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Early Childhood Neurocognition in Relation to Middle Childhood Psychotic Experiences in Children at Familial High Risk of Schizophrenia or Bipolar Disorder and Population-Based Controls: The Danish High Risk and Resilience Study

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***Background and Hypothesis*: Familial high-risk (FHR) studies examining longitudinal associations between neurocognition and psychotic experiences are currently lacking. We hypothesized neurocognitive impairments at age 7 to be associated with increased risk of psychotic experiences from age 7 to 11 in children at familial high risk of schizophrenia (FHR-SZ) or bipolar disorder (FHR-BP) and population-based controls (PBC), and further, impaired functioning in some neurocognitive functions to be associated with greater risk of psychotic experiences in children at FHR-SZ or FHR-BP relative to PBC. *Study Design*: Neurocognition was assessed at age 7 (early childhood) and psychotic experiences from age 7 to 11 (middle childhood) in 449 children from the Danish High Risk and Resilience Study. The neurocognitive assessment covered intelligence, processing speed, attention, visuospatial and verbal memory, working memory, and set-shifting. Psychotic experiences were assessed through face-to-face interviews with the primary caregiver and the child. *Study Results*: Set-shifting impairments at age 7 were associated with greater risk of psychotic experiences from age 7 to 11 in children at FHR-SZ. Children at FHR-BP and PBC showed no differential associations. Working memory and visuospatial memory impairments were related to increased risk of psychotic experiences across the cohort. However, adjusting for concurrent psychopathology attenuated these findings. *Conclusions*: Early childhood neurocognitive impairments are risk markers of middle childhood psychotic experiences, of which impaired set-shifting appears to further increase the risk of psychotic experiences in children at FHR-SZ. More research is needed to examine longitudinal associations between neurocognitive impairments and psychotic experiences in FHR samples.**

Key words: severe mental illness/preadolescence/psychosis/cognitive functions

Introduction

Psychotic disorders are rare in the general population, but psychotic experiences are relatively common phenomena.[1,2] However, prevalence rates of psychotic experiences are difficult to estimate, prone to potential bias, and vary considerably across studies due to methodological variances such as methods of measurement (eg, self-report vs interview).[2] Psychotic experiences are subclinical hallucinations and delusions which may occur without a diagnosable psychotic disorder. They are more prevalent during childhood and adolescence, and prevalence decreases with increasing age.[3] For most individuals these

experiences are transient.[4] Psychotic experiences are thought to lie on a continuum with clinical psychotic disorders at the lower end of the continuum,[4] and they are associated with an elevated risk of subsequent psychotic and nonpsychotic disorders.[5–9]As such, psychotic experiences can be regarded as transdiagnostic vulnerability markers of concurrent and later mental illness.[8–10]

The concept of a continuum between psychotic experiences and psychotic disorders is supported by the existence of shared underlying risk factors, including neurocognitive impairments. Widespread neurocognitive impairments are robust findings in schizophrenia and bipolar disorder, including impairments in processing speed, attention, memory, and executive function.[11–14] Schizophrenia is associated with more severe impairments[15,16] with convincing evidence that neurocognitive impairments precede illness onset.[17–19] Findings regarding premorbid neurocognitive functioning in bipolar disorder are more equivocal.[20,21] Nevertheless, neurocognitive impairments are found in adult and young first-degree relatives of individuals with schizophrenia or bipolar disorder.[22,23] Thus, neurocognitive impairments are considered risk markers or endophenotypes for both schizophrenia and bipolar disorder.[24,25]

