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Long-term Changes in Cognitive Functioning in Individuals With Psychotic Disorders
Findings From the Suffolk County Mental Health Project

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IMPORTANCE It remains uncertain whether people with psychotic disorders experience progressive cognitive decline or normal cognitive aging after first hospitalization. This information is essential for prognostication in clinical settings, deployment of cognitive remediation, and public health policy.

OBJECTIVE To examine long-term cognitive changes in individuals with psychotic disorders and to compare age-related differences in cognitive performance between people with psychotic disorders and matched control individuals (ie, individuals who had never had psychotic disorders).

DESIGN, SETTING, AND PARTICIPANTS The Suffolk County Mental Health Project is an inception cohort study of first-admission patients with psychosis. Cognitive functioning was assessed 2 and 20 years later. Patients were recruited from the 12 inpatient facilities of Suffolk County, New York. At year 20, the control group was recruited by random digit dialing and matched to the clinical cohort on zip code and demographics. Data were collected between September 1991 and July 2015. Analysis began January 2016.

MAIN OUTCOMES AND MEASURES Change in cognitive functioning in 6 domains: verbal knowledge (Wechsler Adult Intelligence Scale–Revised vocabulary test), verbal declarative memory (Verbal Paired Associates test I and II), visual declarative memory (Visual Reproduction test I and II), attention and processing speed (Symbol Digit Modalities Test–written and oral; Trail Making Test [TMT]-A), abstraction-executive function (Trenerry Stroop Color Word Test; TMT-B), and verbal fluency (Controlled Oral Word Association Test).

RESULTS A total of 705 participants were included in the analyses (mean [SD] age at year 20, 49.4 [10.1] years): 445 individuals (63.1%) had psychotic disorders (211 with schizophrenia spectrum [138 (65%) male]; 164 with affective psychoses [76 (46%) male]; 70 with other psychoses [43 (61%) male]); and 260 individuals (36.9%) in the control group (50.5 [9.0] years; 134 [51.5%] male). Cognition in individuals with a psychotic disorder declined on all but 2 tests (average decline: $d = 0.31$; range, 0.17-0.54; all $P < .001$). Cognitive declines were associated with worsening vocational functioning (Visual Reproduction test II: $r = 0.20$; Symbol Digit Modalities Test–written: $r = 0.25$; Stroop: $r = 0.24$; $P < .009$) and worsening negative symptoms (avolition: Symbol Digit Modalities Test–written: $r = -0.24$; TMT-A: $r = -0.21$; Stroop: $r = -0.21$; all $P < .009$; inexpressivity: Stroop: $r = -0.22$; $P < .009$). Compared with control individuals, people with psychotic disrders showed age-dependent deficits in verbal knowledge, fluency, and abstraction-executive function (vocabulary: $\beta = -0.32$; Controlled Oral Word Association Test: $\beta = -0.32$; TMT-B: $\beta = 0.23$; all $P < .05$), with the largest gap among participants 50 years or older.

CONCLUSIONS AND RELEVANCE In individuals with psychotic disorders, most cognitive functions declined over 2 decades after first hospitalization. Observed declines were clinically significant. Some declines were larger than expected due to normal aging, suggesting that cognitive aging in some domains may be accelerated in this population. If confirmed, these findings would highlight cognition as an important target for research and treatment during later phases of psychotic illness.

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Supplemental content

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Cognitive impairment is a central feature of schizophrenia and is associated with poor social and vocational outcomes.[1,2] Prospective studies demonstrate that cognitive deficits predate psychosis onset.[3-5] Ultrahigh-risk and first-episode psychosis studies find that in the short term, levels of cognitive dysfunction are stable or improving.[6-13] However, systematic evidence on the long-term cognitive outcome in first-episode psychosis is very limited.[14] Several studies followed up first-episode psychosis cohorts for 10 years and mostly found stable cognitive performance.[15-18] Others reported declines in at least some cognitive functions.[17,19] Long-term outcomes may be different, and longer-term studies are needed to determine whether cognitive impairment in psychotic disorders is indeed progressive.

To our knowledge, only 1 study went beyond 10-year follow-up. It assessed processing speed and store of general knowledge multiple times over 20 years in 244 patients with schizophrenia, other psychotic disorders, and nonpsychotic depression.[20] Cognition improved initially and showed no decline thereafter in any diagnostic group. However, the sample was relatively young, with a mean age of 43 years at the 20-year assessment, and the authors noted that decline might occur when participants are older.[20] Indeed, some studies found a decline in cognitive performance among older people with schizophrenia.[21-24] Importantly, these declines might be limited to institutionalized populations, and it is unclear whether they are also present in people with psychotic disorders living in the community. We sought to conduct a more comprehensive study of this question by including 11 cognitive tests, a larger sample followed for 20 years, and people with psychotic disorders in middle and late adulthood.

