ORIGINAL ARTICLE

Decline in Cognitive Performance Between Ages 13 and 18 Years and the Risk for Psychosis in Adulthood

A Swedish Longitudinal Cohort Study in Males

James H. MacCabe, MRCPsych, PhD; Susanne Wicks, PhD; Sofia Löfving, MPH; Anthony S. David, FRCPsych, MD; Åsa Berndtsson; Jan-Eric Gustafsson, PhD; Peter Allebeck, PhD; Christina Dalman, MD, PhD

Context: Clear evidence from many prospective, population-based studies indicates that patients who develop psychosis in adulthood experienced various cognitive deficits during childhood and adolescence. However, it is unclear whether these deficits become more severe during adolescence.

Objective: To assess the influence of cognitive developmental trajectories in adolescence and young adulthood on the risk for psychosis in adulthood.

Design: Longitudinal cohort study.

Setting: Academic research.

Population-Based Cohorts: Four population-based cohorts of adolescent boys and young men born in Sweden in 1953, 1967, 1972, and 1977, totaling 10 717 individuals, and followed up through December 31, 2006.

Exposure: Scores on tests of verbal, spatial, and inductive ability at age 13 years and in equivalent tests at army conscription (age 18 years).

Main Outcome Measure: Hospital admissions for nonaffective or affective psychoses in adulthood.

Results: A relative decline (compared with the unaffected population) in verbal ability between ages 13 and 18 years was associated with increased risk for schizophrenia and for other nonaffective and affective psychoses (adjusted hazard ratio for schizophrenia for an increase of 1 SD in verbal ability, 0.59; 95% CI, 0.40-0.88; $P = .009$). Decline between ages 13 and 18 years was a much stronger predictor of psychosis than the verbal ability score at age 18 years alone. The association remained significant after adjustment for urbanicity, parental educational level, and family history of psychosis and persisted when cases with onset before age 25 years were excluded, indicating that this was not a prodromal effect.

Conclusions: A relative decline in cognitive performance in adolescence and young adulthood, particularly in verbal ability, is associated with increased risk for psychosis in adulthood, and a relative decline in verbal ability between ages 13 and 18 years is a stronger predictor of psychosis than verbal ability at age 18 years alone. This suggests an impairment of late neurodevelopment affecting the acquisition of verbal skills in adolescent boys and young men who later develop psychosis.

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Author Affiliations: Department of Psychosis Studies, Institute of Psychiatry, King's College London, London, England (Drs MacCabe and David); and Department of Public Health Sciences, Karolinska Institutet, Stockholm (Drs Wicks, Allebeck, and Dalman and Ms Löfving), and Department of Education and Special Training, University of Gothenburg, Gothenburg (Ms Berndtsson and Dr Gustafsson), Sweden.

POPULATION-BASED COHORT studies using childhood cognitive tests,[1] scholastic achievement,[2] and military conscription tests[3] have consistently demonstrated that individuals who develop psychotic disorders in adulthood performed below the level of their peers in childhood.[4,5] The only exception to this pattern is bipolar disorder, which has been demonstrated in some investigations to be associated with enhanced cognitive ability.[6]

The origin of premorbid cognitive deficits in psychotic disorders is not fully understood, but 3 possible explanations are proposed. The first and most commonly argued explanation is that the premorbid cognitive deficits in schizophrenia are a result of neurodevelopmental impairment.[7,8] The second suggestion is that the association between poor cognitive functioning and schizophrenia may be driven by socioeconomic factors: evidence for this includes the association of social factors with the risk for schizophrenia (urban birth,[9] migration,[10] and low socioeconomic status[11]) and the observation that poor cognitive or educational performance in childhood has associations with a wide range of adult outcomes that are likely mediated by social processes such

as cardiovascular disease and stroke,[12] premature mortality,[13] and nonpsychotic mental disorders.[14] The third suggestion is that the premorbid deficits in IQ found in schizophrenia reflect prodromal, rather than neurodevelopmental, processes.

If a disruption in neurodevelopment accounted for the association, one might hypothesize that its timing would be age dependent, reflecting a falling off of abilities at particular stages in neurodevelopment. Conversely, a prodromal effect would be related to the timing of disease onset rather than age. Of all neurodevelopmental phases, adolescence appears to be a particularly critical period in the development of psychosis: it is a time of synaptic pruning and a rapid reduction in gray matter volume,[15] is associated with a rapid rise in the incidence of psychosis,[16] and seems to be a sensitive period for certain risk factors such as cannabis consumption.[17] The neurodevelopmental hypothesis also predicts that changes in performance over time, relative to the population, should predict the risk for psychosis more strongly than the overall level of performance, reflecting an impairment of certain neurodevelopmental processes.

Further insights into the origin of these deficits, whether biological, psychosocial, or prodromal,[18] can be gained from studying cognitive domains separately. For example, interference in the development of the hippocampus might affect memory, while disruptions in myelination might affect processing speed or reaction time.

To clarify these important issues, it is necessary to study cognitive functioning longitudinally during the course of development and to relate the timing of cognitive changes to the timing of illness onset. No prospective studies to date have measured changes in cognitive functioning during the adolescent and young adult period (age range, 13-18 years). In this study, we linked Swedish population registers to conduct a historical cohort study investigating the associations between cognitive change during adolescence and young adulthood and the risk for nonaffective and affective psychoses during adulthood.

