JAMA Psychiatry | Original Investigation

Assessment of Neurocognitive Functions in 7-Year-Old Children at Familial High Risk for Schizophrenia or Bipolar Disorder
The Danish High Risk and Resilience Study VIA 7

Nicoline Hemager, MSc; Kerstin J. Plessen, MD, PhD; Anne Thorup, MD, PhD; Camilla Christiani, MSc; Ditte Ellersgaard, MD; Katrine Søborg Spang, MD; Birgitte Klee Burton, MD, PhD; Maja Gregersen, MSc; Anne Søndergaard, MSc; Aja Neergaard Greve, MSc; Ditte Lou Gantriis, MSc; Gry Poulsen, PhD; Larry J. Seidman, PhD; Ole Mors, MD, PhD; Merete Nordentoft, MD, PhD; Jens Richardt Møllegaard Jepsen, PhD

IMPORTANCE Children at familial high risk of schizophrenia spectrum disorders (FHR-SZ) or bipolar disorder (FHR-BP) exhibit neurocognitive impairments. Large studies of neurocognition in young children at familial high risk at the same age are important to differentiate the pathophysiology and developmental trajectory of these 2 groups.

OBJECTIVE To characterize neurocognitive functions in 7-year-old children with FHR-SZ or FHR-BP and a control population.

DESIGN, SETTING, AND PARTICIPANTS This multisite population-based cohort study collected data from January 1, 2013, to January 31, 2016, in the first wave of the Danish High Risk and Resilience Study VIA 7 at 2 university hospital research sites in Copenhagen and Aarhus using Danish registries. Participants (n = 514) included 197 children with FHR-SZ, 118 with FHR-BP, and 199 controls matched with the FHR-SZ group for age, sex, and municipality. Assessors were blinded to risk status.

EXPOSURES Parents with schizophrenia, bipolar disorder, or neither diagnosis.

MAIN OUTCOMES AND MEASURES Neurocognitive functions were measured across 23 tests. Four neurocognitive domains were derived by principal component analysis, including processing speed and working memory, verbal functions, executive and visuospatial functions, and declarative memory and attention.

RESULTS A total of 514 children aged 7 years were included in the analysis (46.3% girls), consisting of 197 children with FHR-SZ (46.2% girls), 118 with FHR-BP (46.6% girls), and 199 controls (46.2% girls). Children with FHR-SZ were significantly impaired compared with controls on processing speed and working memory (Cohen *d* = 0.50; *P* < .001), executive and visuospatial functions (Cohen *d* = 0.28; *P* = .03), and declarative memory and attention (Cohen *d* = 0.29; *P* = .02). Compared with children with FHR-BP, children with FHR-SZ performed significantly poorer in processing speed and working memory (Cohen *d* = 0.40; *P* = .002), executive and visuospatial functions (Cohen *d* = 0.35; *P* = .008), and declarative memory and attention (Cohen *d* = 0.31; *P* = .03). Children with FHR-BP and controls did not differ.

CONCLUSIONS AND RELEVANCE Children with FHR-SZ had widespread neurocognitive impairments, supporting the hypothesis of neurocognitive functions as endophenotypes of schizophrenia. The absence of neurocognitive deficits in children with FHR-BP suggests distinct neurodevelopmental manifestations in these familial high-risk groups at this age. Early detection of children with FHR-SZ and cognitive impairments is warranted to investigate associations of neurocognition with transition to psychosis, add to the knowledge of their developmental pathophysiology, and inform early intervention programs.

JAMA Psychiatry. 2018;75(8):844-852. doi:10.1001/jamapsychiatry.2018.1415
Published online June 20, 2018.

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Nicoline Hemager, MSc, Mental Health Centre Copenhagen, Mental Health Services, Capital Region of Denmark, Kildegaardsvej 28, Opgang 15, 4.sal, 2900 Hellerup, Denmark (nicoline.hemager@regionh.dk).

Schizophrenia is widely recognized as a neurodevelopmental disorder,[1-4] with early neurocognitive deficits presenting well before the prodromal phase and first episode of psychosis.[5] The cognitive domains affected include intelligence, processing speed, verbal and visuospatial memory, attention, and executive functions before and after illness onset.[6-8] Bipolar disorder implicates many of the same neurocognitive deficits before and after illness onset, although to a lesser degree.[9-13]

Neurocognitive deficits are core features of schizophrenia and bipolar disorder,[14] and thus research in the premorbid phase may characterize the developmental trajectories of the neurocognitive functions in their pathogenesis. Children of parents with schizophrenia or bipolar disorder are at increased familial (ie, genetic and environmental) risk of developing the same or other mental illnesses.[15] Consequently, a broadly recognized way to examine the pathogenesis of severe mental disorders is to study high-risk populations of first-degree relatives.[16] Previous familial high-risk studies[17] have demonstrated developmental abnormalities or neurocognitive deficits already in infancy in the children of parents with schizophrenia, including lower intelligence and verbal and visuospatial dysfunctions. These deficits are similar to, but less severe than, those seen in individuals diagnosed with schizophrenia.[18] The evidence concerning neurocognitive functioning in children of parents with bipolar disorder is scarce and contradictory.[19-23] Several studies observed deficits in processing speed,[19] attention,[20,21] visual memory,[19] executive functions,[21] and intelligence,[23] whereas other reported spared neurocogntive functions with regard to intelligence,[22] executive functions,[20,21] verbal learning and memory,[21] and attention.[21] Neurocognitive deficits were not necessarily concurrent with significantly lower intelligence.[19]

Neurocognitive functions have a high genetic load and a genetic overlap with illness proneness in individuals with schizophrenia and bipolar disorder.[24,25] Thus, neurocognitive functions are considered endophenotypes or vulnerability markers for schizophrenia and bipolar disorder.[6,26] Neurocognitive assessment of children at familial high risk of schizophrenia spectrum disorders (FHR-SZ) or bipolar disorder (FHR-BP) in early childhood provides a unique possibility for discriminating the neurocognitive profiles and differentiating the pathophysiology and developmental trajectory of these 2 familial high-risk groups with increased long-term risk of psychosis and other mental disorders. Ultimately, the identification of early neurocognitive deficits may enable the development of interventions to reduce the risk of transition.[27]

The study objective was to characterize the neurocognitive functions of children with FHR-SZ or FHR-BP. We hypothesized that both groups would display impairments compared with a control group and that children with FHR-SZ would present more pronounced impairments than children with FHR-BP.

Key Points

Questions Do 7-year-old children at familial high risk of schizophrenia spectrum disorders or bipolar disorder have neurocognitive impairments, and how do their neurocognitive profiles differ?

Findings This multisite population-based Danish cohort study of 514 children demonstrated significant neurocognitive impairments in those at familial high risk of schizophrenia, with the most pronounced deficits in processing speed and working memory. Children at familial high risk of bipolar disorder performed significantly better than children at familial high risk of schizophrenia, but did not differ significantly from controls.

Meaning Early identification of children at familial high risk of schizophrenia with neurocognitive impairments is warranted to monitor their developmental pathophysiology, prevent transition to psychosis, and inform early intervention programs.