Another unanswered question is whether course of cognitive change differs among psychotic disorders. Cross-sectional studies established that cognitive deficits are present in bipolar disorder[25] and major depression with psychosis[26] but are worse in schizophrenia.[27-29] However, it is unclear whether cognitive changes over time differ between mood disorders and schizophrenia.[30-32] We sought to compare cognitive change among diagnostic groups.

Even when cognitive decline is present in psychotic disorders, its clinical significance is uncertain. Although schizophrenia research suggested that cognitive deficits leads to negative symptoms and impairs everyday functioning,[33-35] longitudinal findings have been mixed. Some studies reported that cognitive decline is unrelated to change in symptoms,[36-38] whereas others found that it is associated with increase in symptoms.[18,39] Findings for functioning are similarly mixed, although studies with longer follow-up report links between cognitive and functional declines more consistently.[40-42] One aim of the present investigation was to further investigate clinical and functional correlates of cognitive changes.

In this 20-year study of first-admission psychosis, we sought to address the aforementioned gaps. First, we investigated whether cognitive functioning in individuals with psychotic disorders declines in the long term. Second, we tested whether cognitive changes differ between schizophrenia and other psychotic disorders. Third, we evaluated the clinical significance of cognitive changes by analyzing their association with changes in symptoms and functioning. Fourth, we examined whether relative deficits increased as much as age by comparing cognitive outcomes in psychotic disorders with a matched group who never had psychotic disorders.

Key Points

Question What is the long-term progression of cognitive functioning in individuals after first hospitalization with a psychotic disorder?

Findings In this study of 445 people with psychotic disorders, cognitive performance declined in most domains and some of these changes were larger than expected owing to normal aging. Declines were consistent across psychotic disorders and were associated with worsening functioning and negative symptoms; also, people with psychotic disorders performed worse on all cognitive tests than control individuals (n = 260), especially after age 50 years.

Meaning Cognitive aging may be more rapid in individuals with psychotic disorders than in the general population for some cognitive domains.

Method

Sample

Participants came from the Suffolk County Mental Health Project, a longitudinal study of first-admission patients with psychotic disorders recruited from the 12 psychiatric inpatient units in Suffolk County, New York, between the last quarters of 1989 and 1995.[43-45] Inclusion criteria were age 15 to 60 years, first admission either current or within 6 months, clinical evidence of psychosis, no apparent medical cause, ability to understand assessment procedures in English, baseline IQ higher than 70, and the capacity to provide informed consent. The Stony Brook University Institutional Review Board approved the study annually. Written informed consent was obtained. For participants aged 15 to 17 years, written consent of parents and verbal assent of participants were obtained. The response rate for the baseline assessment was 72%. At 20-year follow-up, a comparison group of adults was recruited using random digit dialing within zip codes where participants with psychotic disorders resided (for details see Velthorst et al[46]). Data were collected between September 1991 and July 2015. Analysis began January 2016.

Neurocognitive Assessment

Six cognitive domains were measured at year 2 and again at year 20.[28,47] Verbal knowledge was assessed with the Wechsler Adult Intelligence Scale-Revised vocabulary test; verbal declarative memory with the Wechsler Memory Scale-Revised and Verbal Paired Associates test I (immediate) and II (delayed); visual declarative memory with Wechsler Memory Scale-Revised Visual Reproduction test I (immediate) and II (delayed); attention and processing speed with the Symbol Digit Modalities Test (SDMT; written and oral) and part A of the Trail Making Test (TMT-A); abstraction-executive function with the

Table 1. Cognitive Performance by Test, Diagnosis Group, and Point at the Year-2 and Year-20 Assessment[a]