METHODS

UGU DATABASE

The population from this study was drawn from 4 representative samples of individuals enrolled in the Utvärdering Genom Uppföljning (Evaluation Through Follow-up) program (UGU).[19] This Swedish longitudinal program was originally designed to study education and career development.

SAMPLING

Study samples comprising approximately 10% of the population were obtained from among children born in 3 birth years (1953, 1967, 1972, and a further sample of approximately 5% of the population in 1977). Sampling for the 1953 sample was by birth date: all children born on the 5th, 15th, and 25th of any month were included. For the later samples, a multistage sampling of school classes was used: a stratified sample of municipalities in Sweden was initially drawn. From these communities, a systematic sample of classes from grade 6 was selected,[20] and all pupils in each selected class were included. For reasons explained herein, only male participants are included in this study.

LINKAGE TO NATIONAL REGISTERS

Linkage to national registers was performed by means of the unique identifiers assigned to all Swedish residents. Individuals from all cohorts were linked to the following registers:

Multigeneration Register

The Multigeneration Register allowed the identification of the biological parents of the cohort members. This allowed linkage to the other databases.

Register of Total Population

All cohort members and their parents were linked to the Register of Total Population. This register contains data on demographics, parental education, urbanicity, and dates of immigration, emigration, and death.

National Patient Register

The cohort members and their parents were then linked to the National Patient Register. This register contains dates and discharge diagnoses for all hospital admissions since January 1, 1973. The *International Classification of Diseases, Eighth Revision* (*ICD-8*) was used until 1988, the *Ninth Revision* from 1987 to 1996, and the *Tenth Revision* from 1997. These discharge diagnosis codes were used to provide data on age at onset and diagnoses of the cohort members. The diagnostic codes used (from the Swedish versions of the *ICD*) were as follows: schizoaffective disorder (*ICD-8* codes 295H and 295.70 and *ICD-10* code F25), other affective psychoses (*ICD-8* code 296.9 and *ICD-9* codes 296B, 296W, and 296X), bipolar disorder (*ICD-8* codes 296.10-296.30, *ICD-9* codes 296A and 296C-E, and *ICD-10* codes F30 and F31), schizophrenia (*ICD-8* code 295 [excluding 295.5 and 295.7]; *ICD-9* codes F295A-E, F295G, F295W, and F295X; and *ICD-10* code F20), and other nonaffective psychoses (*ICD-8* codes 295.5, 297, 298 [excluding 298.00 and 298.10], and 299.9; *ICD-9* codes 295F, 297, and 298; and *ICD-10* codes F21-F24 and F26-F29). Study participants had at least 1 primary diagnosis, defined as the primary reason for that hospital admission, and up to 7 secondary diagnoses, which represented coexisting diagnoses that were not the primary reason for hospital admission; all were included for the purposes of this study. A hierarchy was used whereby bipolar disorder superseded other affective psychoses. Otherwise, 3 individuals who received more than 1 diagnosis at different times were assigned both diagnoses (eg, schizophrenia and bipolar disorder). The date of onset was defined as the date of hospital admission for the first diagnosis within the defined set of codes. The same diagnostic algorithms were used to obtain data on family history of psychosis in the biological parents.

COGNITIVE TESTS AND LINKAGE TO THE SWEDISH CONSCRIPTION REGISTER

All individuals in the sample underwent cognitive testing at age 13 years using standardized timed tests designed to assess verbal, spatial, and inductive ability. These tests were identical in all 4 cohorts and are summarized in **Figure 1**.

We obtained scores on equivalent cognitive tests at age 18 years through linkage of the cohort members to the Swedish Conscription Register. Until 2010, all Swedish young men were assessed for conscription to military training at age 18 years or in rare cases at age 19 or 20 years. As an exception, men with severe disability, including some with severe mental disorders,

were excused from conscription. Because men and not women were conscripted for military training, only male adolescents and young men are included in this study. The enlistment process included screening for psychiatric disorders, which were followed up by full diagnostic interviews in individuals who screened positive, and diagnoses were coded using *ICD-9* and *ICD-10*. The men were assessed using the Swedish Enlistment Battery, a set of cognitive tasks designed to measure the same 3 domains of cognitive abilities as the tests taken at age 13 years. The tests were similar in form but were more demanding to reflect the older age group. The 1977 cohort took slightly different tests at conscription for the inductive ability task than the earlier cohorts. The tests are summarized in Figure 1.

STATISTICAL ANALYSIS

Analytic Cohort and Censoring

All 4 birth cohorts were combined. To minimize the effect of reverse causality, we excluded from the analysis individuals who had already experienced a psychotic disorder by the time of conscription, individuals who received a diagnosis at conscription falling within the set of *ICD* codes aforementioned, and individuals who were admitted to the hospital with such a diagnosis before the first anniversary of their conscription. Study participants were entered into a survival analysis and were censored at their first date of emigration, death, diagnosis of any psychotic disorder, or December 31, 2006, whichever occurred first.

Verbal Ability
Age 13 y: Antonyms: Identify the antonym of a target word among 4 alternatives.
Age 18 y: Synonyms: Identify the synonym of a target word among 4 alternatives.

Spatial Ability
Age 13 and 18 y: Metal Folding: Identify the 3 dimensional object among 4 alternatives that corresponds to a drawing of a flat piece of metal with fold lines marked. The form of the test is identical at both ages, but the items at age 18 are more challenging.

