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Neurocognitive Development in Children at Familial High Risk of Schizophrenia or Bipolar Disorder

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IMPORTANCE Neurocognitive impairments exist in children at familial high risk (FHR) of schizophrenia and bipolar disorder. Studies on preadolescent developmental courses of neurocognition are important to describe shared and distinct neurodevelopmental pathways in these groups.

OBJECTIVE To assess the development in specific neurocognitive functions from age 7 to 11 years in children at FHR of schizophrenia or bipolar disorder compared with children in a population-based control (PBC) group.

DESIGN, SETTING, AND PARTICIPANTS The Danish High Risk and Resilience Study is a prospective, longitudinal, cohort study that collected data from January 1, 2013, to January 31, 2016 (phase 1), and from March 1, 2017, to June 30, 2020 (phase 2). Data were collected at 2 university hospitals in Denmark, and participants included 520 children at FHR of schizophrenia or bipolar disorder along with a PBC group matched with the group of children at FHR of schizophrenia by age, sex, and municipality.

EXPOSURES Parental schizophrenia, bipolar disorder, or neither.

MAIN OUTCOMES AND MEASURES Neurocognitive functioning was assessed with validated tests of intelligence, processing speed, attention, memory, verbal fluency, and executive functioning. Multilevel mixed-effects linear regression models with maximum likelihood estimation were used to estimate neurocognitive development from age 7 to 11 years.

RESULTS At 4-year follow-up, a total of 451 children (mean [SD] age; 11.9 [0.2] years; 208 girls [46.1%]) underwent neurocognitive testing. There were a total of 170 children at FHR of schizophrenia (mean [SD] age, 12.0 [0.3]; 81 girls [47.7%]), 103 children at FHR of bipolar disorder (mean [SD] age, 11.9 [0.2] years; 45 girls [43.7%]), and 178 children in the PBC group (mean [SD] age, 11.9 [0.2] years; 82 girls [46.1%]). At either age 7 or 11 years or at both assessments, 520 children participated in the neurocognitive assessment and were therefore included in the analyses. When correcting for multiple comparisons, no statistically significant time × group interactions were observed across the 3 groups. Compared with the PBC group at 4-year follow-up, children at FHR of schizophrenia showed significant neurocognitive impairment in 7 of 24 neurocognitive measures (29.2%; Cohen *d* range, 0.29-0.37). Compared with children at FHR of bipolar disorder, children at FHR of schizophrenia had significant neurocognitive impairment in 5 of 24 measures (20.8%; Cohen *d* range, 0.29-0.38). Children at FHR of bipolar disorder and those in the PBC group did not differ significantly.

CONCLUSIONS AND RELEVANCE In this cohort study, findings suggest that neurocognitive maturation was comparable across groups of children at FHR of schizophrenia or bipolar disorder compared with PBCs from age 7 to 11 years. Compared with the PBC group, children at FHR of schizophrenia demonstrated widespread, stable, neurocognitive impairments during this period, whereas children at FHR of bipolar disorder showed no neurocognitive impairments, which may indicate distinct neurodevelopmental pathways in children at FHR of schizophrenia and bipolar disorder.

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Supplemental content

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Neurocognitive impairments, such as deficits in processing speed, attention, memory, and executive functions, are core features of schizophrenia and bipolar disorder[1-4] but with less pronounced impairments in bipolar disorder.[5-7] Schizophrenia is considered a neurodevelopmental disorder with neurocognitive impairments presenting years before the manifestation of overt clinical symptoms.[8-12] Findings regarding neurocognitive functioning in the premorbid phase of bipolar disorder are less consistent. Some evidence indicates that there are impairments in executive functioning and visuospatial reasoning,[13] but numerous studies show intact premorbid neurocognitive functioning.[14,15] Investigating the developmental course of neurocognitive functions before illness onset may elucidate shared and illness-specific vulnerability markers.

Prospective familial high-risk (FHR) studies provide a unique way to investigate vulnerability markers of schizophrenia and bipolar disorder[15,16] because both disorders aggregate in families as reflected by high heritability estimates.[17] Across different ages, first-degree relatives of individuals with schizophrenia demonstrate widespread neurocognitive impairments of small to medium effect sizes in processing speed, attention, visual memory, visuospatial functions, executive functions, and intelligence.[18-22] Studies assessing neurocognitive functions in children of individuals with bipolar disorder are fewer and their results more ambiguous. A recent review found no consistent evidence for lower intelligence in the age range of 6 to 27 years.[23] However, meta-analytic evidence on first-degree relatives (aged 10-25 years) of individuals with bipolar disorder suggests impairments of modest effect sizes (Cohen *d* range = 0.15-0.36) in processing speed, sustained attention, and visual and verbal memory.[24]

Results from our baseline study, The Danish High Risk and Resilience Study-VIA 7, support previous findings on neurocognitive impairments in first-degree relatives of individuals with schizophrenia. Results suggested that children aged 7 years at FHR of schizophrenia display widespread neurocognitive impairments.[25-27] In contrast, children aged 7 years at FHR of bipolar disorder only exhibited selective impairments in visual attention[27] and interference control at this early age.[25] Overall, these findings suggest that neurocognitive impairments may be endophenotypic markers for both schizophrenia and bipolar disorder but with a more pronounced neurodevelopmental component in schizophrenia.[28]

