

The Course of General Cognitive Ability in Individuals With Psychotic Disorders

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 Supplemental content

IMPORTANCE Schizophrenia is associated with major cognitive deficits and has been conceptualized as both a neurodevelopmental and a neurodegenerative disorder. However, when deficits develop and how they change over the course of illness is uncertain.

OBJECTIVE To trace cognition from elementary school to old age to test neurodevelopmental and neurodegenerative theories of psychotic disorders.

DESIGN, SETTING, AND PARTICIPANTS Data were taken from the Suffolk County Mental Health Project, a first-admission longitudinal cohort study of individuals with psychotic disorders. Participants were recruited from all 12 inpatient psychiatric facilities in Suffolk County, New York. This analysis concerns the 428 participants with at least 2 estimates of general cognitive ability. Data were collected between September 1989 and October 2019, and data were analyzed from January 2020 to October 2021.

EXPOSURES Psychiatric hospitalization for psychosis.

MAIN OUTCOMES AND MEASURES Preadmission cognitive scores were extracted from school and medical records. Postonset cognitive scores were based on neuropsychological testing at 6-month, 24-month, 20-year, and 25-year follow-ups.

RESULTS Of the 428 included individuals (212 with schizophrenia and 216 with other psychotic disorders), 254 (59.6%) were male, and the mean (SD) age at psychosis onset was 27 (9) years. Three phases of cognitive change were observed: normative, declining, and deteriorating. In the first phase, cognition was stable. Fourteen years before psychosis onset, those with schizophrenia began to experience cognitive decline at a rate of 0.35 intelligence quotient (IQ) points per year (95% CI, 0.29-0.42; $P < .001$), a significantly faster decline than those with other psychotic disorders (0.15 IQ points per year; 95% CI, 0.08-0.22, $P < .001$). At 22 years after onset, both groups declined at a rate of 0.59 IQ points per year (95% CI, 0.25-0.94; $P < .001$).

CONCLUSIONS AND RELEVANCE In this cohort study, cognitive trajectories in schizophrenia were consistent with both a neurodevelopmental and neurodegenerative pattern, resulting in a loss of 16 IQ points over the period of observation. Cognitive decline began long prior to psychosis onset, suggesting the window for primary prevention is earlier than previously thought. A window for secondary prevention emerges in the third decade of illness, when cognitive declines accelerate in individuals with schizophrenia and other psychotic disorders.

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Cognitive deficits are common in individuals with schizophrenia and highly disabling.¹ Indeed, schizophrenia has been alternatively conceptualized as a neurodevelopmental disorder or a neurodegenerative disorder. The neurodevelopmental model posits cognitive deficits emerge because of disruptions in brain development, marking the beginning of a disease process that ends in psychosis.² The neurodegenerative model conceptualizes illness as the result of progressive deterioration.³ The former predicts cognitive deficits stabilize after illness onset, while the latter implies cognitive declines continue.

Despite well-established theories, a great deal remains unknown about when cognitive deficits emerge and how they change over the illness course. Those who develop schizophrenia have a premorbid intelligence quotient (IQ) deficit of approximately half a standard deviation.⁴⁻⁶ By the first episode, this deficit increases to 1 SD.^{7,8} Surprisingly, longitudinal studies of ultrahigh risk and prodromal cohorts have not detected cognitive change among those who develop psychotic disorders.^{9,10} Small population-based studies including less than 40 participants have reported a slowed cognitive development among those who develop schizophrenia.^{11,12} However, these studies examined cognitive trajectories relative to chronological age, rather than illness onset. Since age at illness onset varies widely, these studies may have limited power to detect the cognitive changes accompanying schizophrenia onset. As a result, when and how cognitive deficits develop in individuals with schizophrenia are not well understood.