Inductive Ability
Age 13 y: Number Series: Complete the next 2 items in a number series, where the first 6 numbers are given.
Age 18 y: Instructions
Make markings on the answer sheet by following a set of instructions. The instructions involve simple arithmetic and geometric operations and include distractors.
Age 18 y (1977 Cohort Only):
Figure Series: Complete the next 2 items in a series of figures, where the first 4 are given.
Groups: Five figures are presented. The task is to find the figure that does not fit thematically.

Figure 1. Cognitive tests at ages 13 and 18 years.

Scaling of Cognitive Test Scores

The cognitive test scores all followed normal distributions. For each cognitive test, the scores were standardized within each cohort to a mean (SD) of 0 (1), and then the standardized scores from the 4 cohorts were combined. Change scores were calculated for each cognitive domain by subtracting the standardized score at age 13 years from that at age 18 years.

Modeling

Cox proportional hazards regression was used to model associations between the cognitive test scores and the time to diagnosis. For each diagnosis, 3 sets of results are shown (**Tables 1**, **2**, **3**, and **4**). The unadjusted hazard ratios (HRs) for the cognitive test scores from age 18 years are given to allow comparison with other studies[3,21,22] that have used conscript test scores. The unadjusted HRs for change in standardized scores between ages 13 and 18 years are also given (Tables 1-4, column 1). The scores at age 18 years and the change scores between ages 13 and 18 years were then entered into a single model, adjusted for one another (Tables 1-4, model 1). The analyses were then further adjusted for urbanicity, highest parental educational level, and family history of psychosis (to adjust not only for genetic liability but also for the educational and social consequences of growing up with a parent having psychosis) (Tables 1-4, model 2). These analyses were conducted for each of 4 diagnostic groups, namely, schizophrenia and schizoaffective disorder, other nonaffective psychoses, bipolar disorder, and other affective psychoses.

ETHICS COMMITTEE APPROVAL

The study was approved by the Stockholm Regional Ethical Review Board. It adhered to the tenets of the Declaration of Helsinki.

RESULTS

DESCRIPTION OF THE COHORT

Of 16 233 individuals in the UGU cohorts, 1809 were excluded because they could not be matched to conscription data. The prevalence of any psychotic disorder was higher among individuals with missing conscription data

Table 1. Associations Between Premorbid Cognitive Functioning and the Risk for Schizophrenia or Schizoaffective Disorder[a]

	Unadjusted		Model 1, Adjusted		Model 2, Fully Adjusted	
Variable	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Verbal at age 18 y	0.78 (0.60-1.01)	.06	1.03 (0.65-1.66)	.89	1.06 (0.66-1.69)	.82
Change in verbal from ages 13-18 y	0.58 (0.42-0.79)	<.001	0.60 (0.40-0.88)	.009	0.59 (0.40-0.88)	.009
Spatial at age 18 y	0.82 (0.63-1.07)	.15	0.81 (0.55-1.20)	.29	0.83 (0.57-1.22)	.35
Change in spatial from ages 13-18 y	1.04 (0.76-1.44)	.80	1.22 (0.85-1.76)	.28	1.20 (0.83-1.72)	.33
Inductive at age 18 y	0.97 (0.64-1.48)	.90	0.95 (0.58-1.56)	.84	0.97 (0.59-1.57)	.89
Change in inductive from ages 13-18 y	0.76 (0.55-1.06)	.10	0.86 (0.59-1.25)	.42	0.86 (0.59-1.26)	.43
Urbanicity	...	...	...	...	1.32 (0.64-2.73)	.45
Family history of psychosis	...	...	...	...	4.08 (1.83-9.10)	.001
Highest parental educational level	...	...	...	...	0.68 (0.42-1.10)	.11

Abbreviations: Ellipsis, not applicable; HR, hazard ratio.
[a]Hazard ratios represent increased risk for an increase in performance of 1 SD. Unadjusted hazard ratios are given in the first column. Model 1 includes the same variables adjusted for one another. Model 2 includes potential confounders.

Table 2. Associations Between Premorbid Cognitive Functioning and the Risk for Other Nonaffective Psychoses[a]

	Unadjusted		Model 1, Adjusted		Model 2, Fully Adjusted	
Variable	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Verbal at age 18 y	0.81 (0.64-1.02)	.07	1.08 (0.71-1.63)	.73	1.08 (0.72-1.64)	.71
Change in verbal from ages 13-18 y	0.64 (0.48-0.86)	.002	0.67 (0.48-0.94)	.02	0.67 (0.48-0.95)	.02
Spatial at age 18 y	0.78 (0.62-0.99)	.03	0.87 (0.62-1.22)	.42	0.88 (0.62-1.23)	.44
Change in spatial from ages 13-18 y	0.83 (0.62-1.10)	.19	0.99 (0.71-1.37)	.95	0.99 (0.71-1.37)	.94
Inductive at age 18 y	0.76 (0.60-0.95)	.02	0.82 (0.53-1.27)	.38	0.83 (0.54-1.27)	.39
Change in inductive from ages 13-18 y	0.79 (0.59-1.05)	.11	0.93 (0.67-1.30)	.69	0.94 (0.67-1.31)	.70
Urbanicity	. . .	. . .	. . .	. . .	0.90 (0.43-1.90)	.79
Family history of psychosis	. . .	. . .	. . .	. . .	2.74 (1.18-6.37)	.02
Highest parental educational level	. . .	. . .	. . .	. . .	0.92 (0.64-1.33)	.65

Abbreviations: Ellipsis, not applicable; HR, hazard ratio.
[a]Hazard ratios represent increased risk for an increase in performance of 1 SD. Unadjusted hazard ratios are given in the first column. Model 1 includes the same variables adjusted for one another. Model 2 includes potential confounders.