Most studies on neurocognition in children of individuals with schizophrenia or bipolar disorder are cross-sectional, thus limiting inferences concerning developmental courses. To date and to our knowledge, only a few longitudinal studies have examined neurocognition in these groups of children. One study[29] found that adolescents at FHR of schizophrenia exhibit slower rates of growth in executive functioning compared with controls. A 2-year follow-up study found that processing speed, verbal memory, and executive functioning develop at slower rates in adolescents at FHR of schizophrenia compared with controls, and verbal memory improves more slowly in adolescents at FHR of bipolar disorder relative to controls.[30]

Key Points

Question What is the developmental course of neurocognitive functions from age 7 to 11 years in children at familial high risk (FHR) of schizophrenia or bipolar disorder?

Findings This cohort study of 520 children in Denmark showed comparable neurocognitive maturation from age 7 to 11 years in children at FHR of schizophrenia or bipolar disorder and population-based controls. At age 11 years, children at FHR of schizophrenia continued to show impairment in neurocognitive domains, whereas children at FHR of bipolar disorder did not show evidence of neurocognitive impairment at age 7 nor at age 11 years.

Meaning Results of this study suggest that FHR of schizophrenia, but not bipolar disorder, is associated with stable neurocognitive impairments in children aged 7 to 11 years, which warrants early attention toward this group.

However, larger studies examining preadolescent neurocognitive development in children at FHR of schizophrenia and bipolar disorder are needed.

Our study objective was to assess neurocognitive development from age 7 to 11 in same-aged children at FHR of schizophrenia or bipolar disorder along with population-based controls (PBCs) using a comprehensive neuropsychological test battery. We hypothesized that children at FHR of schizophrenia would display neurocognitive lags in some neurocognitive functions compared with PBCs, and children at FHR of bipolar disorder would show either stable neurocognitive development or few incipient lags.

Methods

This prospective cohort study was part of The Danish High Risk and Resilience Study. The cohort and design are detailed elsewhere.[31,32] The study was approved by the Danish Data Protection Agency. Because of the observational nature of the study, formal approval was deemed unnecessary by The Danish Committee on Health Research Ethics. Written informed consent was obtained from the children's legal guardian before assessment. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines were followed.

Sample

Participants were identified through The Danish Civil Registration System,[33] and The Danish Psychiatric Central Research Register.[34] The cohort consisted of children with at least 1 biological parent with schizophrenia spectrum psychosis, bipolar disorder, or neither of these. PBCs were matched with children at FHR of schizophrenia by sex, age, and municipality. The group at FHR of bipolar disorder was not matched but comparable with the other groups regarding age and sex. Information on race and ethnicity was not collected because all participating children had Danish as their first language and had to be born and living in Denmark at the time of the study.

A total of 522 children were included in the baseline study (the VIA 7 study),[32] of which 520 children underwent

neurocognitive assessment (201 at FHR of schizophrenia, 119 at FHR of bipolar disorder, and 200 PBCs). Thirty-two children were siblings (constituting 16 sibling pairs). At 4-year follow-up (the VIA 11 study),[32] 465 children were included, of which 451 children were neurocognitively reassessed (170 at FHR of schizophrenia, 103 at FHR of bipolar disorder, and 178 PBCs), with a retention rate of 86.8% for the neurocognitive assessment.

Procedures

Baseline data collection took place from January 1, 2013, to January 31, 2016, and follow-up from March 1, 2017, to June 30, 2020. Assessments were conducted at 2 research sites or at the family's home. Trained clinicians administered the neurocognitive assessments. All were certified and supervised by a specialist in clinical child psychology (N.H.) and blinded toward parental diagnosis. Psychology students and the first and the fifth author (C.B.K. and A.K.A.) scored the noncomputerized tests. Interrater reliability tests were performed on 10 patient cases showing intraclass correlation coefficients above 0.90, indicating excellent reliability.

Results from the noncomputerized tests were entered into a secure web-based database, Research Electronic Data Capture (REDCap; Vanderbilt University).[35,36]

Clinical Assessment

The Children's Global Assessment Scale (CGAS)[37] was used to assess the child's current level of functioning. The Child Behavior Checklist School-Age Version (CBCL)[38] was used to assess emotional and behavioral problems and was completed by the primary caregiver (the parent/legal guardian living with the child who knew the child the best).

Neurocognitive Assessment

Neurocognitive functions found to be impaired in schizophrenia and bipolar disorder, including intelligence, processing speed, attention, verbal and visuospatial memory, verbal fluency, working memory, and executive functions,[1-4] were examined using age-appropriate, validated tests (eTable 1 in the Supplement shows an overview of the test battery). For optimal examination of development in specific neurocognitive functions and to maximize test reliability, identical tests were administered at age 7 and 11 years. One key outcome from each test was chosen a priori as the best estimate of the given neurocognitive function.

Statistical Analysis

Differences in background characteristics were examined with 1-way analysis of variance and χ^2 tests. For dropout analyses, χ^2 and *t* tests were used.

