=942–1,031)
	%	95% CI	%	95% CI	%
Mental health treatment (20–38 years)					
Received treatment for a mental health problem	100.00	100.00, 100.00	85.71[b]	57.19, 98.22	46.29
Hospitalized for a mental health problem	58.82	32.92, 81.56	21.43	4.66, 50.80	7.33
Received government benefits (26–38 years)	88.24	63.56, 98.54	92.86	66.13, 99.82	42.01
Persistent substance dependence (18–38 years)					
Tobacco dependence	52.94	27.81, 77.02	64.29	35.14, 87.24	24.13
Alcohol dependence	29.41	10.31, 55.96	28.57	8.39, 58.10	14.96
Cannabis dependence	23.53	6.81, 49.90	28.57	8.39, 58.10	8.87
Hard drug dependence (26–38 years)	0.00	0.00, 0.00	7.14	0.18, 33.87	2.58
	Mean	95% CI	Mean	95% CI	Mean
Full-scale IQ (38 years)	87.16	78.03, 96.29	88.85	79.12, 98.57	100.00
Childhood socioeconomic status[c] (birth–15 years)	–0.02	–0.54, 0.50	–0.57	–1.12, –0.01	0.00
Informant-reported personality[c] (26–38 years)					
Agreeableness	–0.78	–1.50, –0.06	–1.07	–1.51, –0.63	0.00
Conscientiousness	–0.64	–1.08, –0.20	–1.00	–1.75, –0.26	0.00
Extraversion	–0.44	–1.04, 0.15	–0.49	–1.29, 0.32	0.00
Neuroticism	0.93	0.46, 1.41	0.96	0.39, 1.52	0.00
Openness	0.06	–0.57, 0.68	–0.20	–0.96, 0.57	0.00

[a] Ns varied because of different amounts of missing data across study measures.
[b] Based on self-report.
[c] Standardized to cohort (mean=0.00, SD=1.00).

Table S1 in the data supplement that accompanies the online edition of this article.)

Informant-Reported Cognitive Problems

Informant reports of study members' cognitive function were obtained at age 38. Study members nominated people "who knew them well." These informants were mailed questionnaires and asked to complete a checklist, including whether the study member had problems with his or her attention and memory over the past year. The informant-reported attention problems scale consisted of four items: "Is easily distracted, gets sidetracked easily," "Can't concentrate, mind wanders," "Tunes out instead of focusing," and "Has difficulty organizing tasks that have many steps" (internal consistency reliability=0.79). The informant-reported memory problems scale consisted of three items: "Has problems with memory," "Misplaces wallet, keys, eyeglasses, paperwork," and "Forgets to do errands, return calls, pay bills" (internal consistency reliability=0.64). Informant-reported cognitive problems (attention and memory problems combined) were correlated with adult full-scale IQ ($r=-0.22$, $p<0.0001$).

Control Variables

DSM cannabis and alcohol dependence were assessed at ages 18, 21, 26, 32, and 38, and DSM hard drug (e.g., heroin, cocaine, amphetamines) dependence was assessed at ages 26, 32, and 38. Study members who were diagnosed with dependence at two or more assessments were considered persistently dependent on these substances.

Statistical Analysis

We compared the schizophrenia and persistent depression groups to a healthy group (a group of individuals in the cohort who had no current psychiatric disorder; N=518) on change in neuropsychological functioning from childhood to adulthood. Change scores were created by subtracting the childhood test score (averaged across ages 7–13 for the IQ tests and subtests) from the adulthood test score. Negative scores indicate neuropsychological decline. In Tables 4 and 5, childhood and adulthood test scores as well as change scores are presented in standard deviation units (mean=0.00, SD=1.00). Standardized scores reflect effect sizes for how different each group is from the cohort norm. Differences between pairs of groups can also be interpreted as effect sizes. Effect sizes of 0.20, 0.50, and 0.80 reflect small, medium, and large effects, respectively (44). Statistical tests involved planned orthogonal comparisons of each psychiatric group to the healthy group and were adjusted for sex, although results were unchanged when sex was excluded from the model.