Table 3. Associations Between Premorbid Cognitive Functioning and the Risk for Bipolar Disorder[a]

	Unadjusted		Model 1, Adjusted		Model 2, Fully Adjusted	
Variable	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Verbal at age 18 y	1.48 (0.92-2.39)	.11	2.06 (0.89-4.76)	.09	1.81 (0.79-4.11)	.16
Change in verbal from ages 13-18 y	0.88 (0.51-1.53)	.65	0.64 (0.32-1.27)	.20	0.68 (0.34-1.33)	.26
Spatial at age 18 y	1.17 (0.73-1.86)	.51	1.19 (0.60-2.37)	.62	1.20 (0.60-2.39)	.60
Change in spatial from ages 13-18 y	0.82 (0.50-1.35)	.44	0.75 (0.40-1.41)	.37	0.72 (0.38-1.37)	.32
Inductive at age 18	1.25 (0.77-2.00)	.36	0.64 (0.27-1.49)	.30	0.62 (0.27-1.45)	.27
Change in inductive from ages 13-18 y	1.25 (0.72-2.18)	.43	1.40 (0.72-2.65)	.30	1.44 (0.76-2.72)	.26
Urbanicity	. . .	. . .	. . .	. . .	1.65 (0.54-5.05)	.38
Family history of psychosis	. . .	. . .	. . .	. . .	5.66 (1.63-19.64)	.006
Highest parental educational level	. . .	. . .	. . .	. . .	2.23 (1.15-4.34)	.02

Abbreviations: Ellipsis, not applicable; HR, hazard ratio.
[a]Hazard ratios represent increased risk for an increase in performance of 1 SD. Unadjusted hazard ratios are given in the first column. Model 1 includes the same variables adjusted for one another. Model 2 includes potential confounders.

Table 4. Associations Between Premorbid Cognitive Functioning and the Risk for Other Affective Psychoses[a]

	Unadjusted		Model 1, Adjusted		Model 2, Fully Adjusted	
Variable	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Verbal at age 18 y	0.51 (0.33-0.79)	.003	0.81 (0.35-1.91)	.64	0.88 (0.36-2.15)	.78
Change in verbal from ages 13-18 y	0.46 (0.28-0.74)	.002	0.46 (0.24-0.90)	.02	0.45 (0.23-0.89)	.02
Spatial at age 18 y	0.56 (0.36-0.88)	.01	0.56 (0.28-1.10)	.09	0.56 (0.28-1.12)	.10
Change in spatial from ages 13-18 y	1.05 (0.61-1.79)	.87	1.68 (0.89-3.14)	.11	1.66 (0.90-3.07)	.10
Inductive at age 18 y	0.65 (0.42-1.02)	.06	1.06 (0.44-2.59)	.89	1.08 (0.43-2.72)	.87
Change in inductive from ages 13-18 y	1.01 (0.56)-1.82)	.98	1.20 (0.62-2.34)	.59	1.13 (0.57-2.23)	.74
Urbanicity	. . .	. . .	. . .	. . .	0.43 (0.06-3.23)	.41

Abbreviations: Ellipsis, not applicable; HR, hazard ratio.
[a]Hazard ratios represent increased risk for an increase in performance of 1 SD. Unadjusted hazard ratios are given in the first column. Model 1 includes the same variables adjusted for one another. Model 2 includes urbanicity; no study participants with a diagnosis of other affective psychoses had a family history of psychosis or a highest parental educational level beyond 16 years.

than among those with complete data (1.9% vs 1.0%, $\chi^2_1 = 12.0$, $P = .001$). Of 14 424 remaining cohort members, 109 died or emigrated before the first anniversary following conscription and were excluded, leaving 14 315. Of these, 2462 were missing at least 1 item of cognitive data, leaving 11 853 individuals who were included in the analysis. The prevalence of any psychotic disorder during the follow-up period did not differ between those with (0.9%) and without (0.9%) full cognitive data ($\chi^2_1 = 0.1$, $P = .79$). Of these 11 853 individuals, 10 719 (90.4%) had full data on all confounders of interest and were included in the analysis. The prevalence of any psychotic disorder did not differ significantly between those with (0.9%) and without (1.2%) full data on confounders. Fourteen individuals were diagnosed as having psychotic disorders at the time of conscription, but 12 of these had already been excluded for 1 or more of the reasons already given. The remaining 2 (neither of whom had a subsequent hospital admission for psychosis) were excluded from the analysis, leaving 10 717 individuals (**Table 5**).

Table 5. Demographic Characteristics and Cognitive Test Scores[a]