Population-based cohort studies have shown that children and adolescents with psychotic experiences also display impairments in neurocognitive functions such as processing speed, working memory, and verbal intelligence,[26–28] although higher verbal intelligence also appears to be associated with psychotic experiences.[27] A few general population studies have investigated the longitudinal relationship between neurocognition and psychotic experiences. One study found impaired neurocognitive functioning (comprised of a composite of several verbal and nonverbal neurocognitive tests) in childhood and adolescence to be associated with a higher risk of psychotic experiences in adulthood.[29] Another community-based study showed that children with IQ declines from age 4 to 7 had an increased probability of developing psychotic experiences in early adulthood.[30] Additionally, impaired processing speed at age 8 and attention impairments at age 11 are associated with a greater risk of psychotic experiences at age 12.[31] Moreover, early childhood developmental impairments in language and communication abilities and problem-solving skills as early as ages 1–3 years seem to be associated with hallucinatory experiences at ages 10, 14, and 17 years.[32] However, to our knowledge, no prior study has investigated potential associations between different neurocognitive functions in early childhood and psychotic experiences in middle childhood in a sample of children at familial high risk of schizophrenia (FHR-SZ) or bipolar disorder. Studying neurocognitive functioning early in life and associations with subsequent psychotic experiences in familial high-risk (FHR) samples can provide important information on potential impairments that may put these children at higher risk of psychosis and other psychopathology later in life.

In the Danish High Risk and Resilience Study, we have previously found that children at FHR-SZ display widespread neurocognitive impairments at age 7 and age 11 compared with population-based controls (PBC).[33,34] In addition, we have also found that they have a higher prevalence of psychotic experiences at ages 7 and 11 relative to PBC.[35,36] In contrast, we have found that children at familial high risk of bipolar disorder (FHR-BP) only display few, discrete impairments in visual attention and interference control at age 7,[37,38] and they do not report significantly more psychotic experiences at ages 7 or 11 compared with PBC.[35,36] In the present study, we aimed to investigate potential differential longitudinal associations between neurocognitive functioning at age 7 and risk of psychotic experiences from age 7 to age 11 in children at FHR-SZ, FHR-BP, and PBC. We hypothesized that early childhood neurocognitive impairments at age 7 would be associated with an increased risk of middle childhood psychotic experiences from age 7 to age 11 in all 3 groups. We further expected that impaired functioning in some neurocognitive functions at age 7 would be associated with an elevated risk of psychotic experiences from age 7 to age 11 in children at FHR-SZ or FHR-BP relative to PBC.

Methods

Participants

The current study is part of the Danish High Risk and Resilience Study—VIA, which is a prospective cohort study of children with at least one biological parent with schizophrenia spectrum psychosis defined as schizophrenia, delusional disorder, and schizoaffective disorder (ICD-10 codes: F20, F22, and F25), bipolar disorder (ICD-10 codes: F30 and F31), or neither of the two. The VIA study assesses several domains including neurocognition, psychopathology, motor function, and the home environment. The original cohort consisted of 522 7-year-old children (FHR-SZ, n = 202; FHR-BP, n = 120, PBC, n = 200) identified through The Danish Civil Registration System[39] and The Danish Psychiatric Central Research Register.[40] Of these, 32 children were siblings (16 sibling pairs). The PBC group was matched with the FHR-SZ group on sex, age, and municipality. The FHR-BP group was unmatched but did not differ from the other groups on age and sex. Supplementary figure S1 provides a flowchart of the retrieval of the cohort.

Procedures

Data collection at age 7 took place from January 1, 2013 until January 31, 2016 (The VIA 7 study). Data for the follow-up study at age 11 were collected from March 1,

2017 to June 30, 2020 (The VIA 11 study). Trained and certified mental health professionals performed all assessments, and child assessors were blinded to FHR status. The vast majority of assessments was conducted at research sites in Copenhagen or Aarhus. A minority of assessments was conducted at the family's home if the surroundings allowed for it (ie, an undisturbed room and a suitable desk). Data were entered into a secure web-based database, REDcap.[41] The study was approved by The Danish Data Protection Agency and The Danish Committee on Health Research Ethics and in accordance with the principles outlined in the Declaration of Helsinki. Legal guardians provided written informed consent on behalf of the child before study participation. A description of the cohort, study design, and procedures is detailed elsewhere.[42,43]

