The Course of General Cognitive Ability in Psychotic Disorders

Katherine Jonas PhD[1], Wenxuan Lian MS[2], Jennifer Callahan PhD[3], Camilo J. Ruggero PhD[3], Sean Clouston PhD[4], Avraham Reichenberg PhD[5], Gabrielle A. Carlson MD[6], Evelyn J. Bromet PhD[1], Roman Kotov PhD[1]

[1] Department of Psychiatry, Stony Brook University

[2] Department of Applied Mathematics and Statistics, Stony Brook University

[3] Department of Psychology, University of North Texas

[4] Department of Family, Population and Preventive Medicine, Stony Brook University

[5] Department of Psychiatry, Icahn School of Medicine at Mount Sinai

[6] Department of Child Psychiatry, Stony Brook University

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Corresponding Author:

Katherine Jonas, PhD

Assistant Professor

Department of Psychiatry & Behavioral Health

Stony Brook University

Email: Katherine.jonas@stonybrookmedicine.edu

Phone: 206.484.7010

Key Points

Question: Schizophrenia and other psychotic disorders are associated with major cognitive deficits, but when deficits emerge and how they change over the course of illness is uncertain.

Finding: This study traced general cognitive ability in 428 individuals with psychotic disorders, for whom 1,619 estimates of general cognitive ability, spanning childhood to old age, were available. Cognitive decline began 14 years before the onset of psychosis, and was more rapid in schizophrenia than in other psychotic disorders, until 22 years after psychosis onset, at which point cognitive decline accelerated in both groups.

Meaning: The trajectory of general cognitive ability in schizophrenia is consistent with both a neurodevelopmental and neurodegenerative disorder.

Abstract

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: This study's purpose was to trace cognition from elementary school to old age, in order to test neurodevelopmental and neurodegenerative theories of psychotic disorders.

Design: Data are from the Suffolk County Mental Health Project, a longitudinal study of individuals with psychotic disorders. Data were collected between September 1989 and October 2019. Analyses were completed in October 2021.

Setting: The Suffolk County Mental Health Project is a first-admission psychosis cohort.

Participants: 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.

Exposures: Psychiatric hospitalization for psychosis.

Main Outcomes: Preadmission cognitive scores were extracted from school and medical records. Post-onset cognitive scores were based on neuropsychological testing at 6-month, 24-month, 20-year, and 25-year follow-ups.

Results: The cohort of 428 individuals, 212 with schizophrenia and 216 with other psychotic disorders, was 59.6% male, with an average age of psychosis onset of 27 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/year (95% CI -0.29 to -0.42, $p<0.01$), significantly faster

than those with other psychotic disorders (-0.15 IQ points/year, 95% CI -0.08 to -0.22, p<0.01). At 22 years post onset, both groups declined at a rate of -0.59 IQ points/year (95% CI -0.25 to -0.94, p<0.01).

Conclusions and Relevance: Cognitive trajectories in schizophrenia are consistent with both a neurodevelopmental and neurodegenerative pattern, resulting in a loss of 16 IQ points over the period of observation. Cognitive decline begins 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 both schizophrenia and other psychotic disorders.

Introduction

Cognitive deficits are common in 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 due to 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 one standard deviation.[7,8] Surprisingly, longitudinal studies of ultra-high risk and prodromal cohorts have not detected cognitive change among those who develop psychotic disorders.[9,10] Small population-based studies (N<40) 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 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 five 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 ten-year follow-ups have shown cognitive decline in 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 two 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 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.

To our knowledge, no study has charted cognitive trajectories of individuals with schizophrenia and other psychotic disorders across the lifespan. Following 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, in order to test neurodevelopmental and neurodegenerative theories of psychotic disorders.

Methods

This study follows STROBE reporting guidelines.[27] Figure 1 depicts a schematic of the study design. eFigure 1 depicts an inclusion flowchart.

Sample and Procedure

Data are drawn from the Suffolk County Project, a longitudinal first-admission psychosis study.[28] During the enrollment period (1989-1995), 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 15-60, 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. The Stony Brook University Committee on Research Involving Human Subjects and hospital institutional review boards approved the protocol annually. Written consent was obtained from all study participants, or from their parents for those who were minors.

Six-hundred and twenty-eight individuals were ascertained at baseline. 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 to the full cohort, this subgroup had a slightly younger age of onset, although they did not differ by other demographic factors or cognitive ability (eTable 1). eFigure 2 depicts histograms showing 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 colleagues[29]).