Neurocognitive data were inspected for normality and outliers. Two neurocognitive measures at age 7 and 11 years (the Trail Making Test [TMT] number sequencing, and TMT letter sequencing) were log-transformed to approximate normal distribution. Extreme scores were truncated to within 3 SD to limit the effect of a few extreme scores, while still maintaining variability in the data.

Multilevel mixed-effects linear regression models with maximum likelihood estimation were performed using FHR group and time × group interaction as fixed factors and a random factor at identification level to examine the development in each neurocognitive measure from age 7 to 11 years. Cluster robust variance estimation was used to account for clustering at the family level. The same models were used to examine between-group differences at follow-up. Sex was included as a covariate owing to its putative effect on neurocognitive performance.[39] To avoid overcorrection, we did not covary for socioeconomic status given its intrinsic association with high-risk status. Effect sizes were calculated cross-sectionally using Cohen *d*. The Benjamini-Hochberg false discovery rate procedure[40] was used to correct for multiple comparisons. Cutoff for the false discovery rate was set at 10% resulting in 2-sided *P* values < .02 regarded as statistically significant. To check for potential bias owing to skewed dropout (eTable 2 in the Supplement), worst-best case analyses were conducted. This was done by replacing missing values at age 11 years with the value at age 7 years (for the individual) plus the 90th percentile or the 10th percentile of the difference in the outcome measure for the complete case data, respectively.

Post hoc sex-stratified analyses were performed to examine potential sex-specific differences in neurocognitive development. To assess potential associations between neurocognitive development and development in problem behavior, we conducted explorative bivariate Pearson correlation analyses between the change in the CBCL total score (difference between baseline and follow-up) and the change in each neurocognitive measure. Finally, to assess how truncation of extreme scores to within 3 SD affected the results regarding neurocognitive development, sensitivity analyses without truncation were performed. All analyses were conducted using Stata, version 16 (StataCorp).[41]

Results

Background Information

At follow up, 451 children (mean [SD] age, 11.9 [0.2] years; 208 girls [46.1%]; 243 boys [53.9%]) participated in the neurocognitive assessment. There were a total of 170 children at FHR of schizophrenia (mean [SD] age, 12.0 [0.3]; 81 girls [47.7%]; 89 boys [52.4%]), 103 children at FHR of bipolar disorder (mean [SD] age, 11.9 [0.2] years; 45 girls [43.7%]; 58 boys [56.3%]), and 178 children in the PBC group (mean [SD] age, 11.9 [0.2] years; 82 girls [46.1%]; 96 boys [53.9%]). However, the number of children completing each neurocognitive test varied somewhat from test to test (eTable 3 in the Supplement). The 3 groups were similar with regard to age and sex. The 2 FHR groups showed significantly more problem behavior (noted on CBCL) and lower level of functioning (noted on CGAS) relative to PBCs but did not differ significantly from each other (**Table 1**).

Neurocognitive Development From Age 7 to 11 Years

Time × group interactions did not survive correction for multiple comparisons, indicating comparable between-

Table 1. Demographic and Clinical Characteristics of Children Aged 11 Years at FHR of Schizophrenia or Bipolar Disorder and Population-Based Controls

Variable	Mean (SD)			*P* value, pairwise comparisons		
	Population-based control	FHR of schizophrenia	FHR of bipolar disorder	FHR of schizophrenia vs population-based control	FHR of bipolar disorder vs population-based control	FHR of schizophrenia vs FHR of bipolar disorder
Children, No.	178	170	103	NA	NA	NA
Age, y	11.93 (0.23)	11.96 (0.27)	11.94 (0.21)	NA	NA	NA
Female, No. (%)	82 (46.07)	81 (47.65)	45 (43.69)	NA	NA	NA
Male, No. (%)	96 (53.93)	89 (52.35)	58 (56.31)	NA	NA	NA
Children's Global Assessment Scale total score[a,b]	75.12 (13.99)	64.59 (15.66)	68.14 (15.01)	<.001	<.001	.06
Child Behavior Checklist total score[c,d]	12.62 (12.43)	23.30 (20.55)	21.33 (21.17)	<.001	<.001	.46
Living out of home, No. (%)	0	17 (10.00)	<5 (<4.90)[e]	<.001	.19	.004
Intelligence quotient						
Age 7 y[f,g]	100.00 (15.00)	96.30 (16.78)	99.79 (14.95)	.02	.90	.06
Age 11 y[g]	100.00 (15.00)	97.75 (11.74)	99.66 (11.83)	NA	NA	NA

Abbreviations: FHR, familial high risk; NA, not applicable.

[a] Based on data from 174 population-based controls, 170 children at familial high risk of schizophrenia, and 103 children at familial high risk of bipolar disorder.

[b] Higher scores indicate higher level of functioning.

[c] Based on data from 171 population-based controls, 161 children at familial high risk of schizophrenia, and 101 children at familial high risk of bipolar disorder.

[d] Higher scores reflect more emotional and behavioral problems.

[e] Owing to regulations by the Danish Data Protection Agency, numbers below 5 should not be displayed when processing personal data.

[f] Based on data from 198 population-based controls, 200 children at familial high risk of schizophrenia, and 119 children at familial high risk of bipolar disorder.

[g] Intelligence quotient is calculated using the population-based control as a reference group.

group improvements over time (**Table 2**). eFigure 1 in the Supplement illustrates the development in all neurocognitive tests.