Cognitive Measures Test	Range of Scores	Assessment Year	SZ		AP		OP		No Psychotic Disorder		Group Differences
			No.	Mean (SD)	No.	Mean (SD)	No.	Mean (SD)	No.	Mean (SD)	
Verbal knowledge											
Vocabulary[b]	1-28	2	184	17.13 (5.77)	146	19.69 (4.68)	62	16.92 (4.89)	NA	NA	SZ < AP ≈ OP
		20	108	17.73 (6.10)	90	20.58 (5.31)	32	18.78 (5.54)	258	22.35 (3.99)	SZ ≈ OP < AP < NP
Verbal declarative memory											
VPA I	3-24	2	174	14.93 (4.58)	139	17.41 (4.01)	55	15.60 (4.34)	NA	NA	SZ ≈ OP < AP
		20	114	13.38 (5.17)	90	16.04 (4.08)	32	14.56 (4.90)	259	16.52 (3.87)	SZ < AP ≈ OP ≈ NP
VPA II	0-8	2	171	6.50 (1.69)	138	7.04 (1.36)	54	6.61 (1.64)	NA	NA	SZ < AP ≈ OP
		20	111	6.20 (1.74)	90	6.93 (1.38)	31	6.61 (1.58)	258	7.10 (1.09)	SZ < AP ≈ OP < NP
Visual declarative memory											
VR I	0-41	2	184	26.25 (8.46)	144	30.32 (7.09)	59	28.89 (6.76)	NA	NA	SZ < AP ≈ OP
		20	112	23.79 (8.40)	88	26.99 (7.10)	32	27.19 (6.56)	258	30.07 (4.69)	SZ < AP ≈ OP < NP
VR II	0-41	2	183	19.06 (10.70)	142	25.41 (9.52)	59	23.86 (9.49)	NA	NA	SZ < AP ≈ OP
		20	110	16.72 (9.20)	87	21.38 (9.01)	31	21.52 (7.87)	258	30.07 (4.69)	SZ < AP ≈ OP < NP
Attention and processing speed											
SDMT-written	11-88	2	181	37.83 (11.24)	140	47.87 (11.83)	58	44.90 (11.62)	NA	NA	SZ < OP < AP
		20	113	34.18 (10.15)	89	43.93 (11.19)	33	40.64 (9.87)	258	49.55 (9.84)	SZ < AP ≈ OP < NP
SDMT-oral	14-103	2	181	43.46 (13.58)	141	54.18 (13.70)	55	50.62 (13.42)	NA	NA	SZ < AP ≈ OP
		20	112	40.54 (11.77)	90	49.41 (14.25)	33	46.85 (12.00)	256	58.37 (11.36)	SZ < AP ≈ OP < NP
TMT-A	13-136	2	183	41.43 (18.00)	143	34.34 (16.08)	59	34.83 (11.35)	NA	NA	SZ < AP ≈ OP
		20	109	44.28 (20.54)	87	37.76 (21.94)	31	40.26 (23.05)	256	28.46 (9.92)	SZ < AP ≈ OP < NP
Abstraction-executive function											
TMT-B	24-180	2	178	105.49 (43.41)	139	76.70 (33.63)	56	85.18 (36.77)	NA	NA	SZ < AP ≈ OP
		20	106	124.95 (47.85)	87	96.13 (45.32)	31	106.65 (52.67)	253	71.43 (34.19)	SZ < AP ≈ OP < NP
Stroop	11-112	2	169	81.04 (22.76)	136	96.19 (17.66)	55	90.42 (19.82)	NA	NA	SZ < AP ≈ OP
		20	87	77.09 (23.74)	80	94.38 (22.02)	30	85.13 (25.19)	256	100.66 (16.05)	SZ < OP < AP < NP
Verbal fluency											
COWAT	4-72	2	177	31.45 (12.09)	141	37.36 (11.48)	58	34.76 (11.12)	NA	NA	SZ < AP ≈ OP
		20	109	31.65 (11.88)	90	37.61 (15.71)	32	36.34 (11.98)	256	41.58 (13.48)	SZ < AP ≈ OP < NP

Abbreviations: AP, affective psychoses; COWAT, Controlled Oral Word Association Test; NA, not applicable; NP, no psychotic disorder; OP, other psychoses; SZ, schizophrenia spectrum; SDMT, Symbol Digit Modalities Test; Stroop, Trenerry Stroop Color Word Test; TMT-A, Trail Making Test–A; TMT-B, Trail Making Test–B; VPA, Verbal Paired Associates test; VR, Visual Reproduction test; ≈, not statistically different.

[a] For effect sizes (β) of the respective group differences see eTable 7 in the Supplement.

[b] Assessed using the Wechsler Adult Intelligence Scale–Revised vocabulary test.

