Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Participants and Principal Component Analysis

I. Participants

Specification of the included ICD-8 and ICD-10 codes of Schizophrenia spectrum psychosis
ICD-8 diagnoses included:
295 Schizophrenia
297 Paranoid states
298.29 Other psychoses, Reactive confusion
298.39 Other psychoses, Acute paranoid reaction
298.89 Other psychoses, Reactive psychosis
298.99 Other psychoses, Reactive psychosis, unspecified

ICD-10 diagnoses included:
F20 Schizophrenia
F22 Persistent delusional disorders
F25 Schizoaffective disorders

Specification of the included ICD-8 and ICD-10 codes of bipolar affective disorder
ICD-8 diagnoses included:
296.19 Manic-depressive psychosis, manic type
296.39 Manic depressive psychosis, circular type

ICD-10 diagnoses included:
F30 Manic episode
F31 Bipolar affective disorder

Differences between participating and non-participating families
The sample was drawn from the national population of children who were seven years old in the study period and who had parents with schizophrenia or bipolar disorder together with matched control children (Figure 1). The mothers of the participating children were slightly but non-significantly older (0.4 years) compared to the mothers of the non-participating children. The fathers of the participating children were slightly and significantly older (0.5 years, $P = .045$) compared to the fathers of non-participating children with an age difference of 0.1 years ($P = .92$) in the FHR-SZ group, 1.8 years ($P = .01$) in the FHR-BP group, and 0.8 years ($P = .04$) in the control group. A significantly higher proportion of the participating families lived in densely populated areas (46.6% among participating versus 29.3% among non-participating families, $P < .001$). This pattern was exactly the same in the three study groups. Logistic problems most likely explained why fewer families from rural areas chose to take part.

II. Principal Component Analysis
To reduce the number of variables principal component analysis was conducted on the 23 neurocognitive z-scores. Factors with an eigenvalue >1 and scree plots were examined to identify the appropriate number of factors. Factorial invariance was confirmed separately in the three groups. Oblimin rotation with Kaiser normalization was applied. Bartlett's test of sphericity (p<0.0001) was significant and the relatively high Kaiser-Meyer-Olkin measure of sampling adequacy (KMO=0.9) supported factor analysis as a valid method for structure detection. Four factors were identified and considered conceptually interpretable in terms of neurocognitive domains. The four factors cumulatively explained 47% of the total variance. Factor scores were constructed as the sum of the factor coefficients (loadings) times the standardized neurocognitive test scores.

eTable 1. Neurocognitive Functions, Tests, and a Priori Selected Variables

Neurocognitive Function	Tests (Test Battery)	A Priori Selected Test Variables
Verbal Intelligence	Guess What (RIST)	Total correct responses
Nonverbal Intelligence	Odd-Item Out (RIST)	Total number of correctly designated drawings/pictures
Processing Speed	Coding (WISC-IV)	Total number correct
Processing Speed	Symbol Search (WISC-IV)	Total number correct
Processing Speed	Trail Making Test 2 - Number Sequencing (D-KEFS)	Time to complete in seconds
Processing Speed	Trail Making Test 3 - Letter Sequencing (D-KEFS)	Time to complete in seconds
Sustained Attention	Rapid Visual Information Processing (CANTAB)	A' (A Prime)[a]
Verbal Memory	Memory for Stories - Immediate Recall (TOMAL-2)	Total number of units recalled over two stories
Verbal Memory	Memory for Stories - Delayed Recall (TOMAL-2)	Total number of units recalled over two stories
Verbal Memory	Word Selective Reminding - Immediate Recall (TOMAL-2)	Total number of words recalled over six learning trials
Verbal Memory	Word Selective Reminding - Delayed Recall (TOMAL-2)	Total number of words recalled in one trial
Visuospatial Memory	Spatial Recognition Memory (CANTAB)	Percent Correct[b]
Visuospatial Memory	RCFT - Immediate recall	Total number correct
Flexibility/Set Shift	Intra-Extra Dimensional Set Shift (CANTAB)	Extra-Dimensional Stage Errors[c]
Flexibility/Set Shift	Trail Making Test 4 - Number-Letter Switching (D-KEFS)	Time to complete in seconds
Flexibility/Set Shift	Verbal Fluency 3 Switching (D-KEFS)	Total number of correct switching between categories in 60 seconds[d]
Planning	Stockings of Cambridge (CANTAB)	Problems Solved in Minimum Moves
Verbal working memory	Arithmetic (WISC-IV)	Total correct responses
Verbal working memory	Letter-Number Sequencing (WISC-IV)	Number of correct trials
Visual working memory	Spatial Span (CANTAB)	Span Length[e]
Visual working memory	Spatial Working Memory (CANTAB)	Total Errors[f]
Verbal Fluency	Verbal Fluency 1 Phonemic (D-KEFS)	Total number of words beginning with F, A, and S named in 60 seconds respectively
Verbal Fluency	Verbal Fluency 2 Semantic (D-KEFS)	Total number of animals named in 60 seconds