Methods

Participants

The Danish High Risk and Resilience Study VIA 7 (hereafter referred to as the VIA 7 study) is a population-based cohort study of 522 children aged 7 years who have at least 1 parent diagnosed with schizophrenia spectrum psychosis (n = 202), defined as schizophrenia (*International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* [*ICD-10*], code F20; *International Classification of Diseases, Eighth Revision* [*ICD-8*], code 295), delusional disorder (*ICD-10* code F22; *ICD-8* code 297), and schizoaffective disorder (*ICD-10* code F25; *ICD-8* codes 298.29, 298.39, 298.89, or 298.99), bipolar disorder (n = 120) (*ICD-10* codes F30 and F31; *ICD-8* codes 296.19 and 296.39), or none of the above (n = 200). Children of parents with diagnoses of schizophrenia and bipolar disorder were assigned to the FHR-SZ group as per the *ICD-10* hierarchy. The eMethods in the Supplement entails specifications of the *ICD-8* and *ICD-10* codes and information on differences between the participating and nonparticipating families. Approval from the Danish Data Protection Agency was obtained for this study. All procedures were performed according to the guidelines of the National Committee for Health Research Ethics, although formal approval was not deemed necessary by this authority owing to the observational nature of the study. All families received a thorough oral and written description of the study, and the parents or legal guardians of each child gave written informed consent.

The VIA 7 study design has been described in detail elsewhere.[28] Families were identified through the Danish Civil Registration System[29] and the Danish Psychiatric Central Research Register.[30] Data collection took place from January 1, 2013, through January 31, 2016. Contact by mail and subsequently by telephone and text messages was attempted with 410 of 1073 eligible children with FHR-SZ (38.2%) and 214 of 774 eligible children with FHR-BP (27.6%) (eFigure in the Supplement). The reasons for the rather low proportion of families approached were that (1) during part of the data collection period, approximately 20% of the families were registered as protected from being approached for research purposes owing to legislation enacted in May 2011; and (2) for the entire period, some of the eligible children turned 8 years of age before the assessment capacity allowed for them to be enrolled. Dropout rates were less than 2%. The population-based control group was matched with the children with FHR-SZ by age, sex, and municipality. A total of 10 controls were

retrieved for each child in the FHR-SZ group and the FHR-BP group; the original intent was to only select controls matched to children in the FHR-SZ group, but 38 FHR-BP–matched controls were included among the control group. All the participating children had Danish as their first language.

Procedures

The study assessors were trained psychologists (N.H., C.C., M.G., A.N.G., and D.L.G.), physicians (A.T., D.E., K.S.S., and B.K.B.), and nurses (A.S.) and were instructed, supervised, and certified by a specialist in child neuropsychology (J.R.M.J.). Most of the assessments were conducted at the research sites in Copenhagen and Aarhus, Denmark. A small number of assessments were performed in the homes of the participating families if the home allowed for equal conditions of the examination as in the research sites (ie, a quiet room, a suitable work desk, and no distractions). The child assessors were blinded to familial risk status.

Measures

We used the Children's Global Assessment Scale (CGAS)[31] to assess the current level of functioning and the Child Behavior Checklist (CBCL) School-Age Version (completed by the primary caregiver) to assess problem behavior.[32] The neuropsychological test battery (eTable 1 in the Supplement) was designed to map the neurocognitive functions affected in individuals with schizophrenia[33] or bipolar disorder[9,34] using well-established and validated tests. One key variable from each subtest was selected a priori (eTable 1 in the Supplement).

The neurocognitive test performances were scored by trained psychology students who were blinded to the risk status of the children and supervised by a specialist in clinical child psychology (N.H.). A sample of the test performances of at least 40 children on the 17 test scores that were not computerized was rescored by the specialist in child psychology or a second trained psychology student who was blinded to the original scoring and the familial risk status. If the intraclass correlation coefficient was greater than 0.90, the initial scoring was accepted. Intraclass correlation coefficients were greater than 0.90 on all test scores.

Statistical Analysis

We compared demographic and clinical characteristics of the 3 study groups using univariate analysis of variance for continuous data and the χ^2 test for categorical data. Log transformation was used to approximate a normal distribution when appropriate (CBCL Total Score).

Analysis of missing values was conducted on each of the 23 neurocognitive test scores (eTable 2 in the Supplement). Eight children (1 control [0.5%], 5 with FHR-SZ [2.5%], and 2 with FHR-BD [1.7%]) had more than 8 missing values and were excluded. Because the total number of missing values was low (<1.6%) and no systematic pattern of missing values was apparent for the remaining 514 children, we performed univariate mean imputation (in cases of normal distribution) or median imputation (in cases of nonnormal distribution). The 23 neurocognitive test scores were reexamined to determine the normality of distribution. The distribution of the Word Selective Reminding–Delayed Recall score included 8 extreme outliers that were truncated at −3 SDs. In case of deviations from the normal distribution, log transformation (Odd-Item Out, Letter-Number Sequencing, Word Selective Reminding–Immediate Recall, and Trail-Making Test Number Sequencing and Letter Sequencing) and square root transformation (Trail-Making Test Number-Letter Switching) were applied so that all test scores approximated a normal distribution. All 23 test scores were standardized into *z* scores using the means and SDs of the control group as reference. The *z* scores were constructed so that a negative score always denoted a poorer performance. To reduce the risk of type I errors, we compared the 3 study groups on their performance on the 23 neurocognitive functions using multivariate analysis of variance (MANOVA). Significance for the mean comparisons was corrected using the Scheffé method and set at $P < .05$. Estimates of effect size were calculated with Cohen *d*. A multivariate analysis of covariance (MANCOVA) was conducted to control for potential effects of sex and age. In case of a significant result, separate univariate analysis of covariance (ANCOVA) was conducted with sex or age as the covariate. An intelligence composite score was created by restandardizing the mean *z* scores derived from the Reynolds Intellectual Screening Test, included in the Reynolds Intellectual Assessment Scales battery.[35] To assess the potential effects of intelligence on the observed between-group differences of the other neurocognitive *z* scores, we repeated the MANCOVA with the intelligence composite score as covariate. In case of a significant result, a series of ANCOVAs was conducted with intelligence as covariate. Potential associations between neurocognition and problem behavior were assessed by explorative bivariate correlation analyses between all 23 neurocognitive functions and the CBCL Total Score.