The course of cognition after schizophrenia onset is also debated. Longitudinal studies have generally found cognition is stable over the first 5 years of illness.^{13,14} Some studies have even reported cognition improves over time.¹⁵ In contrast, long-term population-based studies observed cognitive declines. Two 10-year follow-ups have shown cognitive decline in individuals with schizophrenia is accelerated,^{16,17} and a 20-year follow-up confirmed this finding.¹⁸ Another 20-year longitudinal study reported no decline, but it was limited to 2 tests of specific abilities and had younger participants.¹⁹ In sum, evidence is mixed but suggests a slow cognitive decline after schizophrenia onset. Studies with longer follow-ups and more frequent assessments, particularly in late adulthood, are needed to detect these changes.

Individuals with psychotic disorders other than schizophrenia also show cognitive deficits, although limited longitudinal data makes it difficult to ascertain when deficits emerge.^{20,21} Those who develop bipolar disorder and other psychotic disorders appear to have normal premorbid IQ,^{22,23} but deficits emerge by illness onset and are half as large as deficits seen in schizophrenia.²⁴ Ten-year follow-ups of individuals with bipolar disorder and other psychotic disorders produced inconsistent evidence of deterioration.^{16,17,25,26} Twenty-year follow-ups also produced conflicting results,^{18,19} although the larger study reported cognitive decline. Altogether, evidence suggests those with other psychotic disorders develop cognitive deficits before illness onset. These impairments are smaller than in schizophrenia and remain stable through the first decade of illness but may worsen in later illness phases.

Key Points

Question When do major cognitive deficits emerge among individuals with schizophrenia and other psychotic disorders, and how do they change over the course of illness?

Finding This cohort study traced general cognitive ability in 428 individuals with psychotic disorders, for whom 1619 estimates of general cognitive ability spanning from childhood to old age were available. Cognitive decline began 14 years before the onset of psychosis and was more rapid in those with schizophrenia than in those with other psychotic disorders until 22 years after psychosis onset, at which point cognitive decline accelerated in both groups.

Meaning In this study, the trajectory of general cognitive ability in schizophrenia was consistent with both a neurodevelopmental and neurodegenerative disorder.

To our knowledge, no study has charted cognitive trajectories of individuals with schizophrenia and other psychotic disorders across the life span. Observing individuals across long periods of time is necessary to identify when cognitive decline begins and how it progresses across the illness course. This study's purpose was to trace cognition from elementary school to old age to test neurodevelopmental and neurodegenerative theories of psychotic disorders.

Methods

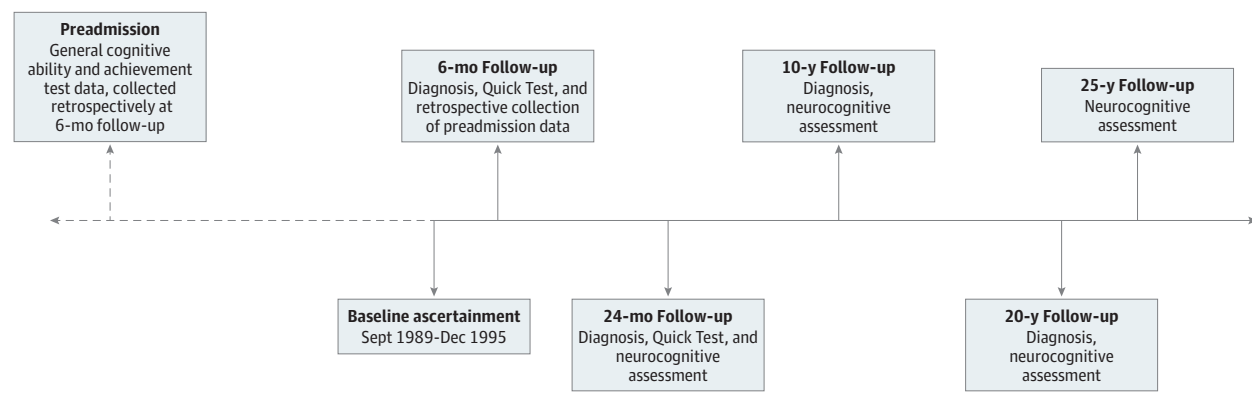
This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.²⁷ Figure 1 depicts a schematic of the study design. eFigure 1 in the Supplement depicts an inclusion flowchart. The Stony Brook University Committee on Research Involving Human Subjects and hospital institutional review boards approved the protocol annually. Written informed consent was obtained from all study participants or from the parents of minors.