Neurocognitive Performance at 4-Year Follow-up

Compared with the PBC group at 4-year follow-up, children at FHR of schizophrenia obtained significantly lower scores on 7 of the 24 measures (29.2%; Cohen *d* range, 0.29-0.37), including the Guess What, TMT number sequencing, TMT letter sequencing, Rey Complex Figure Test immediate recall, TMT number-letter switching, the Wechsler Intelligence Scale for Children, fourth edition (WISC-IV) letter-number sequencing, and WISC-IV arithmetic (**Table 3**). No significant differences were noted between children at FHR of bipolar disorder and the PBC group. Compared with children at FHR of bipolar disorder, children at FHR of schizophrenia obtained significantly lower scores on 5 of the 24 measures (20.8%; Cohen *d* range, 0.29-0.38), including rapid visual information processing A′, Rey Complex Figure Test immediate recall, verbal fluency phonemic, WISC-IV letter-number sequencing, and Spatial Span (eFigure 2 in the Supplement). Neurocognitive performance at baseline is described elsewhere[26] but also displayed in **Table 4**.

Worst-Best Analyses

Children in both high-risk groups who were lost to dropout had significantly lower scores on several neurocognitive measures at baseline (eTable 2 in the Supplement). Results from worst-best case analyses are shown in eTable 4 in the Supplement. Overall, worst-best case analyses indicated unbiased results with regard to the cross-sectional comparisons. However, because the dropout analyses revealed a skewed dropout in the 2 high-risk groups, our results may also reflect a slight underestimation of the between-group differences.

Regarding the time × group interactions, worst-best case analyses overall produced results similar to the findings based on multilevel mixed-effects linear regression models with maximum likelihood estimation. Significant time × group interactions between children at FHR of schizophrenia and PBCs were only likely to be present if those children at FHR of schizophrenia who dropped out had performed above average (best case) at follow-up, which is unlikely given the direction of the dropout.

Explorative Analyses

Most findings revealed no sex-specific associations with neurocognitive development. However, boys at FHR of schizophrenia showed a faster rate of growth on Guess What compared with that of boys in the PBC group. Similarly, girls at FHR of schizophrenia displayed a faster rate of growth on rapid visual information processing A′ relative to that of girls in the PBC group (eTable 5 in the Supplement).

Bivariate correlation analyses showed a significant correlation between the change in the CBCL total score and the change in score of TMT letter sequencing (Pearson $r = -0.15$; 95% CI, −0.06 to −0.25; $P = .002$), explaining 2.3% of the variance. Truncation of extreme scores did not significantly affect the results regarding neurocognitive development (eTable 6 in the Supplement).

Table 2. Time × Group Interactions Across the 3 Study Groups: Children at FHR of Schizophrenia or Bipolar Disorder and Population-Based Controls[a]

		Time × group					
		FHR of schizophrenia vs PBC		FHR of bipolar vs PBC		FHR of schizophrenia vs FHR of bipolar disorder	
Neurocognitive function	Test	χ^2_1	*P* value	χ^2_1	*P* value	χ^2_1	*P* value
Intelligence	Guess What	1.54	.22	0.48	.48	0.15	.69
	Odd item out	0.02	.88	0.93	.34	0.66	.42
Processing speed	WISC, 4th edition, coding	1.13	.29	<0.01	.95	0.91	.34
	WISC, 4th edition, symbol search	4.13	.04	0.34	.56	5.66	.02
	TMT, number sequencing	0.14	.71	1.18	.28	1.79	.18
	TMT, letter sequencing	0.08	.78	1.20	.27	0.67	.41
Sustained attention	CCPT, 2nd edition, hit reaction time by block	1.19	.28	0.04	.84	0.52	.47
	Rapid visual information processing A′	4.07	.04	3.90	.05	0.02	.89
Verbal memory	Word selective reminding, immediate recall	0.32	.57	0.83	.36	0.15	.65
	Word selective reminding, delayed recall	1.07	.30	1.01	.32	0.01	.91
	Memory for stories, immediate recall	0.45	.50	1.27	.26	0.23	.63
	Memory for stories, delayed recall	0.24	.62	3.17	.08	1.94	.16
Visuospatial memory	RCFT, immediate recall	0.13	.72	0.42	.52	0.96	.33
	Spatial recognition memory, percentage correct	4.87	.03	0.93	.34	0.79	.38
Verbal fluency	Verbal fluency phonemic	0.59	.44	0.39	.53	1.69	.19
	Verbal fluency semantic	<0.01	.98	1.81	.18	1.60	.21
Set shifting	TMT, number-letter switching	4.98	.03	0.31	.58	1.84	.18
	Verbal fluency switching	<0.01	.99	4.79	.03	4.72	.03
	Intra-extra dimensional set shift, extradimensional stage errors	4.34	.04	<0.01	.99	3.21	.07
Planning	Stockings of Cambridge problems solved in minimum moves	0.76	.38	0.16	.69	1.30	.26
Verbal working memory	WISC, 4th edition, letter-number sequencing	0.01	.91	0.23	.63	0.28	.60
	WISC, 4th edition, arithmetic	0.05	.83	0.61	.43	0.91	.34
Visual working memory	Spatial working memory, total errors	0.26	.61	1.36	.24	0.53	.47
	Spatial span	0.16	.69	<0.01	.97	0.10	.75

Abbreviations: CCPT, Connors' Continuous Performance Test; FHR, familial high risk; PBC, population-based control; RCFT, Rey Complex Figure Test and Recognition Trial; TMT, Trail Making Test; WISC, Wechsler Intelligence Scale for Children.