Neurocognitive Assessment

The neurocognitive functions included in the current study were selected a priori based on associations with later onset of schizophrenia and/or bipolar disorder: verbal and nonverbal intelligence,[19,44–47] processing speed,[44,45] sustained attention,[46,48–50] verbal memory,[48,49,51,52] visuospatial memory,[49] working memory,[44,46,52] and set-shifting.[52,53] Verbal and nonverbal intelligence were assessed with the subtests Guess What and Odd Item Out from the Reynold's Intellectual Screening Test (RIST).[54] Processing speed was evaluated with Coding from Wechsler's Intelligence Scale for Children—Fourth Edition (WISC-IV),[55] and sustained attention with Rapid Visual Information Processing from the Cambridge Neuropsychological Test Automated Battery.[56] Verbal and visuospatial memory were assessed with Word Selective Reminding immediate recall from the Tests of Memory and Learning—Second Edition[57] and the immediate recall from the Rey Complex Figure Test and Recognition Trial,[58] respectively. Finally, working memory was evaluated with Letter-Number Sequencing from the WISC-IV, and set-shifting was evaluated with Verbal Fluency Switching from the Delis–Kaplan Executive Function System.[59] See supplementary table S1 for an overview of the neurocognitive test battery. Detailed information on neurocognitive performance at age 7 for the current cohort can be found elsewhere.[33]

Assessment of Psychotic Experiences

The psychosis supplement of the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version (K-SADS-PL)[60] was conducted at age 11 and used to assess psychotic experiences from age 7 to 11. The interview was conducted separately with the primary caregiver first, (ie, an adult living with the child and knowing the child the best) and then the child. We inquired about 5 types of hallucinations and 13 types of delusions (more details may be found elsewhere[36]). If a possible or definite psychotic symptom was indicated, additional questions concerning frequency, duration, degree of conviction, distress caused, and impact on functioning were asked. In clinical consensus meetings with a child and adolescent psychiatrist (A.A.E.T.), each symptom was then evaluated on a 7-point scale (range: 0–6) with scores above 2 defined as definite psychotic experiences.

In the current study, the outcome measure was dichotomized into definite or absent psychotic experiences. Results from the baseline and the 4-year follow-up study on psychotic experiences are detailed elsewhere.[35,36]

Global Functioning and Psychopathology

At both assessments, the child's current level of global functioning was assessed with the Children's Global Assessment Scale. Higher scores reflect better functioning.[61] Presence of any Axis I disorder from age 0–7 to age 7–11 was ascertained using K-SADS-PL. Findings regarding mental disorders within this cohort at baseline and 4-year follow-up are described in detail elsewhere.[62,63]

Data Analysis

Differences in demographic and clinical characteristics across the 3 groups were examined with 1-way analysis of variance and chi-square tests. Analyses of missing data were conducted by comparing neurocognitive performance at age 7 of children participating in the assessment of psychotic experiences from age 7 to 11 with that of nonparticipating children using independent *t* tests.

First, all neurocognitive measures were standardized based on the means and standard deviations (SDs) of the PBC group. PBC were used as a reference group owing to the considerably higher number of children in this group compared with Danish norm populations of the various neurocognitive tests included in the current study. Next, to assess whether the association between neurocognitive functioning and psychotic experiences was significantly different in the 3 groups, univariate logistic regression analyses were conducted separately for each of the 8 neurocognitive measures as the independent variable, any psychotic experiences (yes/no) as the dependent variable, and an interaction term between the neurocognitive measure and FHR group. In the event of a nonsignificant interaction, the interaction term was removed, and odds ratios (95% CI) for the overall association between a given neurocognitive measure and psychotic experiences was reported, regardless of FHR group. To control for any effect of sex and psychotic experiences before age 7, all analyses were adjusted for these. Analyses without the interaction term were also adjusted for FHR group. To account for the dependence of observation owing to the inclusion of siblings, cluster robust variance estimation was used. The Benjamini–Hochberg false discovery

rate procedure[64] was applied to correct for multiple comparisons with a cutoff for the false discovery rate set to 10%, yielding an adjusted significance level of $P \leq .030$. Further, we conducted a multivariate logistic regression analysis with all the neurocognitive measures included to assess if any of the neurocognitive measures were uniquely associated with psychotic experiences.