Measures

Demographics. Occupational status was quantified as the occupation of the primary breadwinner in the participants' household, rated on Hollingshead's rating, a scale from 1 ("large business owner/major professional/executive") to 8 ("not working").[30]

Age of Onset. Age of 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 (SCID) at baseline and SCID-IV thereafter. This information was supplemented by informant interviews, school records, and medical records. For details see Jonas and colleagues.[31]

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.[32] 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. Where IQ scores weren't available, academic achievement scores were substituted. Prior research has shown scores on achievement tests are closely correlated with IQ ($r \approx 0.7$-0.8). Those with preadmission cognitive data were younger at symptom onset and baseline assessment, because preadmission data was 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 reports specific test frequencies by diagnostic group.

Post-onset cognitive ability was assessed at 6-month, 24-month, 20-year, and 25-year follow-up interviews. At 6- and 24-month follow-up assessments, IQ was assessed using the Quick Test.[33,34] At 24-month, 20-year, and 25-year follow-up assessments, the cognitive battery included immediate trials of Verbal Paired Associates and Visual Reconstruction,[35] Symbol-Digit Modalities,[36] Trails A and B,[37] the Controlled Oral Word Association Test,[38] Vocabulary,[39] and the Stroop Test.[40] Altogether, 1619 estimates

of cognitive ability were available across the lifespan. The comparison group completed the same neuropsychological assessment as cases.

All test scores were converted to the IQ scale (M=100; SD=15). Details of the conversion are reported in the eMethods. Using the same scoring and rescaling procedure applied to cases, we estimated IQ scores for the comparison group at 20- and 25-year follow-ups. eTable 3 reports correlations and pairwise Ns of scores across time points. Table 1 reports descriptive statistics of general cognitive ability on the IQ scale across time points.

Analyses

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 two phases with different slopes (before and after transition). A model with 2 transition points has three 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.[41] 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 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 model with lower score.[42] All multilevel models were completed using the "nlme" package for R.[43,44]

Among cases, time could be measured either relative to birth or relative to psychosis onset. Figure 2 and eFigure 4 depict LOESS 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,[31] 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 (ΔBIC=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 re-run with diagnosis (schizophrenia or other psychotic disorder) as a covariate.

Results

The 428 participants were, on average, 27 years old at onset. The cohort was fifty-nine percent male. Most participants were on antipsychotic medications across post-admission assessments.

Figure 2 describes cognitive trajectories as a function of age among those with schizophrenia, other psychoses, and the comparison group. In schizophrenia, cognitive decline begins in adolescence. In both diagnostic groups, cognitive decline accelerated in adulthood, preceding that observed in the comparison group by approximately 20 years in schizophrenia, and 10 years in other psychoses.

Among cases, cognitive trajectories were best described as a function of time since psychosis onset, rather than age. The best-fitting model included three phases, moderated by diagnosis (see Table 2 for moderated model parameters, Figure 3 for model-implied trajectories, eTable 4 for fit statistics of competing models, eTable 5 for model parameters without diagnosis as a moderator). 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 13 years old— 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 one point on the IQ scale every seven years. Those with schizophrenia declined at a significantly faster rate of more than one point on the IQ scale every three 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.

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

Discussion

The trajectory of cognition across the lifespan in 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 an analysis of 428 individuals with psychotic disorders, for whom 1,619 estimates of general cognitive ability were available spanning childhood to old age, we identified three 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 is was by age, suggesting 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 psychotic disorders have identified deficits relative to healthy controls.[11,12] However, those studies were smaller (N<40), 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 age 13, 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 one IQ point every 3 years. By psychosis onset, the schizophrenia group had a 5-point cognitive deficit, consistent with meta-analytic findings for premorbid IQ deficits in schizophrenia.[5,6] Those with other psychotic disorders also experience 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 49 years old. At this second inflection point, cognitive decline accelerated among those with other psychotic disorders to a rate of one point on the IQ scale every two years, 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 will experience one half standard deviation of cognitive decline over their life expectancy.[46] By contrast, individuals with schizophrenia in this cohort will have lost a full standard deviation, a loss consistent with mild neurocognitive disorder, by age 55.[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 schizophrenia[48] 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. Post-onset cognitive decline may be a consequence of schizophrenia, rather than intrinsic to it.[52] Cognitive deficits are associated with profound psychosocial impairment in 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 cohort was recruited at first admission and followed back to obtain preadmission cognitive data. Some detail concerning tests forms and conditions are unknown, and tests varied across timepoints. This approach also misses individuals who develop psychotic disorders but are never hospitalized. However, in two epidemiological studies contemporary to this one, more than 90% of individuals with schizophrenia were hospitalized.[56,57] 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. Norms are not as rigorous of a comparison 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. Quasi-experimental 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 psychotic disorders, the advantage provided by the Flynn effect is counteracted by educational disruptions. Further research is needed to test this hypothesis.