[a] No results were considered statistically significant after post hoc correction for multiple comparisons with Benjamini-Hochberg false discovery rate procedure (*P* values < .02).

Discussion

Neurocognitive development from age 7 to 11 years in children at FHR of schizophrenia and bipolar disorder, in addition to PBCs, was examined in this large, longitudinal cohort study. Contrary to our hypothesis that children at FHR of schizophrenia would display some developmental lags, the rates of growth in all neurocognitive functions were comparable across groups. Compared with children in the PBC group, children at FHR of schizophrenia showed stable impairments with respect to intelligence, processing speed, visuospatial memory, set shifting, and verbal working memory from baseline to follow-up.

Children at FHR of schizophrenia showed widespread neurocognitive impairment, whereas children at FHR of bipolar disorder showed intact neurocognitive functioning, suggesting that a substantial overlap between schizophrenia and bipolar disorder in clinical characteristics and predisposing genes[42,43] does not translate to overlapping neurocognitive impairments in their offspring during the ages of 7 and 11 years. Moreover, the finding that children at FHR of schizophrenia continue to demonstrate impairments in several neurocognitive functions suggests that being at FHR of schizophrenia may affect the very basis of neurocognitive development but does not disrupt neurocognitive development from age 7 to 11 years. Explorative sex-stratified analyses generally support these main findings. Furthermore, neurocognitive

Table 3. Neurocognitive Performance at 4-Year Follow-up and Pairwise Comparisons Across Groups of Children at FHR of Schizophrenia and Bipolar Disorder and Population-Based Controls

Neurocognitive function	Test	Raw score, mean (95% CI)[a]			Pairwise comparisons					
					FHR of schizophrenia vs population-based control		FHR of bipolar disorder vs population-based control		FHR of schizophrenia vs FHR of bipolar disorder	
		FHR of schizophrenia	FHR of bipolar disorder	Population-based control	Cohen *d*[b]	*P* value	Cohen *d*[b]	*P* value	Cohen *d*[b]	*P* value
Intelligence	Guess What	40.13 (39.72-40.54)	40.69 (40.19-41.18)	41.02 (40.71-41.33)	0.29	.001[c]	0.12	.26	0.16	.09
	Odd item out	73.86 (72.82-74.89)	74.78 (73.44-76.11)	75.28 (74.24-76.33)	0.18	.06	0.04	.56	0.14	.29
Processing speed	WISC, 4th edition, coding	43.53 (42.07-44.98)	44.87 (43.08-46.67)	45.71 (44.33-47.09)	0.20	.03	0.09	.47	0.11	.25
	WISC, 4th edition, symbol search	25.56 (24.66-26.46)	26.01 (24.97-27.04)	26.30 (25.48-27.11)	0.11	.23	0.04	.66	0.06	.52
	TMT, number sequencing[d,e]	39.25 (37.25-41.35)	38.84 (36.26-41.26)	35.20 (33.65-36.82)	0.33	.002[c]	0.29	.02	0.06	.80
	TMT, letter sequencing[d,e]	42.15 (39.83-44.60)	39.96 (37.20-42.92)	36.50 (34.78-38.31)	0.37	<.001[c]	0.27	.04	0.11	.25
Sustained attention	CCPT, 2nd edition, hit reaction time by block[e]	0.014 (0.010-0.019)	0.009 (0.003-0.014)	0.014 (0.010-0.018)	0.02	.82	0.17	.15	0.18	.11
	Rapid visual information processing A′	0.952 (0.946-0.957)	0.964 (0.958-0.970)	0.959 (0.953-0.965)	0.16	.09	0.21	.23	0.38	.003[c]
Verbal memory	Word selective reminding, immediate recall	54.67 (53.32-56.03)	55.29 (53.65-56.93)	55.70 (54.59-56.81)	0.12	.25	0.06	.69	0.06	.57
	Word selective reminding, delayed recall	9.67 (9.37-9.97)	10.03 (9.72-10.33)	10.11 (9.87-10.35)	0.23	.03	0.04	.69	0.19	.11
	Memory for stories, immediate recall	28.71 (27.13-30.29)	29.47 (27.62-31.33)	30.04 (28.64-31.44)	0.11	.22	0.05	.63	0.06	.54
	Memory for stories, delayed recall	24.05 (22.55-25.55)	24.47 (22.43-26.50)	25.14 (23.78-26.49)	0.06	.29	0.05	.59	0.01	.75
Visuospatial memory	RCFT, immediate recall	15.55 (14.46-16.63)	18.15 (16.98-19.32)	17.95 (16.92-18.97)	0.32	.002[c]	0.02	.80	0.34	.001[c]
	Spatial recognition memory, percentage correct	79.37 (77.88-80.85)	81.10 (79.07-83.14)	80.83 (79.24-82.42)	0.12	.19	0.03	.84	0.15	.18
Verbal fluency	Verbal fluency phonemic	21.71 (20.62-22.81)	24.03 (22.57-25.48)	23.50 (22.35-24.65)	0.20	.03	0.09	.58	0.29	.01[c]
	Verbal fluency semantic	33.97 (32.80-35.14)	36.09 (34.48-37.70)	35.76 (34.61-36.90)	0.21	.03	0.05	.74	0.26	.04
Set shifting	TMT, number-letter switching[e]	100.67 (95.61-105.74)	93.68 (86.54-100.81)	90.27 (86.06-94.48)	0.34	.002[c]	0.14	.42	0.17	.12
	Verbal fluency switching	8.32 (7.93-8.72)	8.21 (7.74-8.69)	8.74 (8.37-9.11)	0.13	.13	0.21	.09	0.07	.72
	Intra-extra dimensional set shift, extradimensional stage errors[e]	13.94 (12.23-15.66)	11.53 (9.43-13.63)	12.18 (10.59-13.77)	0.17	.14	0.07	.60	0.23	.08
Planning	Stockings of Cambridge problems solved in minimum moves	8.55 (8.25-8.84)	8.57 (8.20-8.94)	8.59 (8.29-8.90)	0.02	.83	0.01	.93	0.01	.93
Verbal working memory	WISC, 4th edition, letter-number sequencing	16.49 (15.94-17.04)	17.74 (17.14-18.33)	17.72 (17.33-18.11)	0.37	<.001[c]	0.05	.96	0.38	.003[c]
	WISC, 4th edition, arithmetic	19.26 (18.72-19.80)	20.16 (19.48-20.83)	20.28 (19.79-20.77)	0.27	.006[c]	0.01	.77	0.28	.04
Visual working memory	Spatial working memory, total errors[e]	29.99 (27.61-32.38)	25.98 (22.90-29.06)	26.28 (24.10-28.46)	0.22	.02	0.04	.88	0.26	.04
	Spatial span	6.21 (6.00-6.42)	6.67 (6.41-6.92)	6.51 (6.30-6.72)	0.20	.05	0.12	.36	0.33	.007[c]