Given the associations between psychotic experiences and concurrent mental disorders observed within the current cohort,[36] analyses were performed that examined the potential effect of the presence of any Axis I disorder on the association between neurocognitive functioning and later psychotic experiences by conducting post hoc logistic regression analyses adjusting for Axis I disorder from age 7 to 11.

Moreover, as neurocognitive functions are correlated, we conducted exploratory logistic regression analyses with a global neurocognitive factor to assess potential associations between a nonspecific neurocognitive factor and psychotic experiences. A global neurocognitive factor was created by standardizing the 8 neurocognitive tests into *z*-scores based on the means and SDs from PBC, and then aggregating and restandardizing the *z*-scores into an overall global neurocognitive factor.

All analyses were conducted using Stata version 16.[65]

Results

Sample Characteristics

A total of 519 children (FHR-SZ, $n = 200$; FHR-BP, $n = 119$; PBC, $n = 200$) participated in some part of the neurocognitive assessment at age 7 with some variation across the 8 neurocognitive tests (range: 480–518). Data on psychotic experiences from age 7 to 11 were available for 450 children (FHR-SZ, $n = 172$; FHR-BP, $n = 103$; PBC, $n = 175$). In the current analyses, 449 children (FHR-SZ, $n = 171$; FHR-BP, $n = 103$; PBC, $n = 175$) were included as they participated in the assessment of neurocognition and psychotic experiences.

As shown in table 1, the 3 groups did not differ in sex or age at baseline or follow-up. At both assessments, children at FHR had lower global functioning and a higher prevalence of Axis I disorders. Pairwise comparisons of neurocognitive test performance revealed that children at FHR-SZ showed poorer performance on 4 of 8 measures compared with PBC. Children at FHR-BP and PBC did not differ significantly. Children at FHR-SZ performed worse than children at FHR-BP on 3 of 8 measures. Significantly more children at FHR-SZ reported psychotic experiences at age 7 and 11 compared with PBC, and at age 11, significantly more children at FHR-SZ reported psychotic experiences relative to children at FHR-BP. Children at FHR-BP and PBC did not differ.

Analyses of missing data showed that children at FHR-SZ, who participated in the assessment of psychotic experiences from age 7 to 11, performed significantly better on the 2 measures of intelligence, a measure of working memory, and a measure of set-shifting at age 7 compared with nonparticipating children at FHR-SZ. For children at FHR-BP and PBC, this pattern only applied to one measure of intelligence and a measure of working memory, respectively (supplementary table S2).

Neurocognitive Functioning at Age 7 and Psychotic Experiences From Age 7 to 11

The association between psychotic experiences from age 7 to 11 and performance at age 7 on a measure of set-shifting was significantly different for the 3 groups ($\chi^2(2) = 8.88$, $P = .012$). As depicted in figure 1A–H, relative to children at FHR-BP and PBC, children at FHR-SZ showed a considerably higher predicted probability of psychotic experiences with poor set-shifting performance. For an average *z*-score of 0 on this measure, children at FHR-SZ had a predicted probability of psychotic experiences of 0.28 (95% CI: 0.21–0.36), children at FHR-BP of 0.20 (95% CI: 0.13–0.28), and PBC of 0.17 (95% CI: 0.11–0.23). For the 7 remaining neurocognitive functions, all interactions between FHR group and neurocognitive function in their effect on risk of psychotic experiences did not reach statistical significance, indicating similar associations between neurocognitive performance at age 7 and risk of psychotic experiences from age 7 to 11 in the 3 groups (table 2).

Poor visuospatial memory performance and working memory performance at age 7 were associated with a modest, but significant, increased risk of psychotic experiences from age 7 to 11 regardless of FHR group (visuospatial memory OR = 0.75 [95% CI: 0.58–0.97], $P = .026$; working memory OR = 0.76 [95% CI: 0.61–0.94], $P = .012$). Although nonsignificant, all other neurocognitive functions showed a weaker, but similar relationship. Moreover, on 5 of 7 neurocognitive functions, children at FHR-SZ had an almost 2-fold increased risk of psychotic experiences compared with PBC with equal level of neurocognitive functioning (OR ranging from 1.67 to 1.92, $P \leq .026$). Children at FHR-BP did not differ significantly from PBC or children at FHR-SZ (table 3).