To reduce the number of variables, we conducted a principal component analysis of the 23 neurocognitive *z* scores using oblimin rotation with Kaiser normalization. We then compared the factor structure by study group by means of confirmatory factor analysis.[36] A minimum factor loading of 0.32 was used as a criterion for interpretation,[36] and in cases of cross loadings, the highest loading would determine to which factor a given observed measure would belong. Factor scores were restandardized into *z* scores using the means and SDs of the control group as reference. The factor *z* scores of the 3 study groups were compared using MANOVA to reduce the risk of type I errors. Scheffé post hoc analyses were used to compare mean differences across the 3 groups and the 4 neurocognitive factors. Effect size estimates were calculated using Cohen *d*. MANCOVA was conducted to control for potential effects of sex and age. In case of a significant result, a series of ANCOVAs was conducted with sex or age as the covariate. Data were analyzed using SPSS Statistics software (version 22; IBM Corp).[37]

Results

Demographic and Clinical Characteristics

In this multisite population-based cohort study, the study population of 514 children (238 girls [46.3%] and 276 boys [53.7%]) included 197 with FHR-SZ (91 girls [46.2%]), 118 with FHR-BP

Table 1. Demographic Characteristics of Study Population

Variables	Study Group			P Value	P Value for Pairwise Comparisons[a]		
	Control (n = 199)	FHR-SZ (n = 197)	FHR-BP (n = 118)		Control vs FHR-SZ Groups	Control vs FHR-BP Groups	FHR-SZ vs FHR-BP Groups
Female, No. (%)	92 (46.2)	91 (46.2)	55 (46.6)	>.99[b]	NA	NA	NA
Age at inclusion, mean (SD), y	7.8 (0.2)	7.8 (0.2)	7.9 (0.2)	.09[a]	NA	NA	NA
CBCL total score, mean (SD)[c,d]	17.0 (14.7)	27.2 (21.1)	23.4 (19.7)	<.001[a]	<.001	.009	.06
CGAS score, mean (SD)[e,f]	77.7 (13.5)	68.1 (15.5)	73.6 (14.9)	<.001[a]	<.001	.02	.001

Abbreviations: CBCL, Child Behavior Checklist; CGAS, Children's Global Assessment Scale; FHR-BP, familial high risk for bipolar disorder; FHR-SZ, familial high risk for schizophrenia spectrum disorders; NA, not applicable.

[a] Calculated using 1-way analysis of variance with Fisher least significant difference post hoc test.

[b] Calculated using the Pearson χ^2 test.

[c] Includes 191 controls, 190 children with FHR-SZ, and 111 children with FHR-BP.

[d] Minimum and maximum scores for this scale range from 0 to 226, with higher scores indicating more problems; scores in this cohort range from 0 to 103.

[e] Includes 197 controls, 197 children with FHR-SZ, and 118 children with FHR-BP.

[f] Minimum and maximum scores for this scale range from 1 to 100, with higher scores indicating higher level of functioning; scores in this cohort range from 35 to 100.

(55 girls [46.6%]), and 199 controls (92 girls [46.2%]) aged 7 years (**Table 1**). The 3 study groups did not differ significantly by age or sex. Compared with the control group, the FHR-SZ group displayed significantly more problem behavior (mean [SD] CBCL Total Score 27.2 [21.1] vs 17.0 [14.7]; $P < .001$) and significantly lower functioning (mean [SD] CGAS score, 68.1 [15.5] vs 77.7 [13.5]; $P < .001$). In the FHR-BP group, the problem behavior score (mean [SD], 23.4 [19.7]) and functional score (mean [SD], 73.6 [14.9]) were intermediate between scores in the other study groups and differed significantly from the control group on both scores ($P = .009$ and $P = .02$, respectively) and the FHR-SZ group on the CGAS score ($P = .001$).

Neurocognitive Functions

MANOVA showed a statistically significant effect of group on all 23 functions ($F = 1.93$; $P < .001$; Wilks $\lambda = 0.84$). The results of the pairwise comparisons (**Table 2**) revealed that the FHR-SZ group had a significantly poorer performance compared with controls on 14 of the 23 neurocognitive functions and compared with the FHR-BP group on 8 of the 23 neurocognitive functions with small to medium effect sizes. Results remained significant after adjusting for age and sex. Because the MANCOVA revealed a significant effect of sex, ANCOVAs controlling for sex were conducted on all 23 neurocognitive scores except for Guess What owing to lack of homogeneity of regression between the FHR-SZ and control groups. ANCOVAs controlling for sex did not change the significant between-group effect. Children with FHR-BP and controls did not differ significantly on any of the 23 neurocognitive functions. Owing to multicollinearity of the intelligence composite score and its subtest Guess What and Odd-Item Out scores, we conducted univariate analyses in the pairwise comparisons of the intelligence composite score. The intelligence composite score revealed a significant difference between the FHR-SZ and control groups (mean [SD] *z* score, −0.29 [1.20] vs 0 [1.00]) (Table 2) that remained significant after adjusting for age and sex. Despite a significant effect of intelligence on all other 21 functions, the effect of group remained significant in all comparisons when controlling for intelligence. Owing to the fact that we have a considerably larger control group than the number of children used for this specific age range in the Danish norms of the Reynolds Intelligence Screening Test (n <80), we calculated our own IQ estimate using linear transformation of the *z* scores to IQ scale score, which revealed a mean (SD) IQ estimate of 100.00 (15.00) for the control group, 95.64 (17.92) for the FHR-SZ group, and 99.27 (16.49) for the FHR-BP group. The corresponding mean (SD) Reynolds Intelligence Screening Test index of the 3 groups was 104.95 (9.82) for the control group, 102.10 (11.40) for the FHR-SZ group, and 104.13 (9.32) for the FHR-BP group (Cohen $d = 0.27$ for control vs FHR-SZ groups; 0.09 for control vs FHR-BP groups; 0.20 for FHR-SZ vs FHR-BP groups). Pearson correlations between our own IQ estimate and the Reynolds Intelligence Screening Test index were greater than 0.90 ($P < .001$) in all 3 groups. Explorative bivariate correlation analyses between all 23 neurocognitive functions and the CBCL Total Score revealed 15 significant Pearson correlations ranging from $r = -0.094$ to $r = -0.202$, explaining less than 1% to approximately 4% of the variance.

Neurocognitive Domains

After conducting principal component analysis, the following observed 4 neurocognitive factors were identified: (1) processing speed and working memory, (2) verbal functions, (3) executive and visuospatial functions, and (4) declarative memory and attention (**Table 3**) (factor selection is explained in eMethods in the Supplement). Confirmatory factor analysis supported the 4-factor structure of neurocognitive functioning (factor invariance) across the 3 groups. MANOVA showed a statistically significant effect of group on the 4 factors ($F = 3.76$; $P < .001$; Wilks $\lambda = 0.94$). The results of the pairwise comparisons revealed that the FHR-SZ group was significantly impaired compared with the control group on processing speed and working memory (Cohen $d = 0.50$; $P < .001$), executive and visuospatial functions (Cohen $d = 0.28$; $P = .03$), and declarative memory and attention (Cohen $d = 0.29$; $P = .02$) (Table 2). Children with FHR-SZ also had a significantly poorer performance than children with FHR-BP on the same 3 factors (processing speed and working memory [Cohen $d = 0.40$; $P = .002$]; executive and visuospatial functions [Cohen $d = 0.35$; $P = .008$]; and declarative memory and attention [Cohen $d = 0.31$; $P = .03$]) with small to moderate effect sizes. Results remained