RIST = Reynold's Intellectual Screening test[1]; WISC-IV = Wechsler Intelligence Scale for Children - fourth edition[2]; D-KEFS = Delis-Kaplan Executive Function System[3]; CANTAB = Cambridge Neuropsychological Test Automated Battery[4]; TOMAL-2 = Test of Memory and Learning – Second Edition[5]; RCFT = Rey Complex Figure Test and Recognition Trial[6].

[a] A prime measures target sensitivity

[b] Number of correct responses, expressed as a percentage

[c] Extra-Dimensional Stage Errors denotes the errors made in the extra-dimensional stage of the task, where the child is required to make an extra-dimensional shift

[d] The categories in the Danish version of the subtest Verbal Fluency 3 Switching are 1) furniture and 2) fruit

[e] Span length denotes the longest sequence successfully recalled by the child (three attempts at each level)
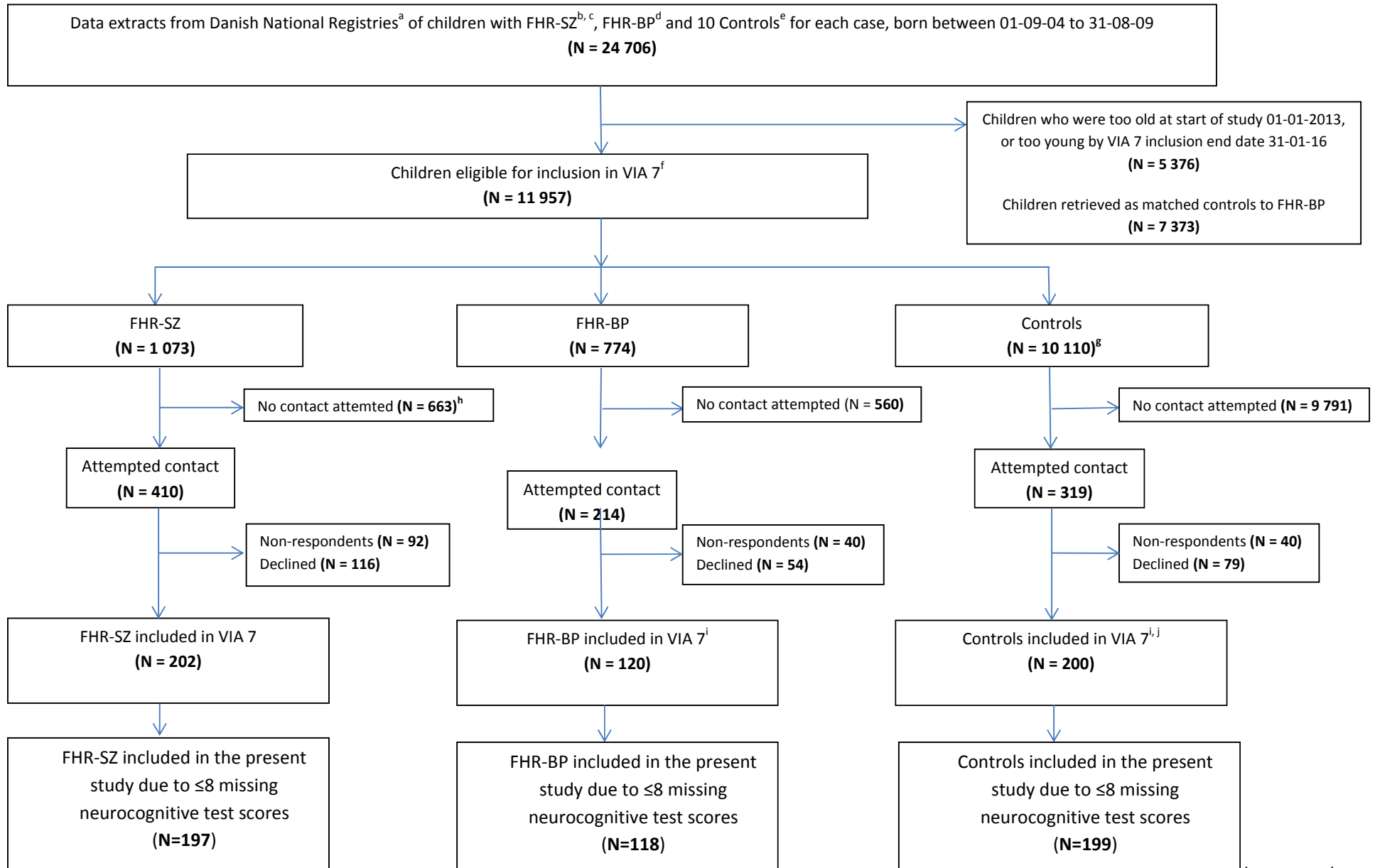
[f] Total errors comprise the number of times a box is selected that is certain not to contain a blue token and therefore should not have been visited by the child