Assessing whether performance on any of the 8 neurocognitive functions was uniquely associated with risk of psychotic experiences, showed that no single neurocognitive measure at age 7 was independently associated with a greater risk of psychotic experiences from age 7 to 11 (table 4).

Examining the potential effect of psychopathology on the association between neurocognitive functioning and later psychotic experiences revealed that the magnitude of all associations was somewhat attenuated. However, the association between impaired working memory and greater risk of psychotic experiences remained statistically significant after adjusting for concurrent psychopathology, whereas the association between visuospatial

Table 1. Demographic and Clinical Characteristics of Children Participating in the Neurocognitive Assessment at Age 7 and the Assessment of Psychotic Experiences From Age 7 to 11 by FHR Group

					Pairwise Comparisons		
					FHR-SZ vs PBC	FHR-BP vs PBC	FHR-SZ vs FHR-BP
Variables	PBC	FHR-SZ	FHR-BP	*P* Value	*P* Value		
Children, *n*	175	171	103	—	—	—	—
Age at baseline, mean (SD)	7.81 (0.21)	7.85 (0.21)	7.87 (0.18)	.06	—	—	—
Age at follow-up, mean (SD)	11.93 (0.22)	11.96 (0.27)	11.94 (0.22)	.60	—	—	—
Female, *n* (%)	82 (46.86)	83 (48.54)	46 (44.66)	.82	—	—	—
CGAS at baseline, mean (SD)[a]	77.87 (13.61)	69.01 (15.60)	74.00 (14.36)	<.001*	<.001*	.03*	.009*
CGAS at follow-up, mean (SD)	75.17 (13.97)	64.82 (15.59)	68.46 (14.60)	<.001*	<.001*	<.001*	.06
Any Axis 1 disorder age 0–7, *n* (%)[b,o]	62 (35.43)	90 (52.63)	57 (55.34)	.001*	.001*	.001*	.66
Any Axis 1 disorder age 7–11, *n* (%)[c,o]	56 (32.00)	91 (53.22)	52 (50.49)	<.001*	<.001*	.002*	.66
Neurocognitive raw scores, age 7							
Verbal intelligence (Guess What)[d]	33.87 (4.16)	32.62 (4.94)	33.41 (4.15)	.09	—	—	—
Nonverbal intelligence (Odd Item Out)[e]	63.62 (8.94)	62.78 (9.25)	64.85 (7.60)	.17	—	—	—
Processing speed (Coding)[f]	29.55 (7.38)	26.68 (7.62)	28.77 (7.09)	.001*	<.001*	.39	.03*
Sustained attention (RVP)[g]	.906 (0.051)	.887 (0.065)	.902 (0.055)	.01*	.004*	.54	.06
Verbal memory (WSR immediate recall)[h]	39.20 (4.98)	38.71 (5.65)	39.25 (4.99)	.62	—	—	—
Visuospatial memory (RCFT immediate recall)[i]	9.80 (5.74)	7.63 (4.99)	9.40 (5.74)	<.001*	<.001*	.58	.009*
Working memory (Letter-Number Sequencing)[j]	13.92 (3.44)	12.76 (3.99)	14.13 (3.69)	.003*	.004*	.64	.005*
Set-shifting (Verbal Fluency Switching)[k]	6.01 (2.60)	5.79 (2.63)	6.31 (2.31)	.28	—	—	—
Any psychotic experience age 0–7, *n* (%)[l,m,o]	61 (35.06)	83 (48.82)	45 (43.69)	.03*	.01*	.15	.41
Any psychotic experience age 7–11, *n* (%)[n,o]	33 (18.86)	55 (32.16)	21 (20.39)	.009*	.004*	.76	.04*