Table 2. Performance of Study Groups on Neurocognitive Functions and Domains

Test Variable	Study Group, Mean (SD) *z* Score[a]			Pairwise Comparisons Between Groups[b]					
				Control vs FHR-SZ		Control vs FHR-BP		FHR-SZ vs FHR-BP	
	Control (n = 199)	FHR-SZ (n = 197)	FHR-BP (n = 118)	*P* Value	Effect Size, Cohen *d*	*P* Value	Effect Size, Cohen *d*	*P* Value	Effect Size, Cohen *d*
SOC PSIMM	0.00 (1.00)	−0.16 (1.01)	0.06 (1.16)	.34	0.15	.87	0.06	.20	0.19
SRM percentage correct	0.00 (1.00)	−0.40 (1.13)	−0.12 (0.92)	<.001[c]	0.35	.63	0.13	.06	0.25
SSP span length	0.00 (1.00)	−0.35 (1.17)	0.15 (1.19)	.008[c]	0.32	.50	0.14	<.001[c]	0.43
SWM total errors	0.00 (1.00)	−0.29 (1.03)	−0.14 (1.12)	.02[c]	0.29	.52	0.13	.44	0.14
RVP A′	0.00 (1.00)	−0.41 (1.24)	−0.16 (1.14)	.002[c]	0.36	.47	0.15	.17	0.21
Guess What	0.00 (1.00)	−0.33 (1.25)	−0.16 (1.05)	.01[c]	0.29	.47	0.16	.41	0.15
Coding	0.00 (1.00)	−0.43 (1.06)	−0.11 (0.97)	<.001[c]	0.42	.65	0.11	.03[c]	0.32
Symbol Search	0.00 (1.00)	−0.38 (1.02)	0.01 (0.93)	<.001[c]	0.38	>.99	0.01	.003[c]	0.40
Arithmetic	0.00 (1.00)	−0.38 (1.19)	0.06 (1.15)	.003[c]	0.35	.91	0.06	.004[c]	0.38
MFS immediate recall	0.00 (1.00)	−0.07 (1.07)	0.07 (1.06)	.79	0.07	.84	0.07	.50	0.13
MFS delayed recall	0.00 (1.00)	−0.08 (1.10)	0.17 (1.11)	.76	0.08	.39	0.16	.13	0.23
Verbal Fluency phonemic	0.00 (1.00)	−0.20 (1.08)	−0.01 (1.03)	.17	0.19	>.99	0.01	.29	0.18
Verbal Fluency semantic	0.00 (1.00)	−0.29 (0.96)	−0.13 (1.00)	.02[c]	0.30	.53	0.13	.38	0.16
Verbal Fluency switching	0.00 (1.00)	−0.17 (1.02)	0.12 (0.88)	.22	0.17	.57	0.13	.04[c]	0.30
RCFT immediate recall	0.00 (1.00)	−0.37 (0.87)	−0.05 (1.00)	<.001[c]	0.40	.90	0.05	.02[c]	0.34
IED EDS errors	0.00 (1.00)	0.15 (1.00)	0.07 (1.04)	.36	0.15	.83	0.07	.82	0.08
Odd-Item Out	0.00 (1.00)	−0.12 (1.06)	0.08 (1.13)	.53	0.12	.80	0.08	.26	0.18
Letter-Number Sequencing	0.00 (1.00)	−0.33 (0.98)	0.13 (1.21)	.008[c]	0.33	.56	0.12	<.001[c]	0.42
WSR Immediate Recall	0.00 (1.00)	−0.06 (1.03)	0.10 (1.07)	.84	0.06	.70	0.10	.39	0.15
WSR Delayed Recall	0.00 (1.00)	−0.03 (1.03)	0.10 (0.98)	.96	0.03	.70	0.10	.56	0.13
TMT Number Sequencing	0.00 (1.00)	−0.35 (1.17)	−0.13 (1.11)	.006[c]	0.32	.58	0.12	.22	0.20
TMT Letter Sequencing	0.00 (1.00)	−0.29 (1.06)	−0.07 (1.04)	.02[c]	0.28	.83	0.07	.20	0.21
TMT Number-Letter Switching	0.00 (1.00)	−0.41 (0.95)	−0.13 (0.95)	<.001[c]	0.42	.52	0.13	.05[c]	0.30
Domain									
Processing speed and working memory[d]	0.00 (1.00)	−0.52 (1.07)	−0.09 (1.07)	<.001[c]	0.50	.78	0.09	.002[c]	0.40
Verbal functions[e]	0.00 (1.00)	−0.26 (1.18)	0.03 (1.09)	.06	0.24	.97	0.03	.07	0.26
Executive and visuospatial functions[f]	0.00 (1.00)	−0.29 (1.08)	0.10 (1.15)	.03[c]	0.28	.72	0.09	.008[c]	0.35
Declarative memory and attention[g]	0.00 (1.00)	−0.31 (1.15)	0.03 (1.08)	.02[c]	0.29	.98	0.03	.03[c]	0.31
Composite Score									
Intelligence	0.00 (1.00)	−0.29 (1.20)	−0.05 (1.10)	.009[c]	0.26	.69	0.05	.07	0.21

Abbreviations: EDS, extradimensional stage; FHR-BP, familial high risk of bipolar disorder; FHR-SZ, familial high risk of schizophrenia spectrum disorders; IED, Intra-Extra Dimensional Set Shift; MFS, Memory for Stories; PSIMM, Problems Solved in Minimum Moves; RCFT, Rey Complex Figure Test and Recognition Trial; RVP, Rapid Visual Information Processing; SOC, Stockings of Cambridge; SRM, Spatial Recognition Memory; SSP, Spatial Span; SWM, Spatial Working Memory; TMT, Trail-Making Test; WSR, Word Selective Reminding.

[a] Calculated after imputation of missing data. Negative values denote poorer performance.

[b] A significant effect of sex was found on SRM percentage correct, Coding, Symbol Search, Verbal Fluency Switching, RCFT Immediate Recall, processing speed and working memory, executive and visuospatial functions, and declarative memory and attention. Being female was associated with better neurocognitive performance compared with being male. Owing to the risk of overcorrecting the neurocognitive data, we did not covary for socioeconomic status, which is intrinsically associated with group status. The presented values are unadjusted for sex, age, and intelligence.

[c] Indicates significance after post hoc correction for multiple comparisons with Scheffé method ($P < .05$).

[d] Includes TMT Number Sequencing, TMT Letter Sequencing, TMT Letter-Number Switching, Symbol Search, Coding, Arithmetic, Letter-Number Sequencing, and SWM total errors.

[e] Includes MFS immediate recall, MFS delayed recall, Guess What, Verbal Fluency phonemic, Verbal Fluency semantic, and Verbal Fluency switching.

[f] Includes SOC PSIMM, SSP span length, Odd-Item Out, IED EDS errors, and SRM percentage correct.

[g] Includes RCFT Recall, WSR Immediate Recall, WSR Delayed Recall, and RVP A′.

significant after adjusting for age and sex. Again, MANCOVA revealed a significant effect of sex on the 4 neurocognitive factors, but after controlling for sex with a series of ANCOVAs, the results remained significant in all comparisons. We found no statistically significant differences between the FHR-BP and control groups on the 4 neurocognitive factors. **Figure 1** and **Figure 2** display the unadjusted neurocognitive profiles of the 3 study groups across all functions and domains.