Sample and Procedure

Data are drawn from the Suffolk County Project, a longitudinal first-admission psychosis study.²⁸ During the enrollment period (1989 to 1995), individuals in their first admission for psychotic symptoms were recruited from all 12 inpatient facilities in Suffolk County, New York. The response rate during this wave was 72%. Eligibility criteria included residence in Suffolk County, age of 15 to 60 years, ability to speak English, no diagnosis of intellectual disability, first admission within the past 6 months, current psychosis, no apparent medical etiology for psychotic symptoms, and capacity to provide informed consent.

A total of 628 individuals were ascertained at baseline (eMethods 1 in the Supplement). Analyses are based on the 428 individuals with at least 2 estimates of general cognitive ability. Table 1 reports descriptive statistics for this subset. Compared with the full cohort, this subgroup had a slightly younger age at onset, although they did not differ by other demographic factors or cognitive ability (eTable 1 in the Supplement). eFigure 2 in the Supplement depicts histograms show-

Figure 1. Overview of Study Design and Data Completed at Each Time Point



ing the 10 most common patterns of available data. At 20-year follow-up, a demographically matched comparison group was recruited using random digit dialing within zip codes where participants with psychotic disorders resided (for details see Velthorst and colleagues³¹).

Measures

Demographic Characteristics

Occupational status was rated on the Hollingshead scale, which ranges from 1 (“large business owner/major professional/executive”) to 8 (“not working”).²⁹ Ratings were based on the occupation of the primary earner in the participant’s household.

Age at Onset

Age at psychosis onset was determined based on symptom timelines obtained during first admission and 6-month follow-up diagnostic interviews conducted using the Structured Clinical Interview for *DSM-III* at baseline and Structured Clinical Interview for *DSM-IV* thereafter. This information was supplemented by informant interviews, school records, and medical records (see Jonas and colleagues³² for details).

Diagnosis

Research diagnoses were made by consensus of study psychiatrists at the 6-month, 24-month, 10-year, and 20-year follow-ups using all available information, including medical records, significant other interviews, and diagnostic interviews. The diagnostic process is outlined in Bromet and colleagues.³³ Analyses used the last available diagnosis for each participant. The cohort was divided into those with schizophrenia spectrum disorders ($n = 216$), including schizophrenia and schizoaffective disorders, and those with other psychotic disorder ($n = 212$), including bipolar disorder ($n = 106$), major depression ($n = 43$), substance-induced ($n = 30$), and not otherwise specified ($n = 33$) psychotic disorders.

Cognition

Preadmission cognitive ability was assessed by collecting data from participants’ school records. When IQ scores were not available, academic achievement scores were substituted. Prior

research has shown scores on achievement tests are closely correlated with IQ (r of approximately 0.7 to 0.8).³⁴ Those with preadmission cognitive data were younger at symptom onset and baseline assessment, because preadmission data were collected retrospectively, and participants who were younger at study entry were more likely to have school records available. Some participants had preadmission scores at multiple ages across childhood and adolescence, for a total of 436 IQ scores from 218 individuals. eTable 2 in the Supplement reports specific test frequencies by diagnostic group.

Postonset cognitive ability was assessed at 6-month, 24-month, 20-year, and 25-year follow-up interviews. At 6-month and 24-month follow-up assessments, IQ was assessed using the Quick Test.^{35,36} At 24-month, 20-year, and 25-year follow-up assessments, the cognitive battery included immediate trials of Verbal Paired Associates and Visual Reconstruction,³⁷ Symbol-Digit Modalities,³⁸ Trails A and B,³⁹ the Controlled Oral Word Association Test,⁴⁰ Vocabulary,⁴¹ and the Stroop Test.⁴² Altogether, 1619 estimates of cognitive ability were available across the life span. The comparison group completed the same neuropsychological assessment as individuals with schizophrenia and other psychotic disorders.