Results

IQ Over Time in Schizophrenia

Figure 1A shows that, consistent with findings from meta-analyses, the schizophrenia group evidenced a 9-point IQ deficit in childhood relative to the healthy group, and a 15-point deficit in adulthood. The greater relative deficit in adulthood was due to an average 6-point IQ

decline in the schizophrenia group from childhood to adulthood (from a mean of 93.63 in childhood to 87.92 in adulthood). There was no evidence of IQ decline for the healthy group (from 102.71 in childhood to 102.44 in adulthood), and IQ decline was significantly greater in the schizophrenia group than in the healthy group (p=0.0009). IQ decline in the schizophrenia group was not attributable to current antipsychotic medication use, as an almost 6-point IQ decline (from 95.29 in childhood to 89.88 in adulthood; paired t=2.83, p=0.0094) was still apparent among the 24 individuals who did not use antipsychotic medication during the year before adult neuropsychological testing.

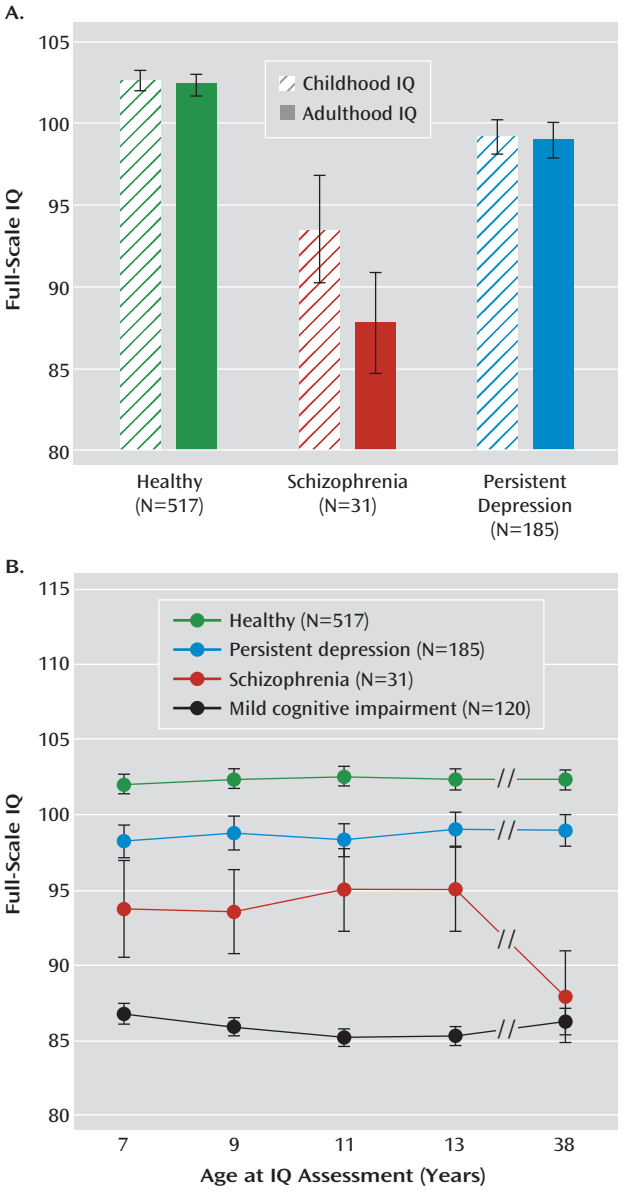
Specificity of IQ Decline to Schizophrenia

Relative to the healthy group, the persistent depression group showed a statistically significant 3-point IQ deficit in both childhood and adulthood (Figure 1A). There was no evidence of IQ decline for the persistent depression group (from 99.30 in childhood to 99.05 in adulthood), and estimates of IQ change for the persistent depression and healthy groups did not differ.

Figure 1B expands the analysis to show that full-scale IQ was relatively stable for the schizophrenia, persistent depression, and healthy groups from ages 7 to 13 but dropped substantially for the schizophrenia group between ages 13 and 38. As a further comparison, we also evaluated IQ decline from childhood to adulthood among children with mild cognitive impairment and children at risk for developing schizophrenia. Children with mild cognitive impairment are of interest because, like children with schizophrenia, they exhibit cognitive difficulties early in life, but unlike those with schizophrenia, they do not develop a psychotic condition. Figure 1B shows that, in contrast to children who develop schizophrenia, children with mild cognitive impairment did not show evidence of IQ decline.