Note: CGAS, Children's Global Assessment Scale; FHR-BP, familial high risk of bipolar disorder; FHR-SZ, familial high risk of schizophrenia; PBC, population-based controls; RCFT, Rey Complex Figure Test and Recognition Trial; RVP, Rapid Visual Information Processing; SD, standard deviation; WSR, Word Selective Reminding.
[a]Based on data from 174 PBCs, 170 children at FHR-SZ, and 103 children at FHR-BP.
[b]Findings are presented elsewhere.[62]
[c]Findings are presented elsewhere.[63]
[d]Based on data from 174 PBCs, 171 children at FHR-SZ, and 103 children at FHR-BP.
[e]Based on data from 173 PBCs, 171 children at FHR-SZ, and 103 children at FHR-BP.
[f]Based on data from 175 PBCs, 170 children at FHR-SZ, and 102 children at FHR-BP.
[g]Based on data from 169 PBCs, 160 children at FHR-SZ, and 101 children at FHR-BP.
[h]Based on data from 174 PBCs, 163 children at FHR-SZ, and 103 children at FHR-BP.
[i]Based on data from 171 PBCs, 161 children at FHR-SZ, and 102 children at FHR-BP.
[j]Based on data from 174 PBCs, 168 children at FHR-SZ, and 103 children at FHR-BP.
[k]Based on data from 164 PBCs, 160 children at FHR-SZ, and 99 children at FHR-BP.
[l]Based on data from 174 PBCs, 170 children at FHR-SZ, and 103 children at FHR-BP.
[m]Findings are presented elsewhere.[35]
[n]Findings are presented elsewhere.[36]
[o]Due to differences in included participants, minor divergencies exist between the previously published results and the results presented here.
*Indicates statistical significance ($P < .05$).

memory impairments and increased risk of psychotic experiences was rendered nonsignificant (supplementary table S3). In addition, the association between set-shifting performance and risk of psychotic experiences from age 7 to 11 remained significantly different for the 3 groups after adjusting for psychopathology from 7 to 11 years (supplementary table S4).

Exploratory analyses assessing associations between a nonspecific global neurocognitive factor and risk of psychotic experiences showed that the 3 groups did not differ significantly in their association between the global cognitive factor and risk of psychotic experiences ($\chi^2(2) = 1.48$, $P = .48$). Poor global cognitive performance was, however, associated with a significantly increased risk of subsequent psychotic experiences in the entire sample (OR = 0.75 [95% CI: 0.61–0.93], $P = .010$).

Discussion

This is, to the best of our knowledge, the first study to examine associations between early childhood neurocognitive functioning and risk of middle childhood psychotic experiences in children at FHR-SZ, FHR-BP, and PBC. Our results suggest that set-shifting stands out