Variable	Population (n = 10 717)	Schizophrenia or Schizoaffective Disorder (n = 50)	Other Nonaffective Psychoses (n = 64)	Bipolar Disorder (n = 18)	Other Affective Psychoses (n = 16)
Urbanicity, No. (%)[b]	1457 (13.6)	9 (18.0)	8 (12.5)	4 (22.2)	1 (6.3)
Family history of psychosis, No. (%)	352 (3.3)	7 (14.0)	6 (9.4)	3 (16.7)	0
Highest parental educational level, No. (%)					
Compulsory, to age 16 y	6311 (58.9)	38 (76.0)	47 (73.4)	11 (61.1)	16 (100.0)
Upper secondary, to age 18 y	2438 (22.7)	9 (18.0)	7 (10.9)	2 (11.1)	0
Further education	1968 (18.4)	3 (6.0)	10 (15.6)	5 (27.8)	0
Age at first hospital admission, mean (SD), y	. . .	28.2 (6.6)	29.5 (7.1)	37.1 (8.6)	31.8 (6.9)
First hospital admission at >25 y, No. (%)	. . .	29 (58.0)	48 (75.0)	17 (94.4)	14 (87.5)
No. of hospital admissions, mean (SD)	. . .	10.6 (12.7)	6.3 (8.1)	6.1 (5.2)	7.6 (6.5)
Ability score, mean (SD)					
Verbal at age 13 y	100.0 (15.0)	100.9 (16.3)	99.9 (16.9)	106.1 (11.4)	99.6 (15.9)
Verbal at age 18 y	100.0 (15.0)	95.1 (15.5)	95.2 (16.2)	104.7 (13.8)	90.0 (17.9)
Spatial at age 13 y	100.0 (15.0)	96.8 (17.0)	97.8 (16.5)	104.3 (16.2)	91.0 (17.4)
Spatial at age 18 y	100.0 (15.0)	96.5 (16.4)	95.7 (15.6)	101.6 (14.1)	92.4 (18.6)
Inductive at age 13 y	100.0 (15.0)	99.0 (16.4)	98.0 (15.6)	100.6 (17.0)	94.0 (16.6)
Inductive at age 18 y	100.0 (15.0)	96.1 (16.0)	95.3 (15.4)	102.8 (12.8)	94.2 (18.7)

Abbreviation: Ellipsis, not applicable.
[a]To allow comparison with IQ scores, test scores are standardized to a population mean (SD) of 100 (15).
[b]Stockholm, Malmö, or Gothenburg, Sweden.

COGNITIVE TEST SCORES

All test results were positively correlated with one another at the level of $P < .001$, and the Pearson product moment correlation coefficients within each cognitive domain across age (eg, verbal at age 13 years with verbal at age 18 years) were all at least 0.65 (Pearson product moment correlation coefficients of 0.66 for verbal, 0.65 for spatial, and 0.65 for inductive). Correlations across domain within age were all lower (range, 0.38-0.61) than those within domain across age, with one exception ($R = 0.71$ for verbal and inductive at age 18 years). These psychometric properties of the tests endorse the validity of analyzing the 3 cognitive domains separately rather than combining them.

CHARACTERISTICS OF THE SAMPLE

The demographic and clinical characteristics of the sample were recorded, along with the mean (SD) of the cognitive test scores at ages 13 and 18 years (restandardized as for IQ scores to a mean [SD] of 100 [15]). These results are summarized in Table 5 and in **Figures 2**, **3**, **4**, and **5**.

COGNITIVE TEST SCORES AND THE RISK FOR PSYCHOSIS

The results of the Cox proportional hazards regression analyses for the cognitive test scores and the risk for psychosis are summarized in Tables 1 through 4. To facilitate interpretation and comparison with other studies, the cognitive test scores for this analysis are standardized to the population to a mean (SD) of 0 (1).

Schizophrenia

Unadjusted associations between cognitive functioning at age 18 years and the risk for schizophrenia later in adulthood (Table 1) were moderate, with verbal ability marginally failing to reach statistical significance. However, when change in cognitive functioning between ages 13 and 18 years was included in the same model as the score at 18 years (Table 1, model 1), a relative decline in verbal ability scores clearly emerged as the strongest and only statistically significant predictor of schizophrenia (HR, 0.60; $P = .009$). These results were not attenuated by adjustment for confounders (Table 1, model 2), suggesting that the results are not confounded by urbanicity, parental educational level, or family history of psychosis. Inspection of the distribution of the verbal change score in patients with schizophrenia (data available from the author on request) revealed a left-shifted normal distribution (mean, −0.38; median, −0.43) rather than a subgroup with severe decline.

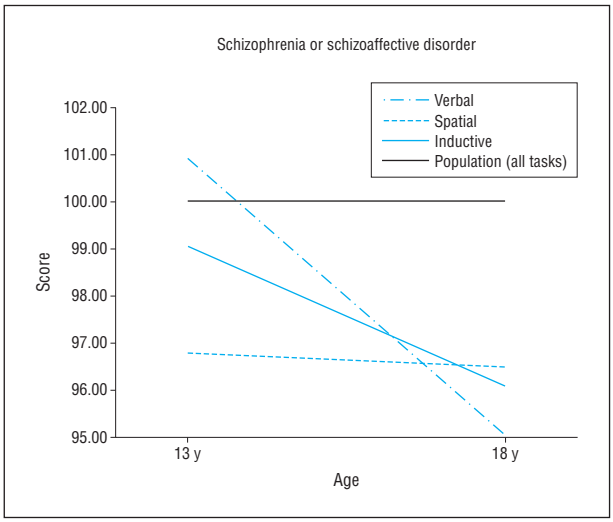

Figure 2. Premorbid cognitive functioning in adolescents and young adults who later develop schizophrenia or schizoaffective disorder. Scores are standardized to a population mean (SD) of 100 (15).