Next, we used data from our cohort to match schizophrenia cases to "at-risk" individuals who did not develop schizophrenia but who shared key childhood risk factors with schizophrenia cases. Low IQ, low socioeconomic status, and a family history of schizophrenia are well-established risk factors for developing schizophrenia (45–47). We used propensity score matching to identify individuals who matched our schizophrenia cases on these risk factors but did not develop psychotic illness (Table 3). IQ decline was not apparent among individuals at risk for schizophrenia. The at-risk group, with a childhood liability to develop schizophrenia similar to that of members of the schizophrenia group, showed an IQ decline of 0.01 standard deviations, whereas the schizophrenia group showed a decline of 0.39 standard deviations. Thus, at-risk children who did not develop schizophrenia showed less IQ decline than their matched counterparts who did (F=8.57, df=1, 91, p=0.0043). In sum, IQ decline was unique to those diagnosed with schizophrenia.

FIGURE 1. IQ in Childhood and Adulthood in Individuals With Schizophrenia, Persistent Depression, or Mild Cognitive Impairment and Healthy Comparison Subjects[a]



[a] Panel A shows full-scale IQ in childhood (averaged across ages 7–13) and adulthood (age 38) for the healthy, schizophrenia, and persistent-depression groups. There was a statistically significant difference (paired t=3.29, p=0.003) between childhood and adulthood IQ for members of the schizophrenia group. Panel B shows full-scale IQ in childhood (ages 7, 9, 11, and 13) and adulthood (age 38) for the healthy, schizophrenia, and persistent-depression groups as well as a group of children with mild cognitive impairment. IQ was stable across childhood for all groups but declined for the schizophrenia group between ages 13 and 38. Error bars indicate standard error.

Decline Across Mental Functions

Table 4 lists test scores (in standard deviation units) in childhood and adulthood for the healthy, schizophrenia, and persistent depression groups on a range of mental functions: IQ (and the subtests of different cognitive abilities

TABLE 3. Mean Scores on Childhood Risk Factors for Cohort Members Who Did (Case) or Did Not (Control) Develop Schizophrenia, Before and After Propensity Score Matching[a]

	Before Matching			After Matching		
Childhood Risk Factor (Age at Assessment)	Case Subjects (N=31)	Control Subjects (N=875)	Standardized Bias (%)	Case Subjects (N=31)	Control Subjects (N=62)	Standardized Bias (%)
Full-scale IQ (7–13 years)	93.63	101.05	46	93.63	93.89	0
Performance IQ (7–13 years)	94.64	100.97	39	94.64	94.80	0
Verbal IQ (7–13 years)	93.64	101.04	40	93.64	94.03	2
Family history of psychotic illness[b]	0.25	–0.01	23	0.25	0.29	–3
Socioeconomic status[b] (birth–15 years)	–0.27	0.04	31	–0.27	–0.31	–5
Average standardized bias			36			–1

[a] We used propensity score matching to perform the match using SAS (SAS, Inc., Cary, N.C.). First, we obtained propensity scores via a logistic regression predicting likelihood of developing schizophrenia based on the childhood correlates listed here. Next, we performed an optimal 2-to-1 (control-to-case) match on these propensity scores, whereby matches were made on the basis of the absolute difference in propensity score between case and control subjects. The maximum absolute difference was set to 0.10. Results were similar across models with different match parameters (i.e., varied number of case subjects matched to control subjects, varied maximum absolute difference). A total of 906 study members (31 case subjects and 875 control subjects) were available for matching, as analyses required nonmissing values for all childhood risk factors. The table shows that matching resulted in a high degree of similarity in the distributions of the childhood risk factors across case and control subjects, as standardized bias after matching was below 10 for each risk factor. Negative standardized bias values indicate higher risk in the control group.
[b] Standardized to cohort (mean=0.00, SD=1.00).