Trenerry Stroop Color Word Test (Stroop) and part B of the Trail Making Test (TMT-B); and verbal fluency with the Controlled Oral Word Association Test (FAS fluency). **Table 1** outlines the domain and range of scores for each cognitive test. eTable 3 in the Supplement reports correlations among cognitive tests.

Table 2. Baseline Demographic and Clinical Characteristics by Diagnosis Group of Participants With Cognitive Assessment at Either Point

Characteristic	Mean (SD)			*P* Value[a]	Group Differences
	SZ (n = 211)	AP (n = 164)	OP (n = 70)		
Male, No. (%)	138 (65.4)	76 (46.3)	43 (61.4)	.001	SZ = OP > AP
White, No. (%)	144 (68.3)	144 (87.8)	45 (64.3)	<.001	SZ = OP > AP
Education (≤high school), No. (%)	135 (64.0)	89 (54.3)	44 (62.8)	.14	NA
Never married, No. (%)	159 (75.4)	97 (59.2)	42 (60.0)	.002	SZ > OP = AP
Employed, No. (%)	86 (40.8)	119 (72.6)	41 (58.6)	<.001	AP > SZ
Age, y	28.51 (8.50)	29.13 (10.09)	29.47 (9.29)	.69	NA
Socioeconomic status[b]	4.68 (2.06)	4.24 (1.80)	4.47 (1.82)	.10	NA
Global assessment of functioning (past year)	52.94 (14.29)	64.57 (11.40)	57.32 (13.69)	<.001	SZ > OP = AP
Reality distortion symptoms	13.17 (10.13)	9.48 (8.52)	8.96 (6.84)	<.001	SZ > OP = AP
Disorganized symptoms	7.35 (7.13)	6.41 (6.09)	6.06 (5.65)	.23	NA
Inexpressivity symptoms	9.89 (8.11)	4.65 (6.66)	5.46 (6.54)	<.001	SZ > OP = AP
Avolition symptoms	12.22 (7.10)	7.38 (6.90)	7.74 (7.16)	<.001	SZ > OP = AP
Social functioning (6-mo wave)	7.80 (3.80)	11.30 (4.06)	10.86 (3.36)	<.001	AP = OP > SZ

Abbreviations: AP, affective psychoses; NA, not applicable; OP, other psychoses; SZ, schizophrenia spectrum; ≈, not statistically different.

[a] *P* value indicates overall differences between diagnostic groups (χ^2 tests were used for categorical variables and analysis of variance for continuous variables).

[b] Range of 1 to 8 with higher scores indicating lower socioeconomic status.

Diagnosis

The Structured Clinical Interview for *DSM-IV*[48] was administered at baseline and at 6-month, 2-year, and 10-year follow-up. A team of 4 or more psychiatrists (L.J.F., G.A.C., and others) formulated longitudinal consensus diagnoses based on the Structured Clinical Interview for *DSM-IV*, medical records, and interviews with key informants after each assessment. We used the last available diagnosis. Diagnoses were grouped into schizophrenia spectrum (schizophrenia and schizoaffective disorders [n = 211]), affective psychoses (psychotic bipolar disorder and major depressive disorder [n = 164]), and other psychoses (eg, brief psychotic disorder, substance induced psychosis, psychosis-not otherwise specified [n = 70]).

Sample Characteristics and Correlates of Cognitive Change

Baseline socioeconomic status was rated on a modified Hollingshead occupational scale (range, 1-8; higher scores indicate lower socioeconomic status)[49] for the primary breadwinner of the household. At year 2 and year 20, symptoms were rated using the Scale for the Assessment of Positive Symptoms[50] to measure reality distortion (α ≥ 0.80; 14 items) and disorganization (α ≥ 0.72; 11 items) and the Scale for the Assessment of Negative Symptoms[51] to measure avolition (α ≥ 0.81; 6 items) and inexpressivity (α ≥ 0.88; 11 items).[46,52] Functioning was assessed by interviewers in 2 domains: vocational (dichotomized as competitive employment [full time or part time] or student vs other) and social, a composite of 3 ratings from the Quality of Life Scale (α ≥ 0.79; range 1-17).[45] Scores on this index ranged from 0 (extremely poor) to 6 (satisfactory) for social activity and sociosexual relationships and from 1 to 5 for relationships with friends.[46]

Data Analyses

Change in each test was modeled using linear mixed-effects regression (Stata command: xtmixed; Stata, version 14 [StataCorp]) with effect of time and a random intercept (from year 2 to 20). Between-individual predictors were diagnosis, sex, age at year 2, and the interaction term between year-2 age and time (to examine whether the magnitude of cognitive declines was age dependent). Also, diagnosis was tested as a predictor of slope of time, and this term was dropped if it was not significant. Missing data were handled with full information maximum likelihood, which used all available data for the 445 participants.