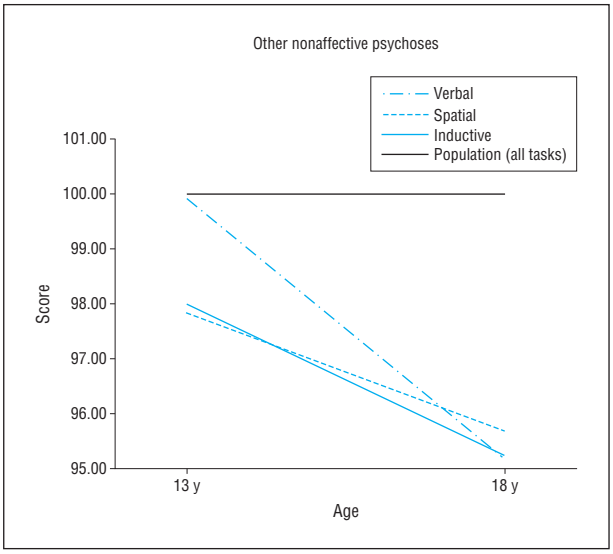

Figure 3. Premorbid cognitive functioning in adolescents and young adults who later develop other nonaffective psychoses. Scores are standardized to a population mean (SD) of 100 (15).

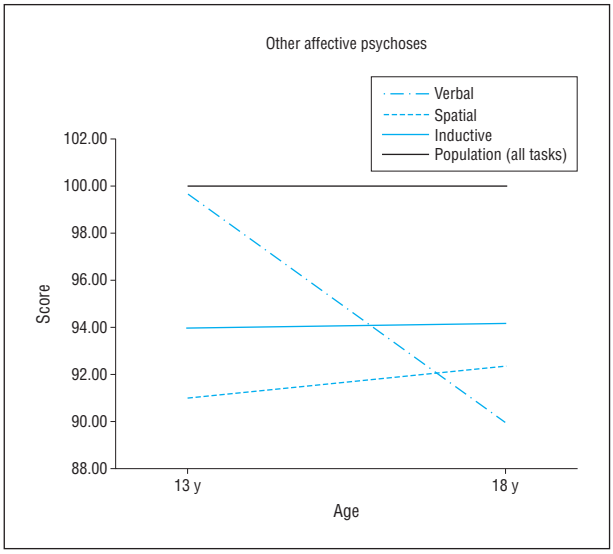

Figure 5. Premorbid cognitive functioning in adolescents and young adults who later develop other affective psychoses. Scores are standardized to a population mean (SD) of 100 (15).

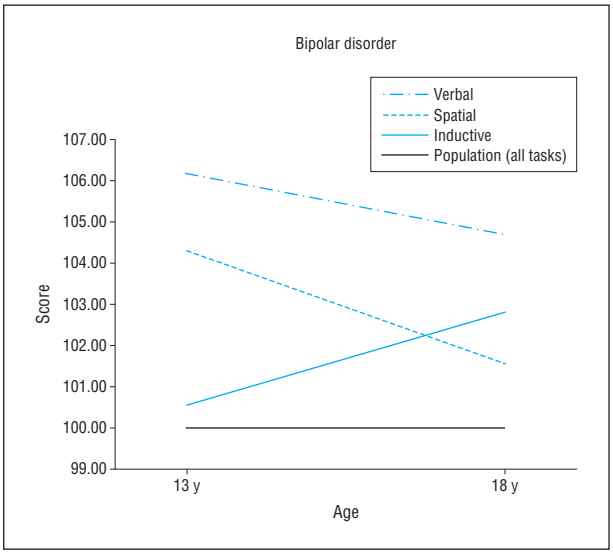

Figure 4. Premorbid cognitive functioning in adolescents and young adults who later develop bipolar disorder. Scores are standardized to a population mean (SD) of 100 (15).

Other Nonaffective Psychoses

The results in other nonaffective psychoses are similar to those in schizophrenia, although in this case spatial and inductive ability at age 18 years were marginally significant. Again, in the adjusted model (Table 2, model 1), a relative decline in verbal ability between ages 13 and 18 years emerges as the strongest predictor other than family history of psychosis, with an HR of 0.67 ($P = .02$).

Bipolar Disorder

Inspection of Figures 2 through 5 and Tables 1 through 4 reveals a clear disparity between bipolar disorder and the other 3 diagnostic groups. Individuals who later developed bipolar disorder outperformed population norms on all tasks and at all time points, and a nonsignificant trend is observed for the association of better verbal ability at age 18 years with increased risk for bipolar disorder.

OTHER AFFECTIVE PSYCHOSES

The pattern in nonbipolar affective psychoses is similar to that seen in nonaffective psychoses and schizophrenia. Again, in the adjusted model (Table 5, model 1), only a relative decline in verbal ability is significantly associated with increased risk for later affective psychosis (HR, 0.46; $P = .02$).

AGE AT ONSET OF PSYCHOSIS

To rule out the possibility that the results were confounded by prodromal effects, we ran separate analyses in which we excluded individuals who developed psychosis before age 25 years (Table 5). The effect of verbal decline became even stronger in the case of schizophrenia (fully adjusted HR, 0.39; 95% CI, 0.24-0.65; $P < .001$) and other nonaffective psychoses (fully adjusted HR, 0.62; 95% CI, 0.42-0.93; $P = .02$) and was essentially unchanged in bipolar disorder (fully adjusted HR, 0.70; 95% CI, 0.35-1.39; $P = .31$) and other affective psychoses (fully adjusted HR, 0.51; 95% CI, 0.24-1.05; $P = .07$).