eTable 2. Observed Raw Scores of 7-Year-Old FHR-SZ, FHR-BP and Control Offspring on Neurocognitive Measures

Test Variable	Total N	1. Controls (N=200) Mean (SD)	N	2. FHR-SZ (N=202) Mean (SD)	N	3. FHR-BP (N=120) Mean (SD)	N
SOC, Problems Solved in Minimum Moves	511	6.44 (1.64)	198	6.18 (1.65)	195	6.53 (1.88)	118
SRM, Percent Correct	511	71.64 (11.36)	198	67.21 (12.93)	195	70.34 (10.47)	118
SSP, Span Length	510	4.77 (1.05)	198	4.41 (1.24)	194	4.93 (1.25)	118
SWM, Total Errors	510	47.03 (15.35)	198	51.49 (15.84)	194	49.17 (17.15)	118
RVP, A'	496	0.91 (0.05)	193	0.89 (0.06)	187	0.90 (0.06)	116
Guess What, Total Correct	518	33.74 (4.10)	199	32.38 (5.97)	200	33.13 (4.27)	119
Coding, Total Correct	516	29.43 (7.32)	199	26.30 (7.76)	199	28.68 (7.14)	118
Symbol Search, Total Correct	508	17.38 (5.29)	194	15.34 (5.37)	196	17.48 (4.86)	118
Arithmetic, Total Correct	512	13.75 (2.86)	199	12.68 (3.40)	196	13.91 (3.31)	117
MFS Immediate Recall, Total Correct	512	20.04 (9.37)	198	19.38 (10.04)	196	20.70 (9.91)	118
MFS Delayed Recall, Total Correct	509	15.58 (8.35)	197	14.92 (9.15)	195	16.99 (9.24)	117
Verbal Fluency Phonemic, Total Correct	503	14.18 (6.04)	195	13.01 (6.53)	193	14.15 (6.26)	115
Verbal Fluency Semantic, Total Correct	502	26.21 (6.46)	195	24.35 (6.23)	192	25.37 (6.50)	115
Verbal Fluency Switching, Total Switching Correct	480	6,03 (2.56)	186	5.61 (2.61)	183	6.33 (2.24)	111
RCFT Immediate Recall, Total Correct	499	9.75 (5.76)	194	7.64 (5.05)	188	9.50 (5.69)	117
IED, Extra-Dimensional Stage Errors	511	19.27 (10.14)	198	17.85 (10.10)	195	18.65 (10.45)	118
Odd-Item Out, Total Correct	517	63.40 (8.94)	198	62.17 (9.30)	200	63.87 (8.59)	119
Letter-Number Sequencing, Total Correct	511	13.73 (3.62)	198	12.44 (4.06)	196	13.92 (3.81)	117
WSR Immediate Recall, Total Correct	506	39.08 (4.91)	198	38.62 (5.68)	191	39.47 (4.87)	117
WSR Delayed Recall, Total Correct	501	6.25 (1.61)	195	6.08 (1.97)	191	6.39 (1.53)	115
TMT Numbers, Seconds	515	58.9 (22.40)	196	67.83 (28.26)	201	62.65 (26.73)	118
TMT Letters, Seconds	515	74.88 (34.61)	196	85.89 (38.48)	201	77.47 (36.20)	118
TMT Switching, Seconds)	507	168.93 (53.58)	195	190.62 (51.49)	195	175.87 (51.26)	117