Finally, this analysis did not distinguish trajectories on specific tests. Vocabulary, for example, is more resistant to decline than other neurocognitive abilities,[59] and was stable between 2- and 20-year follow-ups in this sample.[18] Vocabulary has been shown to decline in dementia,[60] 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).

Conclusions

Schizophrenia has been described as both a neurodevelopmental and a neurodegenerative disorder. Our findings provide support for both theories. We observe 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 schizophrenia, while gradual, resulted in over 16 IQ points lost over the lifespan. In other psychotic disorders, decline begins later relative to psychosis onset, but ultimately results in a loss

of 9 IQ points. 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 pre-empt the onset of cognitive decline, as well as later deterioration and dementia.

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Table 1

Descriptive statistics

	Schizophrenia (N=216)					Other Psychotic Disorders (N=212)				
	N (%)	Range	Median	Mean	SD	N (%)	Range	Median	Mean	SD
Gender (male)	140 (64.8)	-	-	-	-	114 (53.8)	-	-	-	-
Race										
Asian	8 (3.7)	-	-	-	-	2 (0.9)	-	-	-	-
Black	37 (17.1)	-	-	-	-	20 (9.4)	-	-	-	-
Hispanic	18 (8.3)	-	-	-	-	12 (5.7)	-	-	-	-
Native American	0 (0.0)	-	-	-	-	1 (0.5)	-	-	-	-
White	153 (70.8)	-	-	-	-	177 (83.5)	-	-	-	-
Occupational status	-	1-8	4	4.6	2.1	-	1-8	4	4.16	1.8
Age at psychosis onset	-	6-58	24	25.7	7.9	-	5-58	27	28.67	9.9
Symptoms and functioning at baseline assessment										
GAF	-	21-81	50.5	52.6	14.3	-	30-85	65	63.7	11.9
SAPS Hallucinations & Delusions	-	0-52	9.5	11.5	9.5	-	0-36	8	9.4	9.5
SAPS Disorganization	-	0-38	5	6.7	6.4	-	0-28	5	6.4	6.4
SANS Avolition	-	0-29	8	9.4	7.2	-	0-29	5.5	6.9	7.2
SANS Inexpressivity	-	0-36	4	6.9	7.8	-	0-30	2.0	4.8	7.8
Antipsychotic medication										
Preadmission	0 (0.0)	-	-	-	-	0 (0.0)	-	-	-	-
6 month	190 (94.5)	-	-	-	-	122 (63.9)	-	-	-	-
24 month	169 (91.8)	-	-	-	-	71 (40.6)	-	-	-	-
20 year	113 (93.3)	-	-	-	-	38 (36.5)	-	-	-	-
25 year	96 (92.3)	-	-	-	-	46 (44.2)	-	-	-	-
General cognitive ability (expressed on the IQ scale)										
Preadmission 1	104	53-136	101	100.0	15.9	112	62-131	104	103.2	13.6
Preadmission 2	56	42-128	100	98.7	16.9	61	59-140	100	99.7	13.2
Preadmission 3	30	67-135	97	97.6	16.7	35	75-135	98	99.2	12.5
Preadmission 4	17	67-126	92	94.8	15.3	14	74-114	95	95.6	10.9
Preadmission 5	6	64-102	90	86.0	13.2	1	89-89	89	89.0	-

6 month	201	60-130	96	95.3	14.4	191	42-130	100	98.9	13.2
24 month	184	57-117	92	90.9	12.3	175	43-121	102	99.0	11.6
20 year	121	50-116	87	85.6	13.9	104	47-115	98	95.5	13.0
25 year	104	53-109	83	83.0	12.6	104	56-119	96	93.8	12.8

Note. Occupational status is the occupation of the primary breadwinner in the participants' household, rated on Hollingshead's rating, a scale from 1 ("large business owner/major professional/executive") to 8 ("not working").[30] Symptom dimensions were scored according to factor analyses reported in Kotov et al., 2016.[61] Percentage of participants on antipsychotics is calculated within the subset of participants with an estimate of general cognitive ability at that time point. Preadmission 1, 2, 3, 4, and 5 refer to multiple instances of cognitive testing completed by some participants—i.e., statistics for Preadmission 2 reflect the second estimate of general cognitive ability for those participants who had more than one score available. GAF=Global Assessment of Function; SAPS=Schedule for the Assessment of Positive Symptoms; SANS=Schedule for the Assessment of Negative Symptoms.