TABLE 4. Neuropsychological Decline Across Different Mental Functions in Individuals With Schizophrenia or Persistent Depression and Healthy Comparison Subjects[a]

	Healthy Group (N=518)			Schizophrenia Group (N=31)			Persistent Depression Group (N=185)		
Neuropsychological Test	Child	Adult	Δ	Child	Adult	Δ	Child	Adult	Δ
Full-scale IQ	0.18	0.16	–0.02	–0.42[b]	–0.81[b]	–0.39[b]	–0.04[b]	–0.06[b]	–0.02
Performance IQ	0.15	0.15	0.00	–0.36[b]	–0.90[b]	–0.54[b]	–0.02[b]	–0.06[b]	–0.04
Digit symbol coding subtest	0.09	0.10	0.01	–0.22	–0.98[b]	–0.76[b]	0.09	0.02[b]	–0.07
Block design subtest	0.14	0.09	–0.05	–0.25[b]	–0.63[b]	–0.38[b]	–0.02	–0.01	0.01
Picture completion subtest	0.12	0.10	–0.02	–0.44[b]	–0.63[b]	–0.19	–0.04	–0.03	0.01
Verbal IQ	0.17	0.14	–0.03	–0.42[b]	–0.67[b]	–0.25	–0.05[b]	–0.06	–0.01
Information subtest	0.17	0.14	–0.03	–0.28[b]	–0.33[b]	–0.05	–0.05	–0.11	–0.06
Similarities subtest	0.14	0.07	–0.07	–0.42[b]	–0.45[b]	–0.03	–0.01	0.12	0.13[b]
Vocabulary subtest	0.16	0.11	–0.05	–0.36[b]	–0.48[b]	–0.12	–0.04[b]	0.01	0.05
Arithmetic subtest	0.18	0.15	–0.03	–0.45[b]	–0.66[b]	–0.21	–0.08[b]	–0.16[b]	–0.08
Rey total recall	0.08	0.05	–0.03	–0.41[b]	–0.88[b]	–0.47[b]	0.06	0.10	0.04
Rey delayed recall	0.08	0.06	–0.02	–0.37[b]	–0.38[b]	–0.01	0.06	0.10	0.04
Trails A (time in seconds)[c]	–0.01	–0.07	–0.06	0.24	0.73[b]	0.49[b]	0.06	0.01	–0.05
Trails B (time in seconds)[c]	–0.10	–0.11	–0.01	0.69[b]	1.21[b]	0.52[b]	0.08[b]	–0.05	–0.13
Grooved Pegboard Test (time in seconds)[c]	–0.07	–0.11	–0.04	0.37[b]	1.04[b]	0.67[b]	0.01	–0.04[b]	–0.05

[a] The table lists mean childhood and adulthood neuropsychological test scores (in standard deviation units) for each group. The change column (Δ) indicates the change in test scores (in standard deviation units) from childhood to adulthood. Statistical tests are adjusted for sex. Ns for the IQ subtests range from 514 to 518 for the healthy group, 30 to 31 for the schizophrenia group, and 184 to 185 for the persistent depression group. A subset of cohort members completed IQ testing in childhood but did not complete the Rey Auditory Verbal Learning Test, the Trail Making Test (parts A and B), or the Grooved Pegboard Test in childhood; for these tests, the Ns are 384–393 for the healthy group, 21–22 for the schizophrenia group, and 138–140 for the persistent depression group. There were no significant differences in IQ decline between those who completed these tests and those who did not, either for the cohort as a whole or for the healthy, schizophrenia, or persistent depression groups.
[b] Significant difference ($p<0.05$) compared with the healthy group.
[c] Higher scores on these tests indicate worse performance. Positive change scores on these tests reflect decline in performance from childhood to adulthood.

that constitute the IQ), learning (total recall on the Rey Auditory Verbal Learning Test), delayed memory (delayed recall on the Rey test), processing speed (Trails A), executive function (Trails B), and motor function (Grooved Pegboard Test). Table 4 also indicates the change in test performance (in standard deviation units) from childhood to adulthood.

Relative to the healthy group, the schizophrenia group showed significantly greater decline on all mental functions except verbal IQ and delayed memory (Rey delayed recall). Inspection of the means suggests that the greatest declines occurred for processing speed (digit symbol coding, Trails A), learning (Rey total recall), executive

function (Trails B), and motor function (Grooved Pegboard Test). By comparison, the persistent depression group generally did not show neuropsychological decline on any mental function.