Abbreviations: SOC = Stockings of Cambridge; SRM = Spatial Recognition Memory; SSP = Spatial Span; SWM = Spatial Working Memory; RVP = Rapid Visual Information Processing; MFS = Memory for Stories; RCFT = Rey Complex Figure Test and Recognition Trial; IED = Intra-Extra Dimensional Set shift; WSR = Word Selective Reminding; TMT = Trail Making Test.

eFigure 1. Data Extraction and Recruitment Procedure of the VIA 7 Cohort

Data extracts from Danish National Registries[a] of children with FHR-SZ[b, c], FHR-BP[d] and 10 Controls[e] for each case, born between 01-09-04 to 31-08-09
(N = 24 706)

Children who were too old at start of study 01-01-2013, or too young by VIA 7 inclusion end date 31-01-16
(N = 5 376)

Children retrieved as matched controls to FHR-BP
(N = 7 373)

Children eligible for inclusion in VIA 7[f]
(N = 11 957)

| FHR-SZ **(N = 1 073)** | FHR-BP **(N = 774)** | Controls **(N = 10 110)[g]** |

No contact attemted **(N = 663)[h]**

No contact attempted **(N = 560)**

No contact attempted **(N = 9 791)**

Attempted contact **(N = 410)**

Attempted contact **(N = 214)**

Attempted contact **(N = 319)**

Non-respondents **(N = 92)**
Declined **(N = 116)**

Non-respondents **(N = 40)**
Declined **(N = 54)**

Non-respondents **(N = 40)**
Declined **(N = 79)**

FHR-SZ included in VIA 7
(N = 202)

FHR-BP included in VIA 7[i]
(N = 120)

Controls included in VIA 7[i, j]
(N = 200)

FHR-SZ included in the present study due to ≤8 missing neurocognitive test scores
(N=197)

FHR-BP included in the present study due to ≤8 missing neurocognitive test scores
(N=118)

Controls included in the present study due to ≤8 missing neurocognitive test scores
(N=199)

ᵃ Danish National Registries: Danish Civil Registration System and Danish Psychiatric Central Research Register.

ᵇ FHR-SZ: Children at familial high risk of schizophrenia spectrum disorders.

ᶜ Double diagnosed parents: Parents with diagnoses of schizophrenia and bipolar disorder were assigned to the schizophrenia high risk group as per the ICD-10 hierarchy.

ᵈ FHR-BP: Children at familial high risk of bipolar disorder.

ᵉ Controls: Population-based control children of parents with no diagnoses of schizophrenia spectrum disorders or bipolar disorder.

ᶠ Research protection: During part of the data collection period, approximately 20% of the families were registered as protected from being approached for research purposes (due to legislation enacted in May, 2011). Consequently, there were eligible children who were not contacted and enrolled in the VIA 7.

ᵍ Controls selection: A total of 10 controls were retrieved for each child in the FHR-SZ group and the FHR-BP group. Controls were matched to cases on sex, municipality and exact age. The original intent was to only select control cases that were matched to children at FHR-SZ. However, there are 38 FHR-BP-matched controls among the 200 total controls.

ʰ Definition of contact: Initially, by letters sent to the child´s address. If the family did not respond, contact by telephone was attempted (calls and text messages).

ⁱ Re-assigned control parent: One control parent had been diagnosed with bipolar disorder by a private psychiatrist. The diagnosis was not in the national registry extract, as private doctors do not report to the national registry. This family/parent was reassigned to the FHR-BP group. Therefore, the N=201 for controls is now N=200.

ʲ Control children not in the extract: Two younger siblings were included in the VIA 7 by request of the parents. They were not in the original extract.

Reference List

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

(2) Wechsler D. *Wechsler Intelligence Scale for Children - Fourth Edition (WISC-IV)*. San Antonio, TX: The Psychological Corporation, 2003.

(3) Delis DC, Kaplan E, Kramer JH. *Delis-Kaplan Executive Function System*. San Antonio, TX: Psychological Corporation, 2001.

(4) Sahakian BJ, Owen AM. Computerized assessment in neuropsychiatry using CANTAB: discussion paper. *J R Soc Med* 1992;85:399-402.

(5) Reynolds CR, Voress JK. *Test of Memory and Learning - Second Edition (TOMAL-2).* Austin, TX: Pro-Ed Inc., 2007.

(6) Meyers JE, Meyers KR. *Rey Complex Figure Test and Recognition Trial*. Odessa, FL: Psychological Assessment Resources, 1995.