COMMENT

RELATIVE DECLINE IN COGNITIVE PERFORMANCE

In all diagnostic groups, a clear relative decline was observed in verbal ability compared with the male general population between ages 13 and 18 years. In all diagnoses except bipolar disorder, this decline was a significant predictor of later psychoses and was a stronger predictor of later psychosis than poor verbal ability at age

18 years alone. While decline was also observed in other domains, verbal decline was by far the strongest and most consistent finding. Associations with decline between ages 13 and 18 years were at least as strong for later-onset cases (after age 25 years) as for earlier-onset cases. The results remained the same after adjusting for urbanicity, parental educational level, and family history of psychosis.

These declines are relative to the general population and are unlikely to represent an actual deterioration in verbal ability between ages 13 and 18 years. Instead, it is probable that the individuals who will later develop psychosis do not progress as quickly as their peers, analogous to a child's growth curve dropping to a lower percentile on a growth curve chart.

The consistency of the results across all 4 diagnostic groups and the statistical significance in 3 diagnostic groups provide a strong indication that these are not chance findings. However, replication in another sample would add further weight.

OVERALL COGNITIVE PERFORMANCE, WITH COMPARISON BETWEEN DIAGNOSTIC GROUPS

Except for those who developed bipolar disorder, individuals who would later develop psychosis underperformed relative to population means on almost all tasks, although only some of these findings were statistically significant, probably due to low statistical power. This underperformance is consistent with almost every previous study investigating premorbid cognitive functioning in psychosis.[4] Little difference was observed in premorbid cognitive functioning between individuals who developed schizophrenia and individuals who developed nonaffective psychoses, consistent with previous findings.[2,3]

Individuals who would later develop bipolar disorder consistently outperformed the general population on all 3 domains and at all time points. Although none of these differences reached statistical significance, they are consistent with a growing body of literature supporting the notion that individuals who subsequently develop bipolar disorder outperform population norms. This includes studies on Finnish[23] and Swedish[14] conscripts (partial support), data from the Dunedin study[24] in New Zealand, and a study[6] on scholastic achievement among individuals with bipolar disorder in Sweden, in which the possible mechanisms for such an association are discussed.

COMPARISON WITH PREVIOUS STUDIES

To date, few studies have been able to measure premorbid cognitive change prospectively in schizophrenia, and fewer have done so in individuals with bipolar disorder or other psychoses. In the seminal study by Jones et al[25] using the British 1946 birth cohort, the association between low educational scores and the risk for schizophrenia became stronger at increasing ages. However, intraindividual changes in test scores were not examined. Data from 2 different cohorts within the National Collaborative Perinatal Project have been used to examine the cognitive test scores at ages 4 and 7 years and their relationship to the risk for adult psychosis: Kremen and colleagues[26] reported on a Providence, Rhode Island, cohort, demonstrating that 25 of 547 children who showed psychotic symptoms by age 23 years were substantially more likely to have declined in performance on standardized measures of IQ between ages 4 and 7 years. However, a larger study by Cannon and colleagues[27] comparing 72 patients having schizophrenia with almost 8000 control subjects in a Philadelphia, Pennsylvania, cohort found no evidence that intraindividual decline between ages 4 and 7 years predicted the development of schizophrenia.

Recently, Reichenberg and colleagues[28] analyzed longitudinal data from the Dunedin, New Zealand, cohort. The scores on the Wechsler Intelligence Scale for Children at ages 7, 9, 11, and 13 years were compared between 35 patients with schizophreniform disorder and 556 control subjects. The preschizophreniform group differed significantly in slope, indicating a lag in performance, in block design, and in arithmetic and digit symbol tasks compared with controls. Patients with depressive disorders showed no such lag.

We are aware of only 2 previous studies that have assessed a relative decline over the age range covered by the present study (ages 13-18 years), and both of these used retrospective data. Bilder and colleagues[29] used a follow-back design, comparing academic achievement test scores among 59 patients with schizophrenia or schizoaffective disorder and 36 controls throughout their school careers. The patients underperformed at all ages, with some evidence of decline, but it was impossible to differentiate between cognitive domains. Fuller et al[30] used a similar design, obtaining scores retrospectively on 5 domains of the Iowa Tests of Educational Development from ages 9, 13, and 16 years in 70 individuals with schizophrenia. Compared with state norms, the individuals who developed schizophrenia had low scores on all domains, but (as in the present study) only language scores showed significant relative decreases over time.

Although data from other studies are sparse, we believe that it is worthwhile to attempt to synthesize what is known thus far and what this study adds. The data from the Dunedin cohort suggest a relative decline in attention, processing speed, working memory, and arithmetic and visuospatial skills between ages 7 and 13 years in children who develop adult schizophreniform disorder.[28] Our results suggest that this decline is followed by a sharp relative decline in verbal ability between ages 13 and 18 years, and these findings are in agreement with previous follow-back investigations.[30]

LIMITATIONS

Bias

The amount of missing data in our study was small, and the prevalence of psychosis did not differ markedly between those with and without missing data. Therefore, we are confident that the sample is representative of the original cohort and that any sampling bias is likely small.

Validity of Cognitive Tests

The cognitive tests used in the study were necessarily brief and were designed many years ago.[31] Small differences also existed in the tests administered at ages 13 and 18 years, and the test for inductive ability at age 18 years was different for the 1977 cohort than for the other cohorts. Although these tests are well validated by psychometric research[31] and demonstrated good predictive validity in this sample (intraindividual correlations between scores at ages 13 and 18 years within domains all exceeded 0.65), we cannot be certain of the exact equivalence of the tests. We should also be cautious in drawing parallels between the findings on these tests and the results from other studies using more standardized cognitive tests.