Table 2

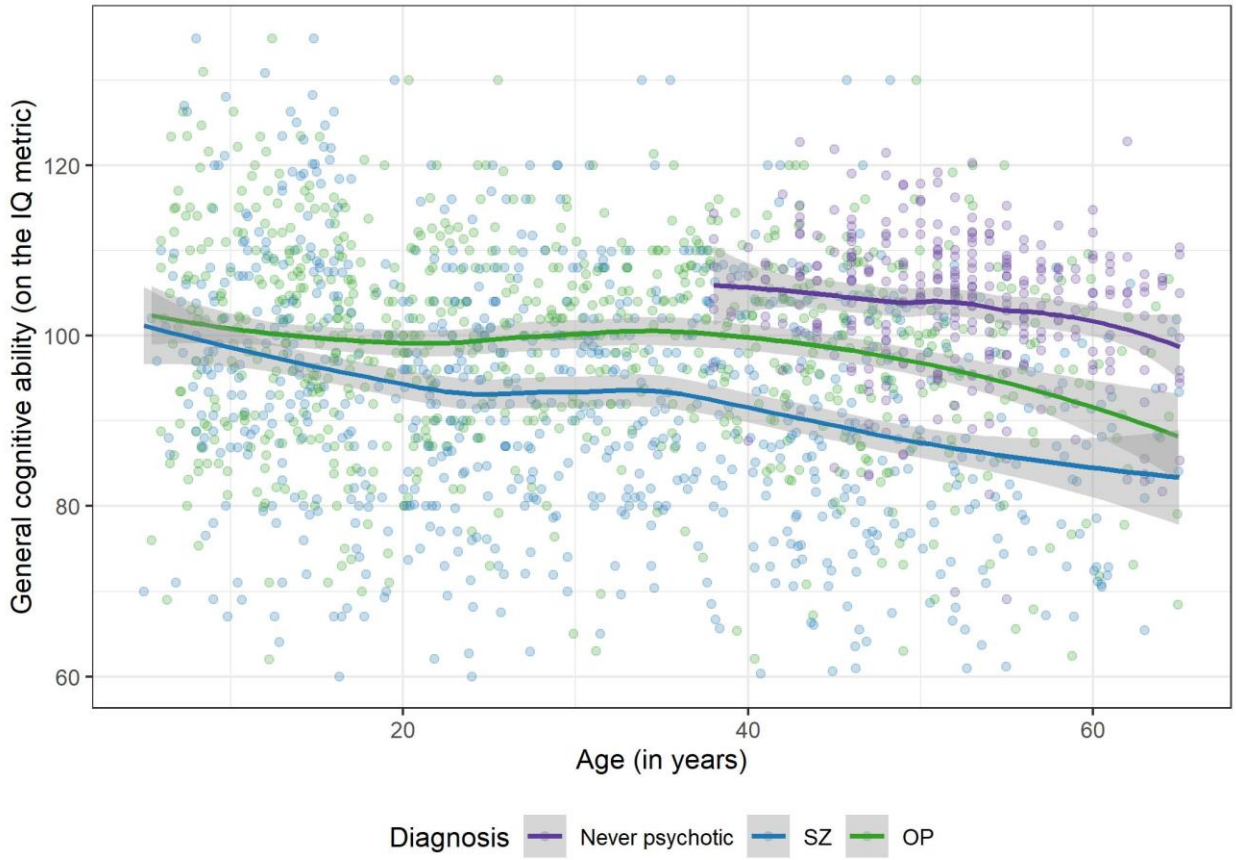
Cognitive trajectories in full sample, moderated by diagnosis (N=428)

Coefficient	B	95% CI	p-value
Intercept	103.71	[99.35, 108.06]	<0.01
Schizophrenia	-1.18	[-7.96, 5.61]	0.73
Normative phase (more than 14 years prior to psychosis onset)	0.13	[-0.09, 0.35]	0.24
Declining phase (14 years prior to 22 years after psychosis onset)	-0.15	[-0.22, -0.08]	<0.01
Deteriorating phase (more than 22 years after psychosis onset)	-0.59	[-0.94, -0.25]	<0.01
Schizophrenia x normative phase	0.06	[-0.31, 0.44]	0.74
Schizophrenia x declining phase	-0.20	[-0.30, -0.10]	<0.01
Schizophrenia x deteriorating phase	0.03	[-0.40, 0.47]	0.88

Note. B = regression coefficient; CI=confidence interval.