All test scores were converted to the IQ scale (mean [SD], 100 [15]). Details of the conversion are reported in the eMethods 2 in the Supplement. Using the same scoring and rescaling procedure applied to individuals with schizophrenia and other psychotic disorders, we estimated IQ scores for the comparison group at 20-year and 25-year follow-ups. eTable 3 in the Supplement reports correlations and pairwise numbers of scores across time points. Table 1 reports descriptive statistics of general cognitive ability on the IQ scale across time points.

Statistical Analysis

Cognitive trajectories were estimated using multilevel models with random intercepts to account for individual differences in mean IQ. Residuals were given a first-order autocorrelation structure with time as a continuous covariate. Four models were compared: a linear model, a quadratic model, and spline models with 1 or 2 transition points where trajectory direction changes. A model with 1 transition includes 2 phases

Table 1. Descriptive Statistics

Measure	Schizophrenia (n = 216)	Other psychotic disorders (n = 212)
Sex, No. (%)		
Female	76 (35.2)	98 (46.2)
Male	140 (64.8)	114 (53.8)
Race and ethnicity, No. (%)		
American Indian	0	1 (0.5)
Asian	8 (3.7)	2 (0.9)
Black	37 (17.1)	20 (9.4)
Hispanic	18 (8.3)	12 (5.7)
White	153 (70.8)	177 (83.5)
Occupational status ^a		
Median (range)	4 (1-8)	4 (1-8)
Mean (SD)	4.6 (2.1)	4.2 (1.8)
Age at psychosis onset, y		
Median (range)	24 (6-58)	27 (5-58)
Mean (SD)	25.7 (7.9)	28.7 (9.9)
Symptoms and functioning at baseline assessment		
GAF		
Median (range)	50.5 (21-81)	65 (30-85)
Mean (SD)	52.6 (14.3)	63.7 (11.9)
SAPS		
Hallucinations and delusions ^b		
Median (range)	9.5 (0-52)	8 (0-36)
Mean (SD)	11.5 (9.5)	9.4 (9.5)
Disorganization ^b		
Median (range)	5 (0-38)	5 (0-28)
Mean (SD)	6.7 (6.4)	6.4 (6.4)
SANS		
Avolition ^b		
Median (range)	8 (0-29)	5.5 (0-29)
Mean (SD)	9.4 (7.2)	6.9 (7.2)
Inexpressivity ^b		
Median (range)	4 (0-36)	2 (0-30)
Mean (SD)	6.9 (7.8)	4.8 (7.8)
Antipsychotic medication use, No. (%) ^c		
Preadmission	0	0
6 mo	190 (94.5)	122 (63.9)
24 mo	169 (91.8)	71 (40.6)
20 y	113 (93.3)	38 (36.5)
25 y	96 (92.3)	46 (44.2)
General cognitive ability (expressed on the IQ scale)		
Preadmission 1 ^d		
No.	104	112
Median (range)	101 (53-136)	104 (62-131)
Mean (SD)	100.0 (15.9)	103.2 (13.6)
Preadmission 2 ^d		
No.	56	61
Median (range)	100 (42-128)	100 (59-140)
Mean (SD)	98.7 (16.9)	99.7 (13.2)

(continued)

Table 1. Descriptive Statistics (continued)