Validity of Diagnoses

In common with all register-based studies, diagnoses were made by clinical psychiatrists, and although these were according to *ICD* criteria, their validity is not assured. Two studies[32,33] have demonstrated good concurrent validity for register-based diagnoses of schizophrenia, as well as another study[34] for bipolar disorder. Because the register captured only hospital admissions, some cases may have been misclassified as unaffected. Furthermore, the age at onset of some patients may have been significantly earlier than their age at the first hospital admission. We must also acknowledge that some diagnostic groups contained few patients.

Confounding

We were able to adjust for urbanicity, parental educational level, and family history of psychotic disorder and found no evidence of confounding by these variables. However, unmeasured or residual confounding cannot be ruled out.

Generalizability

These data were restricted to male adolescents and young men. Therefore, it is uncertain whether the results can be generalized to female adolescents and young women.

Power

Compared with investigations that have measured cognitive functioning at only one time point, our study lacks power. However, we do not believe that another prospective sample is available that would have greater statistical power to examine the associations studied herein.

INTERPRETATION OF FINDINGS

Does the Decline Have a Neurodevelopmental or Social Causation?

Our first hypothesis, that individuals who developed psychosis would show a relative decline in cognitive functioning, was supported. Moreover, the effect was specific to verbal decline, and decline between ages 13 and 18 years was a stronger predictor of psychosis than absolute performance at age 18 years. This suggests that the premorbid cognitive deficit observed in schizophrenia and other psychoses represents a disruption of neurodevelopment during the teenage years.

Does the Observed Decline Reflect a Prodromal or Neurodevelopmental Process?

If individuals who developed psychosis experienced a relative decline in their verbal skills at a particular age that was unrelated to the age at onset of psychosis, we might infer that the verbal decline represented an age-dependent neurodevelopmental process. On the other hand, if the timing of the decline was related to the onset of symptoms, a prodromal effect would be suggested.

Recent data from the North American Prodrome Longitudinal Study[35] showed that, among individuals at high risk for schizophrenia, greater impairment of verbal memory predicted earlier conversion. Inasmuch as both tasks are "verbal," their finding is in broad agreement with ours. However, like most studies of prodromal symptoms, the participants in that study were adolescents or young adults, with a mean age of 18 years. Therefore, it was impossible to determine whether the timing of verbal decline was related to the onset of psychosis or simply to age.

We believe that our data indicate an age-dependent process for the following reasons. First, there was a mean delay of more than 10 years between the relative verbal decline measured in our sample and the first hospital admission of individuals with psychosis. Second, we attempted to prevent contamination by prodromal effects by excluding patients who were identified at conscription as experiencing psychosis or who were hospitalized with psychosis during the first year after testing. Third, restricting the analysis to individuals who developed psychosis after age 25 years did not diminish the association between relative verbal decline and the risk for schizophrenia and other nonaffective psychoses; on the contrary, it strengthened it. This suggests that relative verbal decline in adolescence and young adulthood reflects a neurodevelopmental process that occurs at a fixed age and puts the individual at an increased lifetime risk for psychosis, as opposed to a prodromal process that occurs shortly before the onset of symptoms.

How Does Relative Cognitive Decline Relate to Brain Changes?

The predominant neuroanatomical changes in adolescent brain development are an overall reduction in gray matter volume, which is thought to represent synaptic pruning, and a corresponding increase in white matter volumes and fractional anisotropy, which may indicate maturation of axons or myelin sheaths, although other interpretations of these changes are possible.[16] Feinberg[36] proposed that schizophrenia results from an exaggeration of the typical synaptic elimination that occurs during adolescence, and several lines of evidence support this view.[15] Further support comes from prodromal investigations showing that patients who go on

to develop psychosis have lower gray matter volumes than those who do not.[37]

A recent longitudinal study[38] conducted IQ tests (using the Wechsler Adult Intelligence Scale) and structural magnetic resonance imaging studies in 33 healthy adolescents at 2 time points (mean [SD] ages, 14.1 [1.0] and 17.7 [1.0] years) during the same period of development as our study participants. Verbal IQ showed considerable intraindividual variability between the 2 time points, with an overall mean (SD) change of 3.0 (10.6) in verbal IQ. These changes in verbal IQ were closely correlated with changes in gray matter density in a region of the left motor cortex that is activated by the articulation of speech. Therefore, it is possible that changes in verbal ability detected in the patients who subsequently developed psychosis in our sample were associated with reductions in gray matter density in this area. Large-scale longitudinal studies that simultaneously examine brain structural and cognitive changes in samples large enough to identify substantial numbers of individuals who develop psychosis later in life will be needed to clarify this question.

In summary, we conducted the first prospective, population-based study to date that examines a decline in cognitive functioning relative to the general population during late neurodevelopment and the risk for psychosis in adulthood. We found a relative decline in verbal ability between ages 13 and 18 years that predicts later psychosis more strongly than the absolute score at age 18 years and that this decline is associated independently with the development of schizophrenia and other nonaffective and affective psychoses. We argue that the decline likely represents an age-dependent neurodevelopmental process rather than a prodromal process or a marker of social factors. Further research is required to determine what types of longitudinal changes in cognitive functioning occur in the premorbid phase and how they relate to neuroanatomical changes.

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Correspondence: James H. MacCabe, MRCPsych, PhD, Department of Psychosis Studies, Institute of Psychiatry, King's College London, London SE5 8AF, England (james.maccabe@kcl.ac.uk).
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