Figure 2 expands the analysis to show that the progression of neuropsychological deficits from ages 7 to 38 varies across mental functions. Given our earlier report that children who later develop schizophrenia show developmental lags from ages 7 to 13 in processing speed, working memory, and attention but static deficits in verbal abilities (26), we elected to show results for the two IQ subtests most representative of these processes: the digit symbol coding test and the similarities test. Figure 2A shows that deficits on the digit symbol coding test were not apparent at age 7 but emerged gradually from ages 7 to 38. Figure 2B shows that deficits on the similarities test emerged by age 7 but remained relatively stable from ages 7 to 38.

Possible Alternative Explanations for the Neuropsychological Decline

We ruled out three alternative explanations for the observed association between schizophrenia and neuropsychological decline, namely, that these effects could be explained by cannabis dependence, alcohol dependence, or hard drug dependence. We recalculated the mean change in full-scale IQ for the healthy, schizophrenia, and persistent depression groups, excluding individuals with each form of substance dependence. We elected to show results only for full-scale IQ for this analysis because this measure captures overall intellectual functioning. Table 5 shows that excluding individuals with each form of substance dependence did not alter the initial finding; effect sizes, representing within-person IQ change, remained virtually the same and remained statistically significant. Moreover, even after statistically adjusting IQ change scores for cannabis, alcohol, and hard drug dependence conjointly, members of the schizophrenia group still showed a significantly greater IQ decline than members of the healthy group (mean decline, 0.34 standard deviations and 0.03 standard deviations, respectively; p=0.005).