Measure	Schizophrenia (n = 216)	Other psychotic disorders (n = 212)
Preadmission 3 ^d		
No.	30	35
Median (range)	97 (67-135)	98 (75-135)
Mean (SD)	97.6 (16.7)	99.2 (12.5)
Preadmission 4 ^d		
No.	17	14
Median (range)	92 (67-126)	95 (74-114)
Mean (SD)	94.8 (15.3)	95.6 (10.9)
Preadmission 5 ^d		
No.	6	1
Median (range)	90 (64-102)	89 (89-89)
Mean (SD)	86.0 (13.2)	89.0 (NA)
6 mo		
No.	201	191
Median (range)	96 (60-130)	100 (42-130)
Mean (SD)	95.3 (14.4)	98.9 (13.2)
24 mo		
No.	184	175
Median (range)	92 (57-117)	102 (43-121)
Mean (SD)	90.9 (12.3)	99.0 (11.6)
20 y		
No.	121	104
Median (range)	87 (50-116)	98 (47-115)
Mean (SD)	85.6 (13.9)	95.5 (13.0)
25 y		
No.	104	104
Median (range)	83 (53-109)	96 (56-119)
Mean (SD)	83.0 (12.6)	93.8 (12.8)

Abbreviations: GAF, Global Assessment of Function; NA, not applicable; SANS, Schedule for the Assessment of Negative Symptoms; SAPS, Schedule for the Assessment of Positive Symptoms.

^a Occupational status was quantified as the occupation of the primary earner in the participants' household, rated on the Hollingshead rating, a scale from 1 ("large business owner/major professional/executive") to 8 ("not working").²⁹

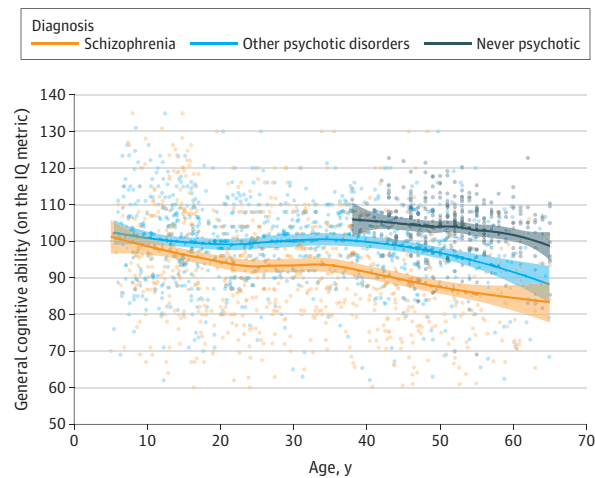
^b Symptom dimensions were scored according to factor analyses reported in Kotov et al.³⁰

^c Percentage of participants taking antipsychotics was calculated within the subset of participants with an estimate of general cognitive ability at that time point.

^d Preadmission 1, 2, 3, 4, and 5 refer to multiple instances of cognitive testing completed by some participants—ie, statistics for preadmission 2 reflect the second estimate of general cognitive ability for those participants who had more than 1 score available.

with different slopes (before and after transition). A model with 2 transition points has 3 phases. We estimated a corpus of models in which change points were placed at each 1-year interval and each pairwise combination of 1-year intervals. For a review of this method, see Howe and colleagues.⁴³ Models were compared using the bayesian information criterion (BIC). BIC is a statistic that balances model fit and parsimony, such that lower scores reflect simpler and better-fitting models. By comparing BIC for linear, quadratic, and spline models, one can infer whether models with a change point are preferable those

Figure 2. Locally Estimated Scatterplot Smoothed Plot of General Cognitive Ability as a Function of Age, Stratified by Diagnosis



Cognitive trajectories expressed relative to age, rather than time since psychosis onset. The shaded areas indicate the 95% CIs.

without. By extension, comparing BIC between models that vary in terms of the change points location allows one to identify the optimal location. A difference in BIC of 10 or more is considered strong evidence for a model with lower score.⁴⁴ All multilevel models were completed using the nlme package for R version 4.0.4 (The R Foundation). Two-sided *t* tests were used to evaluate the statistical significance of regression parameters, with *P* values less than .05 considered significant.