Discussion

In this large, population-based cohort study with comprehensive neurocognitive assessments of familial high-risk offspring, we demonstrated widespread neurocognitive impairments in 7-year-old children with FHR-SZ in the domains of processing speed and working memory, executive and

Table 3. Principal Component Analysis of the 23 Neurocognitive Test Scores[a,b]

Test Variable	Neurocognitive Domain			
	Processing Speed and Working Memory	Verbal Functions	Executive and Visuospatial Functions	Declarative Memory and Attention
SOC PSIMM	0.167	−0.175	0.594[c]	NA
SRM percentage correct	0.176	NA	0.373[c]	NA
SSP span length	0.267	NA	0.459[c]	NA
SWM total errors	0.472[c]	NA	0.399[c]	NA
RVP A′	0.338[c]	NA	0.133	0.367[c]
Guess What	0.137	0.728[c]	0.101	−0.236
Coding	0.526[c]	NA	NA	0.384[c]
Symbol Search	0.625[c]	NA	NA	0.131
Arithmetic	0.514[c]	0.383[c]	0.168	NA
MFS Immediate Recall	−0.257	0.793[c]	NA	0.242
MFS Delayed Recall	−0.188	0.786[c]	NA	0.228
Verbal Fluency phonemic	0.392[c]	0.436[c]	NA	NA
Verbal Fluency semantic	0.226	0.395[c]	−0.232	0.293
Verbal Fluency switching	0.151	0.439[c]	NA	NA
RCFT immediate recall	NA	NA	0.429[c]	0.512[c]
IED EDS errors	−0.169	NA	0.476[c]	NA
Odd-Item Out	0.120	0.194	0.494[c]	NA
Letter-Number Sequencing	0.396[c]	0.393[c]	0.199	NA
WSR Immediate Recall	NA	0.215	NA	0.554[c]
WSR Delayed Recall	0.105	NA	−0.201	0.649[c]
TMT Number Sequencing	0.724[c]	NA	NA	NA
TMT Letter Sequencing	0.776[c]	NA	NA	NA
TMT Letter-Number Switching	0.685[c]	NA	NA	NA

Abbreviations: EDS, extradimensional stage; IED, Intra-Extra Dimensional Set Shift; MFS, Memory for Stories; NA, not applicable; PSIMM, Problems Solved in Minimum Moves; RCFT, Rey Complex Figure Test and Recognition Trial; RVP, Rapid Visual Information Processing; SOC, Stockings of Cambridge; SRM, Spatial Recognition Memory; SSP, Spatial Span; SWM, Spatial Working Memory; TMT, Trail-Making Test; WSR, Word Selective Reminding.

[a] Data are rotated factor matrix after oblimin rotation with Kaiser normalization.

[b] Factor loadings of less than 0.100 are not reported (NA).

[c] Indicates factor loadings of 0.320 or larger.

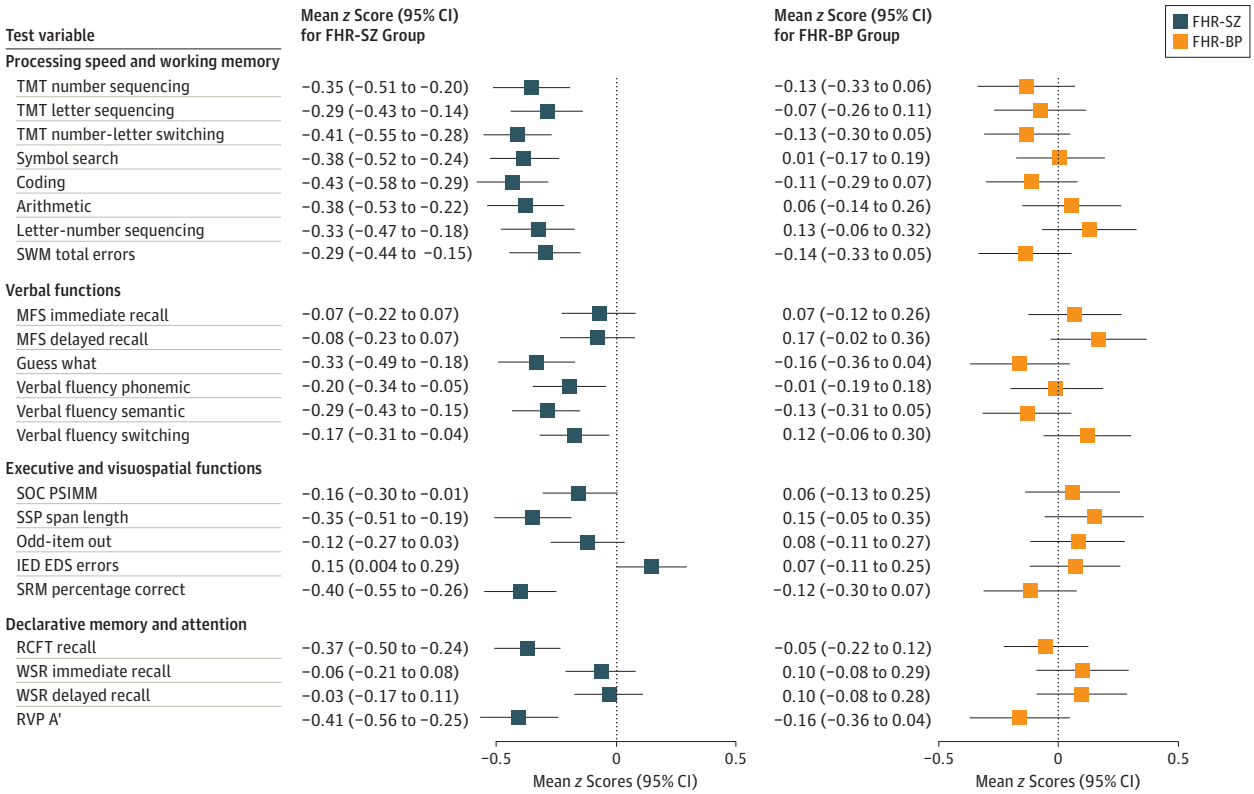
visuospatial functions, and declarative memory and attention. Children with FHR-BD did not show neurocognitive impairments at this young age. Children with FHR-SZ also had a significantly poorer performance than children with FHR-BP in the same domains. These findings suggest distinct neurodevelopmental pathophysiology and trajectory of these familial high-risk groups.