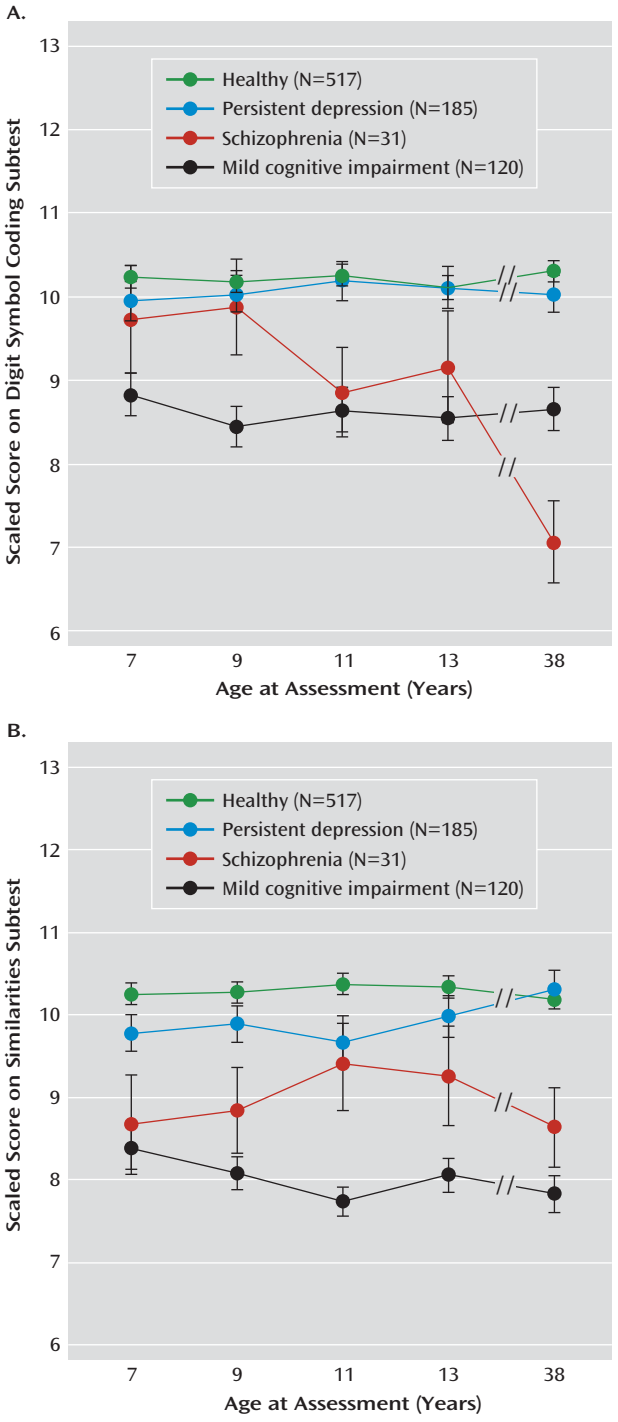
Impairment in Everyday Cognition

Table 6 summarizes ratings of informant-reported attention and memory problems (in standardized units) for each group at age 38. Members of the schizophrenia group were rated 1.00 and 0.95 standard deviations above the cohort mean on attention and memory problems, respectively, whereas members of the healthy group were rated 0.18 and 0.16 standard deviations below the mean. By comparison, informants reported less pronounced attention and memory problems for the persistent depression group.

Discussion

This study provides evidence of neuropsychological decline in schizophrenia from before to after illness onset

FIGURE 2. Scaled Scores on Subtests of the WISC-R and WAIS-IV IQ in Individuals With Schizophrenia, Persistent Depression, or Mild Cognitive Impairment and Healthy Comparison Subjects[a]



[a] Panel A shows scaled scores (population mean=10.00, SD=3.00) on the Wechsler digit symbol coding subtest from age 7 to age 38. The deficit among individuals with schizophrenia increased from ages 7 to 38. Panel B shows scaled scores (population mean=10.00, SD = 3.00) on the Wechsler similarities subtest from age 7 to age 38. The deficit among individuals with schizophrenia was apparent as early as age 7 and remained relatively stable from age 7 to age 38. Error bars indicate standard error.

TABLE 5. Ruling Out Alternative Explanations for the Observed Neuropsychological Decline in Schizophrenia[a]

	Healthy Group		Schizophrenia Group			Persistent Depression Group		
Test	Δ IQ	N	Δ IQ	N	p	Δ IQ	N	p
Full-scale IQ	–0.02	517	–0.39	31	<0.001	–0.02	185	0.98
Excluding those with:								
Persistent cannabis dependence	–0.01	497	–0.41	23	0.002	0.01	162	0.72
Persistent alcohol dependence	–0.01	476	–0.32	22	0.011	0.00	141	0.86
Persistent hard drug dependence	–0.01	512	–0.37	30	0.001	–0.01	178	0.89

[a] Mean change in IQ from childhood to adulthood is listed in standard deviation units. Statistical tests compare each psychiatric group to the healthy group and are adjusted for sex.

TABLE 6. Cognitive Impairment in Everyday Life in Individuals With Schizophrenia or Persistent Depression and Healthy Comparison Subjects[a]

	Healthy Group (N=508)	Schizophrenia Group (N=30)		Persistent Depression Group (N=182)	
Informant-Reported Cognitive Problem	Mean	Mean	p	Mean	p
Attention problems	–0.18	1.00	<0.001	0.11	<0.001
Memory problems	–0.16	0.95	<0.001	0.09	<0.001

[a] Age-38 informant-reported attention and memory problem ratings are listed in standard deviation units. Statistical tests compare each psychiatric group to the healthy group and are adjusted for sex.

in a population-based birth cohort of individuals followed prospectively from birth to age 38. This finding is consistent with previous longitudinal studies showing evidence of neuropsychological decline in schizophrenia (11–16, 18–20).

This study advances knowledge in several ways. First, previous longitudinal studies have focused almost exclusively on IQ. We showed that individuals with schizophrenia experienced declines in IQ as well as in a range of different mental functions, particularly those tapping processing speed, learning, executive function, and motor function. Decline was greatest on the digit symbol coding test, which is consistent with research suggesting that this test, more so than other neuropsychological tests, taps a core impairment in schizophrenia and may reflect network integration problems (48). Decline was not ubiquitous across all mental functions, however. There was little evidence of decline in verbal IQ or delayed memory. Impaired verbal IQ and delayed memory among cohort adults diagnosed with schizophrenia could be traced back to childhood deficits that remained relatively stable across development. These findings highlight the importance of "unpacking" measures of generalized intellectual functioning, such as IQ, into more specific mental functions.