Among individuals with schizophrenia and other psychotic disorders, time could be measured either relative to birth or relative to psychosis onset. **Figure 2** and **eFigure 4** in the **Supplement** depict locally estimated scatterplot smoothed plots of general cognitive ability relative to birth and psychosis onset, respectively. Since psychosocial function in this cohort is a function of time since psychosis onset,³² we tested whether the same was true of cognitive trajectories by estimating trajectories relative to both time frames, comparing them via BIC. Models in which time was measured relative to psychosis onset had better fit than those in which time was measured relative to birth (a change in BIC of 10.82). Therefore, subsequent models were a function of time relative to psychosis onset. Finally, because diagnosis was hypothesized to moderate cognitive trajectories, the best-fitting model above was rerun with diagnosis (schizophrenia or other psychotic disorder) as a covariate.

Results

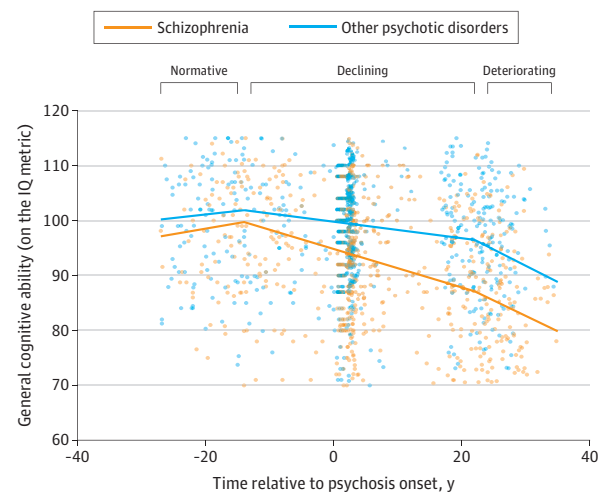
Of the 428 included individuals (212 with schizophrenia and 216 with other psychotic disorders), 254 (59.6%) were male, and the mean (SD) age at psychosis onset was 27 (9) years. Most participants were taking antipsychotic medications across post-admission assessments.

Figure 2 describes cognitive trajectories as a function of age among those with schizophrenia, other psychoses, and the

Table 2. Cognitive Trajectories in 428 Individuals With Schizophrenia and Other Psychotic Disorders, Moderated by Diagnosis

Coefficient	β (95% CI)	<i>P</i> value
Intercept	103.71 (99.35 to 108.06)	<.001
Schizophrenia	-1.18 (-7.96 to 5.61)	.73
Normative phase (>14 y prior to psychosis onset)	0.13 (-0.09 to 0.35)	.24
Declining phase (14 y prior to 22 y after psychosis onset)	-0.15 (-0.22 to -0.08)	<.001
Deteriorating phase (>22 y after psychosis onset)	-0.59 (-0.94 to -0.25)	<.001
Schizophrenia \times normative phase	0.06 (-0.31 to 0.44)	.74
Schizophrenia \times declining phase	-0.20 (-0.30 to -0.10)	<.001
Schizophrenia \times deteriorating phase	0.03 (-0.40 to 0.47)	.88

Figure 3. Trajectories of General Cognitive Ability in Individuals With Schizophrenia and Other Psychotic Disorders



Lines depict model-implied trajectories.

comparison group. In individuals with schizophrenia, cognitive decline began in adolescence. In both diagnostic groups, cognitive decline accelerated in adulthood, preceding that observed in the comparison group by approximately 20 years in the schizophrenia group and 10 years in the other psychoses group.

Among individuals with schizophrenia and other psychotic disorders, cognitive trajectories were best described as a function of time since psychosis onset, rather than age. A locally estimated scatterplot smoothed plot of general cognitive ability as a function of time since psychosis onset is depicted in **eFigure 3** of the **Supplement**. The best-fitting model included 3 phases. The first phase was one of normative development. This was followed by a phase of decline. The last phase was one of continued deterioration. Only the second phase, that of decline, was moderated by diagnosis (**Table 2**; **Figure 3**; **eTables 4** and **5** in the **Supplement**).