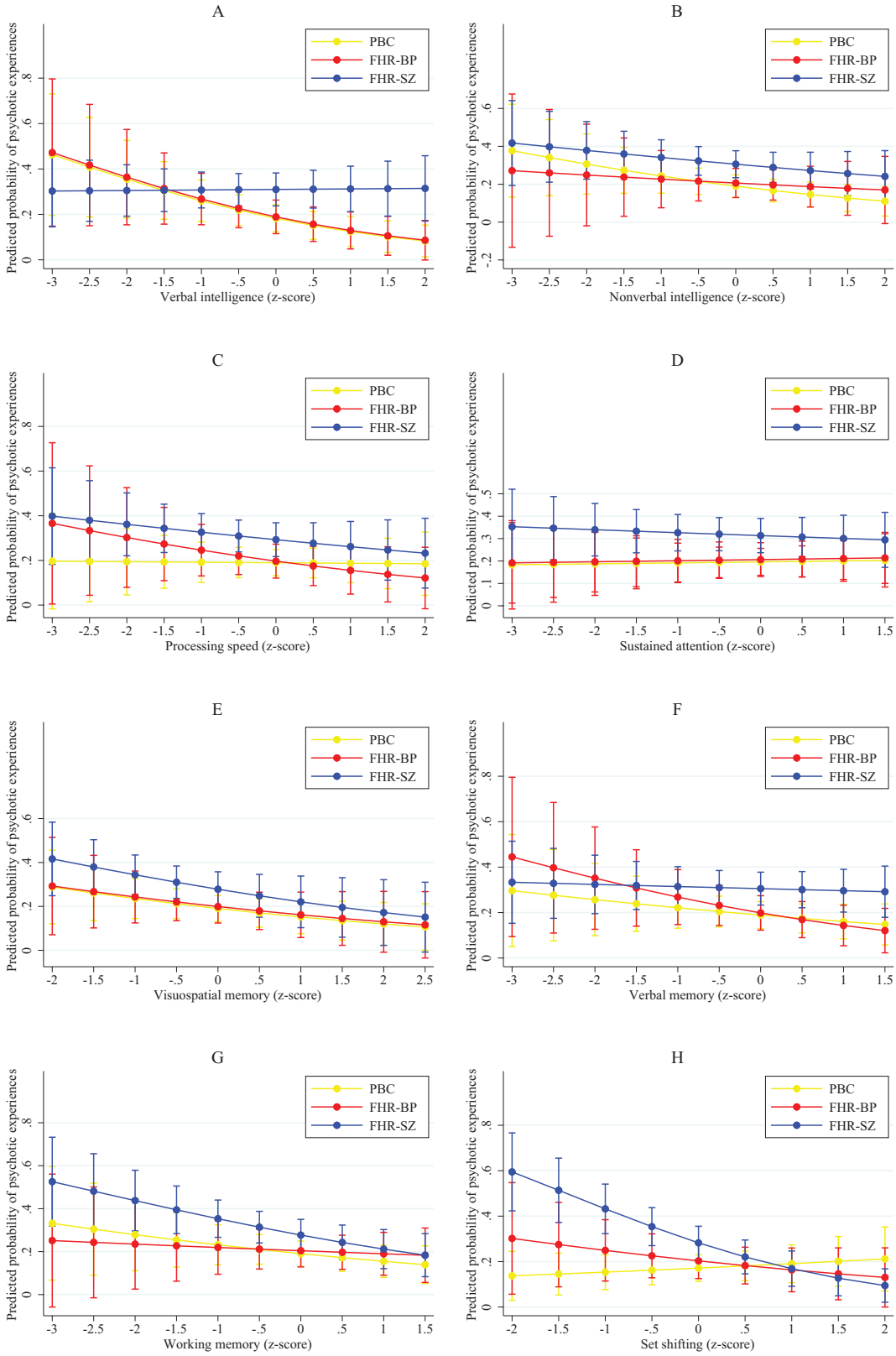

Fig. 1. (A–H) Associations between neurocognitive function and psychotic experiences by familial high-risk (FHR) group. *Note*: Predicted probability of psychotic experiences as a function of performance on individual neurocognitive tests stratified by FHR group.

as a neurocognitive function that is differently related to psychotic experiences in the 3 groups of children. Early childhood set-shifting impairments appear to pose a greater risk of subsequent psychotic experiences in children at FHR-SZ relative to children at FHR-BP and PBC. For all 3 groups, poorer working memory and visuospatial memory at age 7 were associated with a greater risk of later psychotic experiences. Finally, children at FHR-SZ had an almost 2-fold increased risk of psychotic experiences during middle childhood, despite similar neurocognitive performance in several domains as children at FHR-BP and PBC. This result was, however, markedly attenuated after adjusting for psychopathology.

Table 2. Neurocognitive Variable × Group Interactions in Relation to Risk of Psychotic Experiences

Neurocognitive Function	Variable	$\chi^2(2)$	*P* Value
Verbal intelligence	Guess What	5.76	.06
Nonverbal intelligence	Odd Item Out	0.55	.76
Processing speed	Coding	0.64	.73
Sustained attention	RVP A′	0.23	.89
Visuospatial memory	RCFT	0.03	.98
Verbal memory	Verbal Selective Reminding, IR	1.73	.42
Working memory	Letter-Number Sequencing	0.81	.67
Set-shifting	Verbal fluency switching	8.88	.012*

Note: A′, A prime; IR, immediate recall; RCFT, Rey Complex Figure Test and Recognition Trial; RVP, Rapid Visual Information Processing. Analyses were adjusted for sex and psychotic experiences from age 0 to 7 years. Cluster robust variance estimation was used to adjust for dependent observations between siblings.
*Indicates statistical significance after adjusting for multiple comparisons with Benjamini–Hochberg false discovery rate procedure (*P* values ≤ .030).