Second, we showed that neuropsychological decline was relatively specific to schizophrenia, as there was no evidence of decline among individuals in key comparison groups: children with mild cognitive impairment, at-risk children who did not develop schizophrenia, and individuals diagnosed with persistent depression. Research on the association between depression and neuropsychological decline has focused mainly on older adults and has yielded inconsistent findings, with some studies finding no association between depression and accelerated neuropsychological decline (49, 50) and others finding a positive association (51). Ours is the first study, to our knowledge, to examine depression-associated changes in neuropsychological functioning from before to after illness onset in a relatively young cohort. Notably, in our study, individuals with persistent depression performed worse than healthy individuals on a handful of neuropsychological tests in adulthood and were rated by informants as having more cognitive problems as adults than healthy individuals. Neuropsychological test deficits, however, were apparent from childhood, consistent with the interpretation that lower IQ constitutes a risk for depression (52, 53).

Third, our findings suggest that neuropsychological decline in individuals with schizophrenia is nontrivial. Estimates of decline ranged from 1/3 to 3/4 of a standard deviation unit more than average for the healthy group on tests tapping processing speed, learning, attention, working memory, and motor function. Moreover, cognitive impairment in individuals diagnosed with schizophrenia was apparent in everyday life, as third-party informants noticed substantially more attention and memory problems in adults diagnosed with schizophrenia.

The results of this study should be viewed in the context of its limitations. First, although we found evidence of neuropsychological decline in schizophrenia from before to after illness onset, we could not fully map the developmental progression of neuropsychological deficits in schizophrenia from childhood to adulthood (funding agencies were unwilling to support repeated intellectual testing between ages 13 and 38). Nonetheless, we examined how deficits progressed from ages 7 to 13 for different

mental functions and linked these deficits to data obtained at age 38. Deficits on the digit symbol coding test were not apparent at age 7 but increased gradually from ages 7 to 13, and by age 38, individuals with schizophrenia scored 1.08 standard deviations below the healthy group on this test. Notably, in an earlier report of the ages 7–13 neuropsychological test data (26), we showed that children who would later develop schizophrenia exhibited slowed growth in performance on the digit symbol coding test, and based on this trajectory of slowed growth, we predicted the adulthood deficit of >1 standard deviation that we report here. This suggests that the "decline" in processing speed that we observed reflects a gradual, progressive process of slowed growth in this mental function that begins in childhood and continues beyond the early teen years. Exactly when in childhood the deficit in processing speed becomes evident is difficult to pinpoint, as at least two other studies have reported statistically significant deficits on the digit symbol coding test at approximately age 7 (12, 54). Conversely, we showed that deficits on the similarities test emerged early but remained relatively static from age 7 through midlife. These findings imply that different pathophysiological mechanisms underlie the various neuropsychological deficits observed in schizophrenia patients.

A second limitation is that our findings are based on a relatively small group of individuals diagnosed with schizophrenia. The small group size prevented us from conducting an in-depth exploration of heterogeneity in neuropsychological decline. However, given reports of schizophrenia patients with IQs in the normal range (55, 56) and the presumption that these patients have escaped neuropsychological decline, we asked if any of the individuals with schizophrenia in our cohort fit this profile. Of the 31 individuals diagnosed with schizophrenia, three individuals had both a childhood IQ of >100 and an IQ decline of <3.19 IQ points (the standard error of measurement of the WISC-R). While one of these three individuals performed in the normal range on all adult neuropsychological tests, each showed decline on the digit symbol coding test (mean=−0.88 standard deviations), suggesting that decline in processing speed is a core feature of schizophrenia. These findings further suggest that average to above-average neuropsychological test performance in a subset of adults diagnosed with schizophrenia cannot be used to infer that neuropsychological decline has not occurred. Rather, prospective baseline tests of neuropsychological functioning are necessary to document decline.