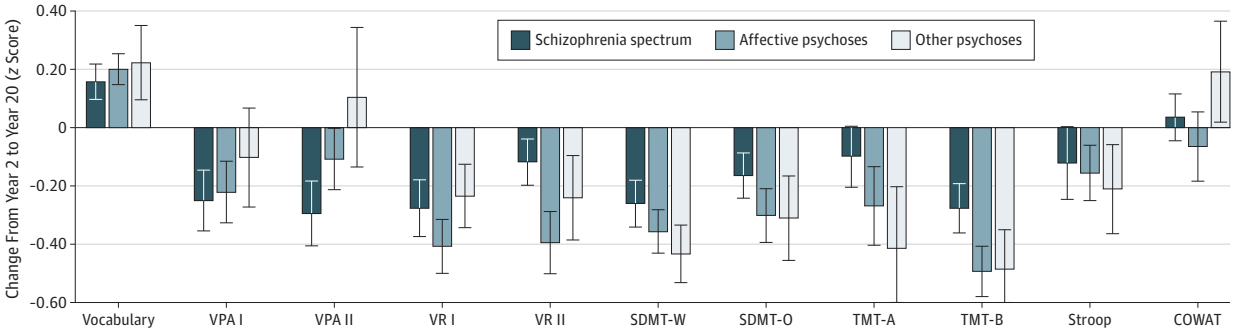
Correlations between cognitive and clinical change were examined in the retest subsample (n = 195) by computing partial correlations between change (year 20 - year 2) on a neuropsychological test and on a clinical feature, controlling for age at year 2. Each significant association was further examined using cross-lagged panel model to estimate the direction of the association.

Year-20 cognitive performance on each test was regressed on sex, age (<40, 40-49, 50-59, ≥60 years), group (psychotic disorder vs control), and age by group interaction. Sizes of the resulting cells are given in eTable 4 in the Supplement. Analyses were conducted in Stata version 14 (StataCorp). All analyses used raw rather than normed scores as recommended for longitudinal studies.[53] Figures were standardized to year 2 scores to enhance clarity.

Results

The initial sample comprised 628 eligible participants; 445 of them completed a broad neuropsychological assessment at either 2-year (n = 399) or 20-year follow-up (n = 241) and constitute the analysis sample. Their characteristics at study entry are described in **Table 2**. The 195 participants who completed assessments at both points (retest subsample) did not differ from those who completed testing only at 1 point on any of the study variables, other than slightly lower disorganiza-

Figure 1. Change in Cognitive Performance by Diagnosis Group for Retest Subsample



Change in cognitive performance was standardized according to standard deviation of the corresponding variable at year 2, and 1 point represents a change of 1 SD. Error bars represent standard errors. COWAT indicates Controlled Oral Word Association Test; SDMT-O, Symbol Digit Modalities Test–oral; SDMT-W, Symbol Digit Modalities Test–written; Stroop, Trenerry Stroop Color Word Test; TMT-A, Trail Making Test–A; TMT-B, Trail Making Test–B; VPA, Verbal Paired Associates test; VR, Visual Reproduction test.

tion symptoms in the 2-year–only group (Cohen d = 0.20) and a lower prevalence of never married participants in the 20-year–only group (52.2%) (eTables 1 and 2 in the Supplement).

The comparison group was frequency matched to the clinical cohort on sex (257 [55.9%] vs 134 [58.1%] male) and age (mean [SD] age, 50.5 [9.0] years vs 48.0 [8.8] years). The participation rate for the comparison group was 67%, and 260 of 262 participants completed cognitive testing.

Diagnostic Differences in Cognitive Performance

Cognitive performance on each test and point is shown in Table 1, stratified by diagnosis (for retest subsample and change scores see eTables 5 and 6 in the Supplement). At years 2 and 20, participants with schizophrenia spectrum disorders performed worse than participants with affective and other psychoses (Table 1). At year 20, all groups performed worse than the control group (Table 1; eTable 7 and eFigure 1 in the Supplement). However, the diagnostic groups did not differ in the degree of change over 18 years on any test (P >.09; χ^2 range, 0.22-4.61) (eFigure 1 in the Supplement); therefore, all subsequent analyses combined psychotic disorders into a single group.