In the first phase, which spanned childhood to 14 years before psychosis onset, general cognitive ability was stable. Fourteen years before psychosis onset—when the average participant was aged 13 years—those with schizophrenia diverged

from those with other psychotic disorders, and the trajectory in both groups changed to one of decline. Among those with other psychotic disorders, cognitive decline proceeded at a rate of approximately 1 point on the IQ scale every 7 years (Table 2). Those with schizophrenia declined at a significantly faster rate of more than 1 point on the IQ scale every 3 years. In the final phase, cognitive decline accelerated to a rate of more than 1 point on the IQ scale every 2 years, and diagnosis no longer moderated the slope (Table 2).

Sensitivity analyses are described in the eResults in the Supplement. Analyses were not adjusted for age, as younger and older participants had similar cognitive trajectories (eFigure 4 in the Supplement). Sensitivity analyses tested whether results differed within diagnostic groups (eTables 6 to 8 in the Supplement), were affected by the point at which diagnoses were made (eFigure 5 in the Supplement), or by including academic achievement data (eTable 9 in the Supplement). eTable 10 in the Supplement reports demographic characteristics and eFigure 6 in the Supplement depicts cognitive trajectories for the subset of participants with preadmission data. eFigure 7 in the Supplement depicts trajectories of performance ability. Results were consistent with the primary analysis.

Discussion

The trajectory of cognition across the life span in individuals with schizophrenia and other psychotic disorders has remained unclear, despite the major role cognitive deficits play in these disorders. This is in part due to small sample sizes and short follow-ups of prior studies, many of which have been unable to detect gradual changes in cognition. In this analysis of 428 individuals with psychotic disorders, for whom 1619 estimates of general cognitive ability were available spanning childhood to old age, we identified 3 distinct phases of cognitive change in schizophrenia: the normative, declining, and deteriorating phases. Importantly, cognitive change in this cohort was better explained by time relative to psychosis onset than by age, suggesting that a disease process defined these trajectories.

The normative phase spanned childhood to 14 years before psychosis onset. During this phase, children who went on to develop psychotic disorders had a normal cognitive trajectory. The distribution of premorbid cognitive ability in this cohort was consistent with that of the general population. Other studies of childhood IQ in individuals with psychotic disorders have identified deficits relative to healthy controls.^{11,12} However, those studies were smaller, including less than 40 participants, and did not track IQ relative to symptom onset, meaning premorbid IQ estimates likely reflected the cognitive decline we observed in the second phase of cognitive change.

The second phase of cognitive change, the declining phase, spanned the period from 14 years prior to psychosis onset to 22 years after. Consistent with the neurodevelopmental theory, the decline began when the average person with schizophrenia in this cohort was aged 13 years, a period of neural development that appears to be disrupted in schizophrenia.⁴⁵ In this phase, individuals who were ultimately diagnosed with schizophrenia began experiencing cognitive decline at a rate of more

than 1 IQ point every 3 years (Table 2). By psychosis onset, the schizophrenia group had a 5-point cognitive deficit, consistent with meta-analytic findings for premorbid IQ deficits in individuals with schizophrenia.^{5,6} Those with other psychotic disorders also experienced cognitive decline but at a slower rate. If cognitive decline begins a decade before psychosis onset, clinical high-risk studies—whose participants already have subthreshold psychotic symptoms—may miss the critical window for detecting perturbed neural and cognitive development. Studying adolescents with significant familial and genetic risk for psychosis may be more fruitful.