A third limitation concerns three unusual aspects of our sample that may limit the generalizability of our findings. First, the prevalence of schizophrenia is high. As we discussed earlier, this may be explained in part by a combination of our comprehensive repeated-measurement ascertainment strategy, high retention rates, and geographical variation. Second, a portion of individuals diagnosed with schizophrenia had not, to our knowledge, received treatment specifically for psychotic illness. These individuals had, however, come into contact with the mental health care system and were virtually indistinguishable on a variety of correlates from those who had been treated for psychotic illness. The one exception was that those who had not received treatment specifically for psychotic illness were from families of lower socioeconomic status, which might reflect an association between socioeconomic status and quality of care. Third, most individuals with schizophrenia were not taking antipsychotic medication in the year before adult testing. While this increases confidence that neuropsychological decline between ages 7–13 and age 38 is not due to recent antipsychotic medication use, it raises the question of whether our results are generalizable to patients currently taking antipsychotic medication. We noted very little difference in IQ decline between those who were (N=7; IQ decline, ~7 IQ points) and those who were not (N=24; IQ decline, ~6 points) taking antipsychotic medication in the year before testing. Bolstering the generalizability of our findings is the fact that our estimates of the IQ deficit in both childhood (9 points) and adulthood (15 points) precisely match estimates from meta-analyses of the premorbid IQ deficit in schizophrenia (3) and the IQ deficit in first-episode schizophrenia (1, 4).

This study has a number of implications. First, the results suggest that individuals diagnosed with schizophrenia experience neuropsychological decline from before to after illness onset. Second, however, the extent of decline and the developmental progression of decline varies considerably across mental functions that can be generally organized as fluid and crystallized abilities. Fluid abilities (e.g., processing speed, learning, executive function) showed the most substantial decline, with deficits in processing speed, for example, increasing gradually from childhood to beyond the early teen years. In contrast, crystallized abilities (e.g., verbal IQ) did not decline. Rather, these deficits were already apparent in childhood and remained static through midlife. This suggests that different pathophysiological mechanisms underlie the deficits in fluid and crystallized abilities seen in adult schizophrenia patients. Moreover, the findings highlight the fact that a substantial proportion of the neuropsychological deficits seen in adult schizophrenia patients is apparent before the onset of puberty, and future research on the emergence of neuropsychological deficits in schizophrenia should target early childhood to ascertain deficits in crystallized abilities and later childhood to ascertain deficits in fluid abilities. Finally, pharmacological and cognitive remediation therapies should target neuropsychological functioning as well as cognitive impairment in everyday life (57), as treatment strategies that target both outcomes may have the greatest chances of success (58).

Received Nov. 19, 2012; revisions received April 14 and May 23, 2013; accepted June 3, 2013 (doi: 10.1176/appi.ajp.2013.12111438). From the Department of Psychology and Neuroscience, Duke University, Durham, N.C.; the Duke Transdisciplinary Prevention Research Center, Center for Child and Family Policy, Duke University, Durham; the Institute for Genome Sciences and Policy, Duke University, Durham; the Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham; the Department of Psychosis Studies and the Social, Genetic, and Developmental Psychiatry Centre, Institute of Psychiatry, King's College London; and the Dunedin Multidisciplinary Health and Development Research Unit, Department of Preventive and Social Medicine, School of Medicine, University of Otago, Dunedin, New Zealand. Address correspondence to Dr. Moffitt (terrie.moffitt@duke.edu).

Dr. Keefe has received investigator-initiated research funding support from the Department of Veterans Affairs, Feinstein Institute for Medical Research, GlaxoSmithKline, NIMH, Novartis, Psychogenics, Research Foundation for Mental Hygiene, and Singapore National Medical Research Council; he has received honoraria from or served as a consultant or advisory board member for Abbott, Akebia, Amgen, Astellas, Asubio, BiolineRx, Biomarin, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly, EnVivo, Helicon, Lundbeck, Merck, Mitsubishi, Novartis, Otsuka, Pfizer, Roche, Shire, Sunovion, Takeda, and Targacept; he receives royalties for the BACS testing battery and the MATRICS Battery (BACS Symbol Coding) and is a shareholder in NeuroCog Trials. The other authors report no financial relationships with commercial interests.

Supported in part by the National Institute on Aging (grant AG032282) and the U.K. Medical Research Council (grant MR/K00381X). The Dunedin Multidisciplinary Health and Development Research Unit is supported by the New Zealand Health Research Council. Dr. Meier was supported by National Institute on Drug Abuse grant P30 DA023026 and by the Jacobs Foundation.

The authors thank the Dunedin Study members, their families, the Dunedin Multidisciplinary Health and Development Research Unit staff, and study founder Phil Silva.

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