Change in Cognitive Performance From Year 2 to 20

Over 18 years, performance did not change on verbal fluency and significantly increased on verbal knowledge, as indicated by the vocabulary test (d = 0.34; P < .01). Performance declined significantly on all other tests, with a mean decrease of d = 0.31 (range, 0.17-0.54; small to medium effect size; **Figure 1**). Older age at first cognitive assessment was associated with worse performance on cognitive tests (P < .05), except verbal knowledge (b = −0.04; P = .08) and fluency (b = −.05; P = .46). However, the magnitude of cognitive change was generally not associated with initial age, with year-2 age associated with greater decline only in abstraction-executive function (Stroop) (b = −0.68; P < .001), attention and processing speed (SDMT-oral) (b = −.20; P = .02), and verbal fluency (b = −.23; P = .01).

Correlates of Cognitive Change

We correlated changes on each cognitive test in retest subsample with changes in symptom and functioning (**Table 3**). Increase in reality distortion was associated with decline on only 1 test, increase in disorganization was associated with decline on 3 tests, increase in inexpressivity was associated with decline on 4 tests, and increase in avolition correlated with declines on 7 tests (vocabulary, SDMT-written, SDMT-oral, TMT-A, Stroop, TMT-B, and Controlled Oral Word Association Test) with small to medium effect sizes. For these tests, the greatest observed declines were associated with an increase in avolition of 1 to 2 standard deviations, underscoring the clinical significance of cognitive change (eFigure 2 in the Supplement). Worsening of social functioning was associated with change on only 1 test, but decrease in vocational status was associated with decline on 5 tests (vocabulary, Visual Reproduction test II [delayed], SDMT-written, Stroop, and TMT-B). For these tests, a clear gradient was present with the worst cognitive change in participants who became unemployed and the best cognitive change in those who became employed (eFigure 3 in the Supplement). Individuals who remained unemployed and those who maintained employment showed intermediate cognitive changes. Associations between change in vocational functioning and change on most cognitive tests, apart from TMT-B and vocabulary, remained significant after controlling for changes in symptoms (ie, negative, positive, disorganized symptoms), highlighting the specificity of cognition-employment links. The association between cognitive change and change in social functioning became nonsignificant when symptom change was controlled. eTable 8 in the Supplement shows the correlations between symptom and functioning changes in the retest subsample. We found medium to large associations between increases in symptoms and decreases in social functioning and similar but weaker associations for change in vocational functioning. Cross-lagged models consistently found that cognitive impairments predicted worse vocational function-

Table 3. Associations Between Change in Cognitive Performance and Change in Symptoms and Functioning From Year 2 to 20 for Retest Subsample, Partial Correlations Adjusted for Age

Variable	Verbal Knowledge and Vocabulary	Verbal Declarative Memory		Visual Declarative Memory		Attention and Processing Speed			Abstraction Executive Function		Verbal Fluency, COWAT
		VPA I	VPA II	VR I	VR II	SDMT-W	SDMT-O	TMT-A	Stroop	TMT-B	
Symptoms											
Reality distortion	0.03	−0.11	−0.06	−0.06	−0.20[a,b]	0.01	0.02	0.13	−0.13	0.02	−0.06
Disorganized	0.03	−0.09	−0.03	−0.26[a,b]	−0.09	−0.23[a,b]	−0.09	−0.06	−0.22[a,b]	−0.12	0.04
Inexpressivity	−0.09	−0.12	0.01	−0.11	−0.13	−0.16[c]	−0.20[b]	−0.05	−0.22[a,b]	−0.09	−0.19[c]
Avolition	−0.19[c]	−0.13	−0.06	−0.02	−0.13	−0.24[a,b]	−0.15[c]	−0.21[a,b]	−0.22[a,b]	−0.16[c]	−0.17[c]
Functioning											
Vocational	0.16[c]	0.00	−0.17[c]	0.03	0.20[a,b]	0.25[a,b]	0.12	0.13	0.24[a,b]	0.20[b]	0.13
Social	0.11	0.11	0.13	0.01	0.13	0.13	0.15[c]	0.14	0.09	0.07	0.03

Abbreviations: COWAT, Controlled Oral Word Association Test; SDMT-O, Symbol Digit Modalities Test–oral; SDMT-W, Symbol Digit Modalities Test–written; Stroop, Trenerry Stroop Color Word Test; TMT-A, Trail Making Test–A; TMT-B, Trail Making Test–B; VPA, Verbal Paired Associates test; VR, Visual Reproduction test.