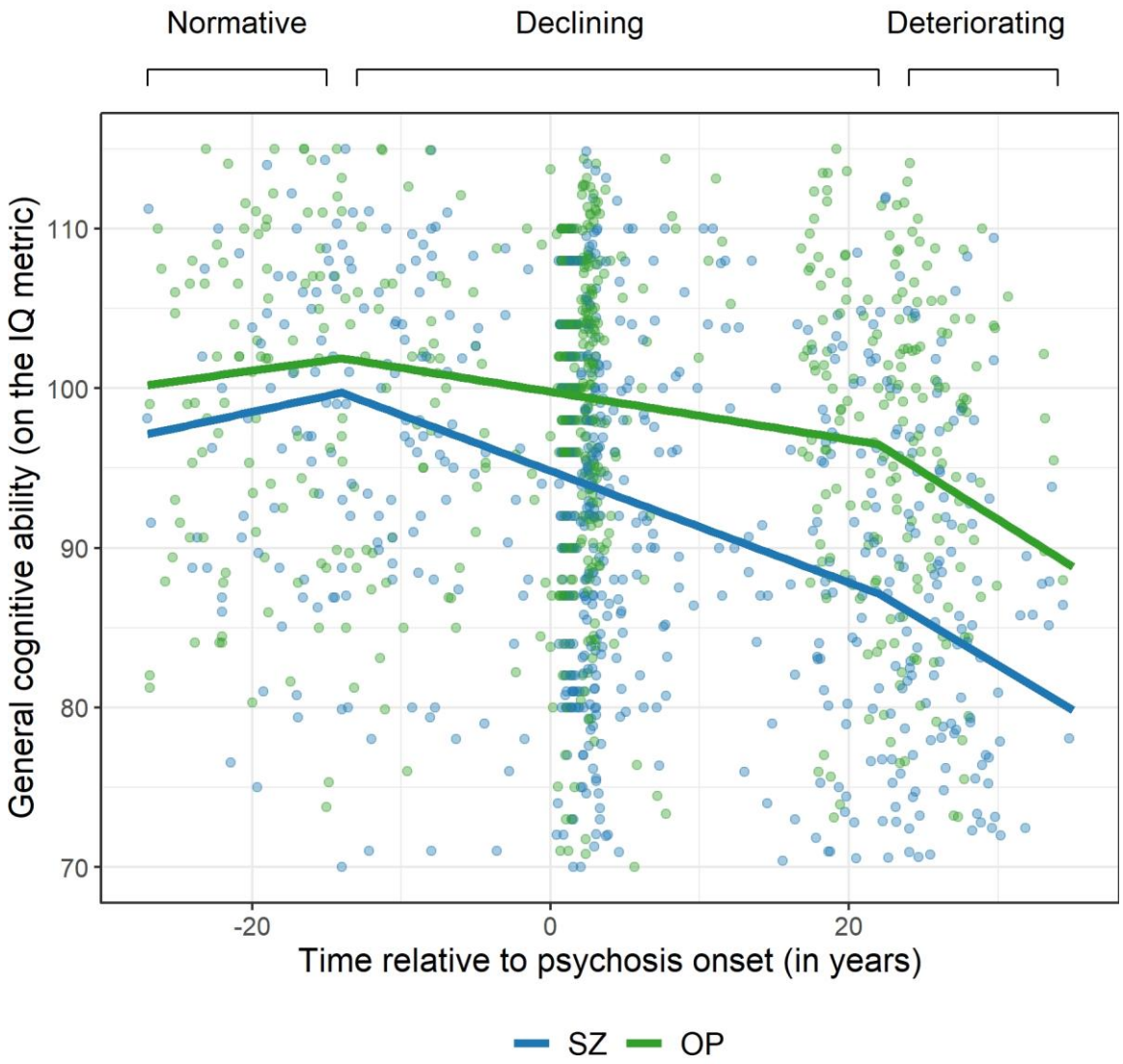
Figure 1. Overview of study design and data completed at each time point

Figure 2. LOESS plot of general cognitive ability as a function of age, stratified by diagnosis.



Note. Cognitive trajectories expressed relative to age, rather than time since psychosis onset. SZ = schizophrenia; OP = other psychotic disorder.

Figure 3. Trajectories of general cognitive ability in schizophrenia and other psychotic disorders



Note.

Lines depict model-implied trajectories. SZ = schizophrenia; OP = other psychotic disorder.