The third phase of cognitive change, one of further deterioration, began 22 years after psychosis onset, when the average person was aged 49 years. At this second inflection point, cognitive decline accelerated among those with other psychotic disorders to a rate of 1 point on the IQ scale every 2 years (Table 2), and the rapid decline observed among those with schizophrenia continued. The deterioration preceded that of the comparison group by approximately 20 years. The modal adult without dementia experienced 0.5 SDs of cognitive decline over their life expectancy.⁴⁶ By contrast, individuals with schizophrenia in this cohort lost 1 SD of cognitive decline, a loss consistent with mild neurocognitive disorder, by age 55 years.⁴⁷ These analyses cannot determine whether this represents a dementing process, but a second downward turn is consistent with the neurodegenerative theory of schizophrenia, and the high incidence of dementia in individuals with schizophrenia⁴⁸ and other psychotic disorders.^{49,50}

The onset of cognitive decline preceded psychosis onset by more than a decade and was unaltered by psychosis onset. This pattern is consistent with the argument that psychosis is a secondary symptom of schizophrenia, whereas cognitive deficits reflect core pathophysiology.⁵¹ However, it is possible that post-onset cognitive declines are at least partially explained by risk factors known to be associated with schizophrenia, such as metabolic syndrome, smoking, and antipsychotic exposure. Postonset cognitive decline may be a consequence of schizophrenia rather than intrinsic to it.⁵² Cognitive deficits are associated with profound psychosocial impairment in individuals with schizophrenia.¹ Interventions that ameliorate or prevent cognitive decline could preempt decades of disability. Antipsychotics' effects on cognitive impairment are small,⁵³ if present,⁵⁴ but cognitive remediation has produced encouraging results.⁵⁵

Limitations

This study has limitations. This cohort was recruited at first admission, and preadmission cognitive data were collected retrospectively. Some detail concerning test forms and conditions are unknown, and tests varied across time points. This approach also misses individuals who developed psychotic disorders but were never hospitalized. However, in 2 epidemiological studies contemporary to this one,^{56,57} more than 90% of individuals with schizophrenia were hospitalized. In addition, this design allowed for the ascertainment of a larger sample ($N = 428$) than prospective cohorts drawn from the general population.

Tests of general cognitive ability from childhood to the 6-month follow-up were scored relative to age-based population norms, which were not stratified by socioeconomic status or race and ethnicity. Norms are not as rigorous of a com-

parison as a matched control group. However, change relative to population norms is a standard approach that has been useful for understanding cognitive development and dementia. A dementia comparison group was not available. However, estimates of general cognitive ability from a demographically matched comparison group ascertained at the 20-year follow-up were in the normal range.

In a healthy cohort, we would expect younger individuals to have higher estimates of general cognitive ability than older individuals, a phenomenon called the Flynn effect. The Flynn effect was not observed in this cohort. Quasiexperimental prospective studies have shown that education improves intelligence.⁵⁸ We suspect that since this cohort was ascertained at first admission, the youngest individuals in this cohort experienced more educational disruption. It is possible that in individuals with psychotic disorders, the advantage provided by the Flynn effect is counteracted by educational disruptions. Further research is needed to test this hypothesis.

Additionally, this analysis did not distinguish trajectories on specific tests. Vocabulary, for example, is more resistant to decline than other neurocognitive abilities⁵⁹ and was stable between 2-year and 20-year follow-ups in this sample.¹⁸ Vocabulary has been shown to decline in individuals with dementia⁶⁰ and therefore may provide insight into whether the third phase,

that of cognitive deterioration, is neurodegenerative in nature. However, trajectories of performance IQ were consistent with trajectories of general cognitive ability (eFigure 7 in the Supplement).

Conclusions

Schizophrenia has been described as both a neurodevelopmental and a neurodegenerative disorder. Our findings provide support for both theories. We observed cognitive decline beginning in adolescence, implying abnormal neural development. However, continued cognitive decline after psychosis onset and into the third decade of illness is consistent with the neurodegenerative theory. The pace of decline in individuals with schizophrenia, while gradual, resulted in more than 16 IQ points lost over the period of observation. In those with other psychotic disorders, decline began later relative to psychosis onset but ultimately resulted in a loss of 9 IQ points over the period of intervention. Interventions to prevent this cognitive cascade are urgently needed, as cognitive deficits leave millions unable to function in society. Both primary and secondary prevention is needed, to preempt the onset of cognitive decline as well as later deterioration and dementia.

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