[a] When corrected for multiple comparison/false discovery rate (66 comparisons with q = 0.05) *P* values were significant at .009. For interpretability, scores on TMT-A and TMT-B were reversed so that a decrease in score would indicate worse cognitive function.

[b] *P* < .01.

[c] *P* < .05

ing and negative symptoms 18 years later, but symptoms and functioning never predicted cognition (eTable 9 in the Supplement).

Cognitive Outcomes in Individuals With Psychotic Disorders Compared With Control Individuals

At year 20, the control group (n = 260) performed better on all cognitive tests than the group with psychotic disorders (n = 241). These differences were larger in older participants for verbal knowledge, verbal fluency, and abstraction-executive function (vocabulary: β = −0.32; Controlled Oral Word Association Test: β = −0.32; TMT-B: β = 0.23; all *P* < .05). Performance differences on these tests increased until age 50 years and plateaued thereafter (**Figure 2**), with relative deficits increasing by as much as 0.5 standard deviation from the 30s to 50s. When adjusted for education, associations for age with group differences in verbal knowledge and fluency remained significant (β = −0.28, *P* = .02), but TMT-B results became a trend (β = 0.19; *P* = .09).

Discussion

This 18-year study of a first-admission psychosis cohort found that cognitive performance declined over time in verbal memory, visual memory, attention and processing speed, and abstraction-executive function. These changes were similar in magnitude across all psychotic disorders. They were associated with worsening of negative symptoms and loss of gainful employment. Compared with a matched control group, year-20 cognitive outcomes were poor in psychotic disorders, especially for older participants. These results provide the first comprehensive picture of long-term cognitive changes and associated clinical and functional outcomes in psychotic disorders.

Change in Cognitive Functioning From Year 2 to 20

Cognitive decline observed in our cohort contrasts with evidence suggesting that in the general population, most cognitive functions are stable or improve until at least age 50 years; processing speed is the clearest exception as it decreases across adulthood.[54-57] However, the pattern of findings is complex, and some studies reported broad cognitive declines in adulthood.[58] In data from a national US longitudinal cohort,[59] only processing speed showed a prominent decline in the age range of interest, and our sample showed significantly faster declines in executive function and immediate verbal memory than the national cohort (eTable 10 in the Supplement).

Furthermore, studies of schizophrenia that included a control group reported no cognitive declines in the healthy participants even after more than 5 years.[11,60] Cognitive changes in our cohort are consistent with previous findings of accelerated cognitive aging in older individuals with schizophrenia[21-24] and evidence of accelerated aging of neural functions, health, mobility, and premature mortality in schizophrenia.[61-65]

Although observed cognitive changes potentially exceed normal aging in some domains, the evidence is indirect, and longitudinal studies with matched controls are needed. To our knowledge, only 1 longitudinal study examined cognition in psychotic disorder and matched groups over 10 years.[19] Similar to our results, their findings also suggested accelerated aging in some domains. They observed accelerated aging in memory and verbal knowledge but not executive functions or fluency. Additional data are needed to determine whether this discrepancy between the studies is due to difference in sampling methods, cognitive measures, follow-up duration, or reference data (matched control or general population).

We also observed that although schizophrenia showed greater initial cognitive impairment than other psychotic disorders, change over time was similar across disorders. This is consistent with findings of prior longitudinal studies.[12,20]

Clinical Significance of Cognitive Change

Observed cognitive changes were associated with changes in symptoms and vocational functioning of small to moderate effect size. Avolition and employment showed the strongest effects, whereas reality distortion and social functioning were largely not associated with cognitive changes. Changes in vocational functioning and cognition remained linked, even controlling for symptom changes. This is consistent with cross-sectional findings linking cognitive impairment to vocational rather than social outcomes[35] and to negative rather than positive symptoms.[34] Correlated change may point to bidirectionality (ie, the factors influence each other) or to the influence of a third underlying variable.[36,66] The present data suggested directional effects from cognition to symptoms and functioning. The observed association likely is not limited to psychotic disorders, as cognitive and functional declines have been linked in other populations.[67,68] Importantly, our results showed wide variability in the level of cognitive change in the Suffolk County Mental Health Project cohort (eTable 6 in the Supplement).