Our findings of widespread neurocognitive impairments in children with FHR-SZ are consistent with findings of previous high-risk studies of first-degree relatives.[38] However, previous high-risk studies were small, including a wide age range, which introduces cognitive heterogeneity, or included adult relatives, which implicates attrition bias. A broad age range obscures the effects of cognitive maturation in the event of a neurocognitive developmental lag. Children developing schizophrenia in adulthood display developmental lags between the ages of 7 to 13 years in some neurocognitive functions.[39] Although speculative, the currently observed neurocognitive impairments may also reflect a developmental lag suggesting worse deficits with increasing age. Also, the larger effect sizes (predominantly in the medium range) reported in most of the studies on neurocognition in children with FHR-SZ (compared with the small to medium effect sizes in our study) may be explained by higher mean ages.[17] Thus, comparable small to medium effect sizes were observed in another study of 7-year-old children of parents with schizophrenia.[40] Finally, several studies included relatives of currently hospitalized patients.[38] This recruitment procedure may bias toward poorer functioning associated with poorer neurocognition,[14] which may lead to larger effect sizes. On a similar note, previous neurocognitive studies on children with FHR-BP may have been affected by a broader age range (implicating different neurocognitive maturational stages) and a higher mean age (allowing deficits to emerge owing to developmental lag)[19-21,23] and, in 2 studies,[25,41] by including individuals at extreme risk, which may explain the differences between earlier findings and the currently observed absence of neurocognitive deficits in children with FHR-BP.

We observed no difference between children with FHR-SZ and controls in the domain of verbal functions. This finding is consistent with those in older children with FHR-SZ,[42] individuals at clinical high risk,[43] and individuals with established schizophrenia,[44] although inconsistent with a study selectively including 7-year-old children who later developed schizophrenia.[45]

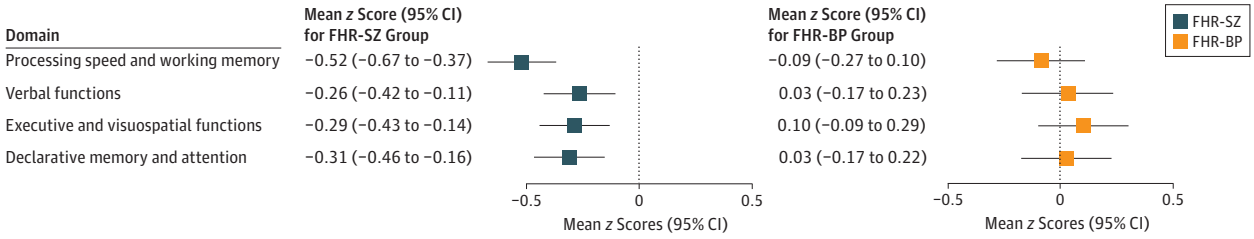
Our observation of widespread neurocognitive dysfunctions in children with FHR-SZ supports the hypothesis that schizophrenia is a disorder with substantial neurodevelopmental deficits, even in individuals with a mere vulnerability for the disorder.[46] We found no evidence of shared neurocognitive impairments between familial high risk of schizophrenia and bipolar disorder. Our findings suggest unimpaired early neurocognitive maturation in children with FHR-BP, although neurocognitive dysfunctions are reported to emerge later.[19,21] In alignment with the model of Craddock and Owen,[46] our findings suggest more pronounced neurodevelopmental pathologic findings in children with FHR-SZ compared with

Figure 1. Unadjusted Profile of Neurocognitive Functions by Familial High-Risk Groups



Includes 197 children with FHR-SZ and 118 with FHR-BP, with 199 controls as reference. EDS indicates extradimensional stage; FHR-BP, familial high risk for bipolar disorder; FHR-SZ, familial high risk for schizophrenia spectrum disorders; IED, Intra-Extra Dimensional Set Shift; MFS, Memory for Stories; PSIMM, Problems Solved in Minimum Moves; RCFT, Rey Complex Figure Test and Recognition Trial; RVP, Rapid Visual Information Processing; SOC, Stockings of Cambridge; SRM, Spatial Recognition Memory; SSP, Spatial Span; SWM, Spatial Working Memory; TMT, Trail-Making Test; and WSR, Word Selective Reminding.

Figure 2. Unadjusted Profile of Neurocognitive Domains by Familial High-Risk Groups



Includes 197 children with FHR-SZ and 118 with FHR-BP, with 199 controls as reference. FHR-BP indicates familial high risk for bipolar disorder; FHR-SZ, familial high risk for schizophrenia spectrum disorders.

FHR-BP. Despite partly shared genetic underpinnings,[47] the shared genetic risk factors may not affect early neurocognitive development. Finally, neurocognition appeared to be unrelated or very weakly related to psychopathology.

Heterogeneity within these high-risk groups must be recognized. Cross-diagnostic latent class analysis may identify different subgroups based on neurocognitive functioning[48] and reveal potential neurocognitive subtypes. Furthermore, potential associations between neurocognition in offspring at high risk and the severity of parental illness as well as functional impairment are important to consider. Although meta-analytic evidence comparing individuals with bipolar I and II disorder suggests nonsignificant differences in several neurocognitive functions,[49] the transmission of neurocognitive endophenotypes to their offspring may be different. Finally, our study provides insight into neurocognitive profiles of children at familial high risk, which may not be representative of children who develop sporadic schizophrenia or bipolar disorder.

Follow-up assessments will elucidate whether our current results reflect stable or dynamic neurocognitive group

differences.[39] In addition, they may identify neurocognitive predictors of conversion to psychosis and clarify which neurocognitive dysfunctions emerge in bipolar offspring and when.

Strengths and Limitations

Our study is, to our knowledge, the largest and most comprehensive familial high-risk study of neurocognition to date, including offspring with FHR-SZ and FHR-BP. All children were examined at the same age, which is unique within this field. The detailed assessment battery consisted of validated tests, and scoring was reliable. Register-based recruitment ensured an epidemiologically identified population with no referral bias. Finally, the dropout rate was low.

Representativity analyses revealed that participating parents were slightly older than nonparticipating parents and that a higher proportion of participating families lived in densely populated areas in all 3 groups. We prioritized visuospatial memory, and a visuospatial construction score was not included. Finally, inclusion of children at familial high risk from an even younger age would have ensured the capturing of neurocognitive development from early childhood and onwards.

Conclusions

Neurocognitive impairments are widespread in 7-year-old children with FHR-SZ, supporting the notion of neurocognition as an endophenotype for schizophrenia and a target for intervention. Children with FHR-BP do not display neurocognitive deficits at this age, suggesting a less pronounced neurodevelopmental component. Early detection of children with FHR-SZ and cognitive impairments is warranted to (1) investigate associations of neurocognition with functional outcome and transition to psychosis, (2) add to the knowledge of their developmental pathophysiology, and (3) inform early intervention programs.

ARTICLE INFORMATION

Accepted for Publication: April 8, 2018.

Published Online: June 20, 2018. doi:10.1001/jamapsychiatry.2018.1415

Author Affiliations: Mental Health Centre Copenhagen, Mental Health Services, Capital Region of Denmark, Copenhagen (Hemager, Thorup, Christiani, Ellersgaard, Gregersen, Søndergaard, Nordentoft, Jepsen); Child and Adolescent Mental Health Centre, Mental Health Services, Capital Region of Denmark, Copenhagen (Hemager, Plessen, Spang, Burton, Jepsen); The Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH), Aarhus, Denmark (Hemager, Plessen, Thorup, Christiani, Ellersgaard, Spang, Burton, Gregersen, Søndergaard, Greve, Gantriis, Poulsen, Mors, Nordentoft, Jepsen); Service of Child and Adolescent Psychiatry, Department of Psychiatry, University Medical Center, University of Lausanne, Lausanne, Switzerland (Plessen); Psychosis Research Unit, Aarhus University Hospital, Aarhus, Denmark (Greve, Gantriis, Mors); Section of Biostatistics, Department of Public Health, University of Copenhagen, Copenhagen, Denmark (Poulsen); Department of Psychiatry, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts (Seidman); Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston (Seidman); Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark (Nordentoft); Center for Neuropsychiatric Schizophrenia Research, Mental Health Services, Capital Region of Denmark, Copenhagen (Jepsen); Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research, Mental Health Services, Capital Region of Denmark, Copenhagen (Jepsen).