Abbreviations: CCPT, Connors' Continuous Performance Test; FHR, familial high risk; RCFT, Rey Complex Figure Test and Recognition Trial; TMT, Trail Making Test; WISC, Wechsler Intelligence Scale for Children.

[a] Mean raw scores are estimated by use of multilevel mixed-effects linear regression models with maximum likelihood estimation.

[b] Effect sizes are calculated cross-sectionally.

[c] Indicates significance after post hoc correction for multiple comparisons with Benjamini-Hochberg false discovery rate procedure (*P* values < .02 were considered statistically significant).

[d] Mean raw scores are back-transformed estimated means.

[e] Higher scores indicate worse performance.

Table 4. Neurocognitive Performance at Baseline and Pairwise Comparisons Across Groups of Children at FHR of Schizophrenia and Bipolar Disorder and Population-Based Controls

Neurocognitive function	Test	Raw score, mean (95% CI)[a]			Pairwise comparisons					
					FHR of schizophrenia vs population-based control		FHR of bipolar disorder vs population-based control		FHR of schizophrenia vs FHR of bipolar disorder	
		FHR of schizophrenia	FHR of bipolar disorder	Population-based control	Cohen *d*[b]	*P* value	Cohen *d*[b]	*P* value	Cohen *d*[b]	*P* value
Intelligence	Guess What	32.40 (31.70-33.10)	33.13 (32.35-33.91)	33.75 (33.19-34.32)	0.30	.003[c]	0.15	.20	0.15	.17
	Odd item out	62.23 (60.97-63.48)	63.99 (62.52-65.46)	63.52 (62.33-64.70)	0.15	.14	0.06	.63	0.20	.07
Processing speed	WISC, 4th edition, coding	26.31 (25.26-27.35)	28.66 (27.39-29.93)	29.43 (28.46-30.40)	0.42	<.001[c]	0.11	.35	0.31	.005[c]
	WISC, 4th edition, symbol search	15.35 (14.61-16.08)	17.48 (16.59-18.36)	17.37 (16.64-18.09)	0.39	<.001[c]	0.03	.85	0.42	<.001[c]
	TMT, number sequencing[d,e]	62.78 (59.45-66.31)	58.02 (54.04-62.29)	55.38 (52.77-58.13)	0.35	.001[c]	0.16	.29	0.19	.08
	TMT, letter sequencing[d,e]	77.66 (72.87-82.76)	70.12 (64.76-75.94)	68.12 (64.11-72.39)	0.30	.004[c]	0.07	.57	0.22	.05
Sustained attention	CCPT, 2nd edition, hit reaction time by block[e]	0.030 (0.025-0.036)	0.021 (0.014-0.027)	0.025 (0.020-0.030)	0.16	.12	0.11	.33	0.27	.02
	Rapid visual information processing A′	0.887 (0.879-0.895)	0.898 (0.888-0.909)	0.906 (0.899-0.913)	0.35	<001[c]	0.14	.23	0.20	.08
Verbal memory	Word selective reminding, immediate recall	38.52 (37.73-39.30)	39.51 (38.59-40.43)	39.07 (38.39-39.74)	0.08	.30	0.08	.45	0.15	.11
	Word selective reminding, delayed recall	6.09 (5.82-6.37)	6.42 (6.16-6.68)	6.28 (6.07-6.49)	0.11	.29	0.10	.41	0.19	.09
	Memory for stories, immediate recall	19.39 (17.96-20.82)	20.70 (18.90-22.51)	20.02 (18.71-21.32)	0.07	.53	0.07	.55	0.13	.26
	Memory for stories, delayed recall	14.96 (13.69-16.23)	17.00 (15.29-18.71)	15.60 (14.44-16.76)	0.08	.47	0.16	.19	0.23	.06
Visuospatial memory	RCFT, immediate recall	7.65 (6.95-8.34)	9.41 (8.37-10.45)	9.78 (8.99-10.57)	0.39	<.001[c]	0.05	.58	0.35	.006[c]
	Spatial recognition memory, percentage correct	67.18 (65.44-68.92)	70.32 (68.44-72.21)	71.64 (70.07-73.22)	0.36	<.001[c]	0.12	.29	0.26	.02[c]
Verbal fluency	Verbal fluency phonemic	12.90 (11.99-13.81)	14.10 (12.91-15.29)	14.13 (13.29-14.97)	0.18	.05	<0.01	.97	0.18	.12
	Verbal fluency semantic	24.31 (23.46-25.16)	25.30 (24.07-26.52)	26.12 (25.22-27.02)	0.29	.004[c]	0.13	.29	0.16	.20
Set shifting	TMT, number-letter switching[e]	190.76 (183.52-197.99)	175.75 (166.43-185.07)	169.20 (161.71-176.70)	0.41	<.001[c]	0.13	.28	0.29	.01[c]