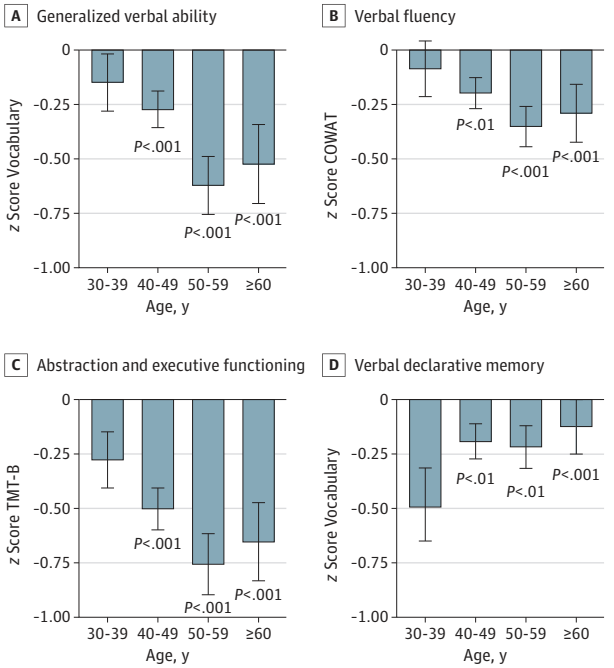
Cognitive Performance in Group With Psychotic Disorders vs Control Group

Compared with the control group, 20-year cognitive performance in psychotic disorders was impaired, especially in schizophrenia spectrum disorders, consistent with extensive literature.[69-71] This relative impairment was consistent across ages, except for greater deficits in older people on vocabulary knowledge, verbal fluency, and abstraction-executive function. In the general population, vocabulary and verbal fluency tend to improve with age,[57] and age gradients on these tests might indicate that psychotic disorders interfere with new learning, leading to smaller than expected improvement. The steep age gradient in abstraction-executive function is consistent with longitudinal results that in psychotic disorders abstraction-executive function declines faster than expected owing to aging. The shape of these age gradients suggests that accelerated cognitive aging in psychotic disorders is maximal after age 50 years. However, this acceleration needs to be further investigated using longitudinal data.

Limitations

The findings need to be interpreted in the light of the following limitations. First, we used raw rather than normed scores because raw scores are more informative for follow-up studies.[53] Norms need to be longitudinal to capture the cognitive trajectory of a person over time, and paucity of longitudinal norms is a major gap in neuropsychology. Use of cross-sectional norms for comparison would introduce biases due to birth cohort differences in cognitive performance. Second, a matched comparison group was only included at the 20-year point. Instead, we compared cognitive changes in our cohort with follow-up studies of the general population and control groups matched to psychotic disorders in prior research, which are imperfect benchmarks. We are continuing to follow both the group with psychotic disorder and the control group, which will allow us to comprehensively address this limitation in the future. Third, while we considered the most studied potential correlates of cognitive change—symptoms and functioning—a broader range of variables should be examined to fully explicate drivers and consequences of cognitive decline. Fourth, participant attrition was sizeable, although similar to other longitudinal studies of cognition.[19,20,72] Nevertheless, cognitive change may have been different in participants who did not complete the follow-up, especially if attrition was due to illness remission or worsening. Fortunately, attrition was not associated with any substantial biases in the variables studied. Also, we obtained 20-year global outcome on 124 cohort members without 20-year cognitive data and found that their outcomes did not differ from those who completed cognitive assessment, further mitigating concern that attrition substantially biased results.

Figure 2. Cognitive Performance in Group of Individuals With Psychotic Disorders vs Control Group by Age



Depicted are 3 tests (A-C) that showed a significant association with age (performance deficits in group with psychotic disorders vs control group differed across ages) and a reference test without significant association with age (Verbal Paired Associates test I; D). Error bars indicate ±1 SE. TMT-B indicates Trail Making Test–B.

Conclusions

We found that most cognitive functions in individuals with psychotic disorders declined over 2 decades after first hospitalization. These declines were small to moderate in size, but some (abstraction-executive function and memory) appeared to be larger than normal age-related changes and were associated with worsening of symptoms and functioning. These findings agree with other evidence of accelerated aging in individuals with psychotic disorders.[18,20-23,61-65]

However, the present results are novel and require replication in a sample with a longitudinal control group. If replicated, they will highlight the importance of studying cognitive and neural functioning in later phases of psychotic illness to develop strategies for prevention of progressive deterioration. Some efficacious strategies may be translated from the general aging research, such as increased physical activity and reduction of social isolation.[73,74] Cognitive aging in psychotic disorders remains poorly understood and deserves further study.[62]

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