Author Contributions: Ms Hemager had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Hemager, Plessen, Thorup, Mors, Nordentoft, Jepsen.
Acquisition, analysis, or interpretation of data: Hemager, Plessen, Thorup, Christiani, Ellersgaard, Spang, Burton, Gregersen, Søndergaard, Greve, Gantriis, Poulsen, Mors, Nordentoft, Jepsen.
Drafting of the manuscript: Hemager, Plessen, Jepsen.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Hemager, Poulsen, Nordentoft, Jepsen.
Obtained funding: Plessen, Mors, Nordentoft.
Administrative, technical, or material support: Hemager, Thorup, Christiani, Ellersgaard, Spang, Burton, Gregersen, Søndergaard, Greve, Gantriis, Mors, Nordentoft, Jepsen.
Supervision: Hemager, Plessen, Thorup, Greve, Poulsen, Mors, Nordentoft, Jepsen.

Conflict of Interest Disclosures: None reported.

Funding/Support: This study was supported by the Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH), the Mental Health Services of the Capital Region of Denmark, TrygFonden, and the Beatrice Surovell Haskell Fund for Child Mental Health Research of Copenhagen.

Role of the Funder/Sponsor: The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: Carsten Bøcker Pedersen, DrMedSc and Marianne Giørtz Pedersen, MSc (National Centre for Register-based Research, Department of Economics and Business Economics, Aarhus University, Aarhus, Denmark), provided assistance with data extraction from the Danish registers. Statistical consultation was provided by Klaus Kaae Andersen, PhD (Unit of Statistics, Bioinformatics and Registry, Danish Cancer Society Research Center, Copenhagen, Denmark) regarding the factor analyses and by Jamal Uddin, PhD (Mental Health Centre Copenhagen, Mental Health Services, Capital Region of Denmark, Copenhagen) regarding the representativity analyses. Manon Chaine, MSc (Department of Infectious Disease Epidemiology and Prevention, Statens Serum Institut, Copenhagen, Denmark), and Jessica Ohland, MSc (Mental Health Centre Copenhagen, Mental Health Services, Capital Region of Denmark), provided data management support. Preben Bo Mortensen, MD, DrMed (National Centre for Register-based Research, Department of Economics and Business Economics, Aarhus University), Thomas Werge, PhD (Institute of Biological Psychiatry, Mental Health Centre Sct Hans, Mental Health Services, Copenhagen), David Hougaard, PhD (Center for Neonatal Screening, Department for Congenital Disorders, Statens Serum Institut, Copenhagen), and Anders Børglum, MD, PhD (Centre for Integrative Sequencing, Department of Biomedicine and iSEQ, Aarhus University) from iPSYCH, Aarhus, provided study support. Mette Skjærbæk, BSc, Anne Ranning, PhD, Heidi Jensen, BSc, Marianne Melau, PhD, Cecilie Gregersen, MSc, Henriette Stadsgaard, MSc, Kate Kold Zahle, MSc, and Maria Toft Henriksen, MSc, provided assistance with the study at the Mental Health Centre Copenhagen site and the Psychosis Research Unit, Aarhus University Hospital site. No financial compensation was given to any of these contributors with the exception of Dr Andersen.

Additional Information: Dr Seidman died September 7, 2017.

REFERENCES

1. Murray RM, Lewis SW. Is schizophrenia a neurodevelopmental disorder? *BMJ (Clin Res Ed)*. 1987;295(6600):681-682.

2. Weinberger DR. Implications of normal brain development for the pathogenesis of schizophrenia. *Arch Gen Psychiatry*. 1987;44(7):660-669.

3. Rapoport JL, Addington AM, Frangou S, Psych MR. The neurodevelopmental model of schizophrenia: update 2005. *Mol Psychiatry*. 2005;10(5):434-449.

4. Owen MJ, O'Donovan MC, Thapar A, Craddock N. Neurodevelopmental hypothesis of schizophrenia. *Br J Psychiatry*. 2011;198(3):173-175.

5. Trotta A, Murray RM, MacCabe JH. Do premorbid and post-onset cognitive functioning differ between schizophrenia and bipolar disorder? a systematic review and meta-analysis. *Psychol Med*. 2015;45(2):381-394.

6. Reichenberg A, Harvey PD. Neuropsychological impairments in schizophrenia: integration of performance-based and brain imaging findings. *Psychol Bull*. 2007;133(5):833-858.

7. Mesholam-Gately RI, Giuliano AJ, Goff KP, Faraone SV, Seidman LJ. Neurocognition in first-episode schizophrenia: a meta-analytic review. *Neuropsychology*. 2009;23(3):315-336.

8. Fusar-Poli P, Deste G, Smieskova R, et al. Cognitive functioning in prodromal psychosis: a meta-analysis. *Arch Gen Psychiatry*. 2012;69(6):562-571.

9. Bora E, Yucel M, Pantelis C. Cognitive endophenotypes of bipolar disorder: a meta-analysis of neuropsychological deficits in euthymic patients and their first-degree relatives. *J Affect Disord*. 2009;113(1-2):1-20.

10. Bora E, Yücel M, Pantelis C. Cognitive impairment in affective psychoses: a meta-analysis. *Schizophr Bull*. 2010;36(1):112-125.

11. Bora E, Pantelis C. Meta-analysis of cognitive impairment in first-episode bipolar disorder: comparison with first-episode schizophrenia and healthy controls. *Schizophr Bull*. 2015;41(5):1095-1104.

12. Bora E. Differences in cognitive impairment between schizophrenia and bipolar disorder: considering the role of heterogeneity. *Psychiatry Clin Neurosci*. 2016;70(10):424-433.

13. Zanelli J, Reichenberg A, Morgan K, et al. Specific and generalized neuropsychological deficits: a comparison of patients with various first-episode psychosis presentations. *Am J Psychiatry*. 2010;167(1):78-85.

14. Green MF. Cognitive impairment and functional outcome in schizophrenia and bipolar disorder. *J Clin Psychiatry*. 2006;67(suppl 9):3-8.

15. Rasic D, Hajek T, Alda M, Uher R. Risk of mental illness in offspring of parents with schizophrenia, bipolar disorder, and major depressive disorder: a meta-analysis of family high-risk studies. *Schizophr Bull*. 2014;40(1):28-38.

16. Niemi LT, Suvisaari JM, Tuulio-Henriksson A, Lönnqvist JK. Childhood developmental abnormalities in schizophrenia: evidence from high-risk studies. *Schizophr Res*. 2003;60(2-3):239-258.