	Verbal fluency switching	5.60 (5.22-5.97)	6.35 (5.94-6.75)	6.02 (5.66-6.38)	0.16	.11	0.12	.23	0.29	.007[c]
	Intra-extra dimensional set shift, extradimensional stage errors[e]	17.85 (16.46-19.24)	18.65 (16.80-20.50)	19.27 (17.86-20.67)	0.14	.16	0.06	.60	0.08	.50
Planning	Stockings of Cambridge problems solved in minimum moves	6.19 (5.96-6.41)	6.53 (6.20-6.87)	6.44 (6.22-6.67)	0.16	.11	0.05	.67	0.20	.09
Verbal working memory	WISC, 4th edition, letter-number sequencing	12.45 (11.88-13.01)	13.92 (13.23-14.62)	13.72 (13.22-14.22)	0.33	.001[c]	0.05	.64	0.37	.001[c]
	WISC, 4th edition, arithmetic	12.67 (12.20-13.15)	13.91 (13.30-14.53)	13.77 (13.36-14.17)	0.35	.001[c]	0.05	.69	0.37	.002[c]
Visual working memory	Spatial working memory, total errors[e]	51.59 (49.42-53.76)	49.19 (46.23-52.14)	46.97 (44.84-49.10)	0.28	.003[c]	0.13	.23	0.14	.20
	Spatial span	4.43 (4.26-4.59)	4.94 (4.72-5.15)	4.79 (4.65-4.93)	0.33	.001[c]	0.14	.26	0.43	<.001[c]

Abbreviations: CCPT, Connors' Continuous Performance Test; FHR, familial high risk; RCFT, Rey Complex Figure Test and Recognition Trial; TMT, Trail Making Test; WISC, Wechsler Intelligence Scale for Children.

[a] Mean raw scores are estimated by use of multilevel mixed-effects linear regression models with maximum likelihood estimation. Owing to the use of different analysis methods, estimations may slightly deviate from those reported in Hemager et al.[26]

[b] Effect sizes are calculated cross-sectionally.

[c] Indicates significance after post hoc correction for multiple comparisons with Benjamini-Hochberg false discovery rate procedure (*P* values < .02 were considered statistically significant).

[d] Mean raw scores are back-transformed estimated means.

[e] Higher scores indicate worse performance.

development appeared to have a weak association with development in psychopathology. The real-world relevance of impaired neurocognition during childhood is considerable given that associations between neurocognitive functions (such as attention, working memory, and general intelligence) and academic performance,[44,45] as well as adaptive functioning,[46] are found in the general population.

Our study aligns with several others reporting widespread neurocognitive impairments in children of individuals with schizophrenia during childhood and adolescence[18,20,22] and in young adult first-degree relatives.[19] Contrary to findings on young adult first-degree relatives[19] and children aged 7 to 12 years,[47] we did not find children at FHR of schizophrenia and PBCs to differ with respect to sustained attention at follow-up. This may relate to the use of different assessment methods across studies. The standard version of Connors' Continuous Performance Test used in the present study has been criticized for being unable to detect subtle impairments in sustained attention.[19] However, other studies have also reported nonsignificant differences in sustained attention between children of individuals with schizophrenia (aged 10.4-17.3 years),[20,22,48] first-degree relatives, including siblings (aged 12-25 years),[49,50] and controls. Overall, this suggests that the evidence regarding sustained attention as an early risk marker or endophenotype for schizophrenia may be equivocal. Future studies should examine the role of sustained attention with several different measures owing to the complex nature of this function.