17. Hameed MA, Lewis AJ. Offspring of parents with schizophrenia: a systematic review of developmental features across childhood. *Harv Rev Psychiatry*. 2016;24(2):104-117.

18. Kremen WS, Seidman LJ, Pepple JR, Lyons MJ, Tsuang MT, Faraone SV. Neuropsychological risk indicators for schizophrenia: a review of family studies. *Schizophr Bull*. 1994;20(1):103-119.

19. de la Serna E, Vila M, Sanchez-Gistau V, et al. Neuropsychological characteristics of child and adolescent offspring of patients with bipolar disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2016;65:54-59.

20. Diwadkar VA, Goradia D, Hosanagar A, et al. Working memory and attention deficits in adolescent offspring of schizophrenia or bipolar patients: comparing vulnerability markers. *Prog Neuropsychopharmacol Biol Psychiatry*. 2011;35(5):1349-1354.

21. Klimes-Dougan B, Ronsaville D, Wiggs EA, Martinez PE. Neuropsychological functioning in adolescent children of mothers with a history of bipolar or major depressive disorders. *Biol Psychiatry*. 2006;60(9):957-965.

22. McDonough-Ryan P, DelBello M, Shear PK, Ris DM, Soutullo C, Strakowski SM. Academic and cognitive abilities in children of parents with bipolar disorder: a test of the nonverbal learning disability model. *J Clin Exp Neuropsychol*. 2002;24(3):280-285.

23. Sharma A, Camilleri N, Grunze H, et al. Neuropsychological study of IQ scores in offspring of parents with bipolar I disorder. *Cogn Neuropsychiatry*. 2017;22(1):17-27.

24. Blokland GA, Mesholam-Gately RI, Toulopoulou T, et al. Heritability of neuropsychological measures in schizophrenia and nonpsychiatric populations: a systematic review and meta-analysis. *Schizophr Bull*. 2017;43(4):788-800.

25. Glahn DC, Almasy L, Barguil M, et al. Neurocognitive endophenotypes for bipolar disorder identified in multiplex multigenerational families. *Arch Gen Psychiatry*. 2010;67(2):168-177.

26. Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. *Am J Psychiatry*. 2003;160(4):636-645.

27. Keshavan MS, Kulkarni S, Bhojraj T, et al. Premorbid cognitive deficits in young relatives of schizophrenia patients. *Front Hum Neurosci*. 2010;3:62.

28. Thorup AA, Jepsen JR, Ellersgaard DV, et al. The Danish High Risk and Resilience Study–VIA 7: a cohort study of 520 7-year-old children born of parents diagnosed with either schizophrenia, bipolar disorder or neither of these two mental disorders. *BMC Psychiatry*. 2015;15:233.

29. Pedersen CB, Gøtzsche H, Møller JO, Mortensen PB. The Danish Civil Registration System: a cohort of eight million persons. *Dan Med Bull*. 2006;53(4):441-449.

30. Mors O, Perto GP, Mortensen PB. The Danish Psychiatric Central Research Register. *Scand J Public Health*. 2011;39(7)(suppl):54-57.

31. Shaffer D, Gould MS, Brasic J, et al. A Children's Global Assessment Scale (CGAS). *Arch Gen Psychiatry*. 1983;40(11):1228-1231.

32. Achenbach TM, Rescorla LA. *Manual for the ASEBA School-Age Forms and Profiles*. Burlington: University of Vermont, Research Center for Children, Youth, & Families; 2001.

33. Nuechterlein KH, Barch DM, Gold JM, Goldberg TE, Green MF, Heaton RK. Identification of separable cognitive factors in schizophrenia. *Schizophr Res*. 2004;72(1):29-39.

34. Robinson LJ, Ferrier IN. Evolution of cognitive impairment in bipolar disorder: a systematic review of cross-sectional evidence. *Bipolar Disord*. 2006;8(2):103-116.

35. Reynolds CR, Kamphaus RW. *Reynolds Intellectual Assessment Scales (RIAS)*. Lutz, FL: Psychological Assessment Resources Inc; 2003.

36. Tabachnick GB, Fidell LS. *Using Multivariate Statistics*. 5th ed. Needham Heights, MA: Allyn & Bacon Inc; 2006.

37. Corp IBM. *IBM SPSS Statistics for Windows, Version 22.0*. Armonk, NY: IBM Corp; 2013.

38. Agnew-Blais J, Seidman LJ. Neurocognition in youth and young adults under age 30 at familial risk for schizophrenia: a quantitative and qualitative review. *Cogn Neuropsychiatry*. 2013;18(1-2):44-82.

39. Reichenberg A, Caspi A, Harrington H, et al. Static and dynamic cognitive deficits in childhood preceding adult schizophrenia: a 30-year study. *Am J Psychiatry*. 2010;167(2):160-169.

40. Goldstein JM, Seidman LJ, Buka SL, et al. Impact of genetic vulnerability and hypoxia on overall intelligence by age 7 in offspring at high risk for schizophrenia compared with affective psychoses. *Schizophr Bull*. 2000;26(2):323-334.

41. Maziade M, Rouleau N, Gingras N, et al. Shared neurocognitive dysfunctions in young offspring at extreme risk for schizophrenia or bipolar disorder in Eastern Quebec multigenerational families. *Schizophr Bull*. 2009;35(5):919-930.

42. Carter JW, Schulsinger F, Parnas J, Cannon T, Mednick SA. A multivariate prediction model of schizophrenia. *Schizophr Bull*. 2002;28(4):649-682.

43. Seidman LJ, Shapiro DI, Stone WS, et al. Association of neurocognition with transition to psychosis: baseline functioning in the second phase of the North American Prodrome Longitudinal Study. *JAMA Psychiatry*. 2016;73(12):1239-1248.

44. Seidman LJ, Kremen WS, Koren D, Faraone SV, Goldstein JM, Tsuang MT. A comparative profile analysis of neuropsychological functioning in patients with schizophrenia and bipolar psychoses. *Schizophr Res*. 2002;53(1-2):31-44.

45. Seidman LJ, Cherkerzian S, Goldstein JM, Agnew-Blais J, Tsuang MT, Buka SL. Neuropsychological performance and family history in children at age 7 who develop adult schizophrenia or bipolar psychosis in the New England Family Studies. *Psychol Med*. 2013;43(1):119-131.

46. Craddock N, Owen MJ. The Kraepelinian dichotomy: going, going… but still not gone. *Br J Psychiatry*. 2010;196(2):92-95.

47. Lichtenstein P, Yip BH, Björk C, et al. Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. *Lancet*. 2009;373(9659):234-239.

48. Bora E, Veznedaroğlu B, Vahip S. Theory of mind and executive functions in schizophrenia and bipolar disorder: a cross-diagnostic latent class analysis for identification of neuropsychological subtypes. *Schizophr Res*. 2016;176(2-3):500-505.

49. Bora E, Yücel M, Pantelis C, Berk M. Meta-analytic review of neurocognition in bipolar II disorder. *Acta Psychiatr Scand*. 2011;123(3):165-174.