The finding that children at FHR of bipolar disorder exhibited neurocognitive performance comparable with that of PBCs was somewhat surprising, given that previous studies have reported impairments in attention,[21,51] spatial memory, and executive functioning[51] in children born to parents with bipolar disorder (aged 14.0-15.1 years). Meta-analytic evidence also suggests various neurocognitive impairments in adolescent first-degree relatives of individuals with bipolar disorder.[24] However, our results parallel those from another FHR study examining children of individuals with bipolar disorder (mean [SD] age, 14.6 [3.2] years).[30] The varying findings across studies may be due to important differences in sample ascertainment and characteristics. The sample in the present study was recruited through Danish registers and has a mean (SD) age of 11.9 (0.2) years at follow-up with a very narrow age range. In contrast, several other studies have included smaller sample sizes drawn from inpatient or outpatient clinics, with higher mean ages and broader age ranges,[21,51,52] therefore hampering interpretation of their findings. As of now, findings from the present study suggest unimpaired neurocognition in children at FHR of bipolar disorder during ages 7 to 11 years. However, neurocognitive heterogeneity within this group is an important area for further research, as some evidence suggests the existence of subgroups with impaired neurocognition.[53-55]

Regarding the longitudinal development of neurocognitive functions, we observed a few exceptions from the overall finding that both FHR groups showed age-normative neurocognitive growth. Although speculatively, as these findings did not remain statistically significant after post hoc correction for multiple comparisons, it was somewhat surprising that children at FHR of schizophrenia displayed a tendency toward subtle developmental delays (early impairments that even out over time)[56] on some neurocognitive functions compared with PBCs and children at FHR of bipolar disorder. This may merely reflect a slight overestimation of the performance of children at FHR of schizophrenia (bearing in mind the findings from worst-best case analyses) but nevertheless highlights the importance of further longitudinal assessment to distinguish simple fluctuations in neurocognitive performance from stable changes or persistent lags over time.

To our knowledge, studies examining neurocognitive development in children of individuals with schizophrenia or bipolar disorder are few and have obtained somewhat varying results. One recent 2-year follow-up study of adolescents of individuals with schizophrenia or bipolar disorder found developmental lags on measures of verbal memory (age range at follow-up, 12.7-14.6 years).[30] Moreover, adolescents at FHR of schizophrenia also displayed lags on measures of processing speed and executive functioning.[30] Another study identified developmental delays in intelligence, word reading, and switching[56] but stable impairments in verbal working memory and inhibition from age 9 to 16 years in youth with a family history of schizophrenia.[56]

The findings of stable neurocognitive development without either of the FHR groups displaying developmental lags or delays may very well reflect that follow-up assessments were constrained to age 11 years, as dynamic developmental trajectories have been identified in previous studies of children born to parents with schizophrenia or bipolar disorder that include higher ages at follow-up.[30,56,57] It may also be that a 4-year interval is too short to discover differences in neurocognitive development at this young age.

Prospective cohort studies that have observed individuals who later develop psychosis have demonstrated developmental lags in processing speed, attention, and working memory during childhood and early adolescence.[8,9,58] Although only a minority of children at FHR of schizophrenia or bipolar disorder will develop these disorders, one may speculate that lags in the same areas will occur in the most impaired neurocognitive subgroup.

Assessments beyond age 11 years are warranted to uncover the expected emergence of neurocognitive impairments in children of parents with bipolar disorder and to identify potentially distinct neurocognitive trajectories in these high-risk groups that may be differentially related to the risk of developing schizophrenia or bipolar disorder later in life.

Strengths and Limitations

This study has several strengths. It was one of the largest FHR studies to date of children at FHR of schizophrenia and bipolar disorder and PBCs with a retention rate of 86.8%. The study included an extensive neurocognitive test battery allowing detailed assessment of specific neurocognitive functions. The sample consisted of same-aged children, making the findings less likely to be influenced by the effect of age-associated changes. Both assessments were con-

ducted before adolescence, thereby restricting potential effects of prodromal symptoms likely to present during adolescence or early adulthood.

Some limitations should also be noted. The study had a relatively short follow-up period, and hence may have been underpowered in capturing discrete developmental changes. The group at FHR of bipolar disorder was smaller than the group at FHR of schizophrenia, potentially weakening the ability to detect subtle changes in this group. Additionally, potential associations between parental severity of illness and children's neurocognitive development were not assessed. Finally, several significant differences were revealed between participants and nonparticipants at follow-up. Although this was addressed through our statistical method, results from worst-best case analyses could indicate a tendency toward a modest overestimation of the performance in the 2 high-risk groups.

Conclusions

Findings of this prospective cohort study suggest that numerous neurocognitive impairments were detectable early in development in children at FHR of schizophrenia and appeared stable during the ages of 7 and 11 years. This suggests that being at familial high-risk of schizophrenia may affect the basis of neurocognitive development but does not disrupt neurocognitive development during middle childhood. At age 7 and 11 years, children at FHR of bipolar disorder showed neurocognitive functioning comparable with that of PBCs, which suggests distinct neurodevelopmental pathways in children at FHR of schizophrenia and bipolar disorder. These findings may have the potential to inform early intervention programs targeting cognitive impairments in children at FHR of schizophrenia as these impairments may be susceptible to remediation.

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