The finding that set-shifting is differently related to later psychotic experiences in children at FHR-SZ compared with children at FHR-BP and PBC may suggest that early set-shifting abilities are particularly important for children at FHR-SZ regarding risk of later psychotic experiences. Set-shifting or cognitive flexibility denotes the mental ability to appropriately and flexibly adjust one's thinking and behavior in accordance with changes in the environment.[66] Set-shifting impairments have been associated with impaired awareness of illness (poor insight) in psychotic disorders,[67] which in turn is related to clinically important factors such as prognosis and treatment compliance.[68,69] Research has identified impairments in set-shifting in children and young adults at FHR-SZ,[22,33,34] but the current study is the first to indicate poor set-shifting abilities during early childhood

Table 3. Associations Between Neurocognitive Functions at Age 7 and Psychotic Experiences From Age 7 to 11 Years in Children at FHR-SZ, FHR-BP, and PBC

		Overall		FHR-SZ vs PBC		FHR-BP vs PBC		FHR-SZ vs FHR-BP	
Neurocognitive Function	Variable	Odds Ratio (95% CI)	*P* Value	Odds Ratio (95% CI)	*P* Value	Odds Ratio (95% CI)	*P* Value	Odds Ratio (95% CI)	*P* Value
Verbal intelligence	Guess What	0.82 (0.67–1.00)	.047	1.83 (1.09–3.09)	.023*	1.06 (0.58–1.94)	.85	1.73 (0.97–3.09)	.07
Nonverbal intelligence	Odd Item Out	0.81 (0.65–1.01)	.06	1.87 (1.11–3.13)	.018*	1.11 (0.61–2.03)	.73	1.68 (0.94–2.99)	.08
Processing speed	Coding	0.87 (0.68–1.12)	.29	1.80 (1.07–3.03)	.026*	1.08 (0.59–1.98)	.80	1.67 (0.93–2.98)	.09
Sustained attention	RVP A′	0.98 (0.81–1.19)	.83	1.92 (1.14–3.23)	.014*	1.06 (0.58–1.95)	.84	1.81 (1.01–2.24)	.048
Visuospatial memory	RCFT	0.75 (0.58–0.97)	.026*	1.67 (0.99–2.84)	.06	1.05 (0.57–1.94)	.87	1.59 (0.88–2.87)	.13
Verbal memory	Verbal Selective Reminding, IR	0.85 (0.69–1.05)	.13	1.87 (1.11–3.15)	.019*	1.09 (0.59–1.99)	.79	1.72 (0.96–3.08)	.07
Working memory	Letter-Number Sequencing	0.76 (0.61–0.94)	.012*	1.70 (1.01–2.87)	.046	1.10 (0.60–2.03)	.76	1.55 (0.86–2.78)	.15
Set-shifting	Verbal fluency switching[a]	—	—	—	—	—	—	—	—

Note: A′, A prime; FHR-BP, familial high risk of bipolar disorder; FHR-SZ, familial high risk of schizophrenia; IR, immediate recall; PBC, population-based controls; RCFT, Rey Complex Figure Test and Recognition Trial; RVP, Rapid Visual Information Processing. Analyses were adjusted for sex, FHR status, and psychotic experiences from age 0 to 7 years. Cluster robust variance estimation was used to adjust for dependent observations among siblings.
[a]Due to a statistically significant interaction between this neurocognitive variable and FHR group in the effect on risk of psychotic experiences (see table 2), analyses without the interaction term were not conducted.
*Indicates statistical significance after adjusting for multiple comparisons with Benjamini–Hochberg false discovery rate procedure (*P* values ≤ .030).

Table 4. Associations Between Neurocognitive Functions Assessed at Age 7 and Psychotic Experiences Assessed From Age 7 to 11 Years Adjusted for Each Neurocognitive Function[a]

Neurocognitive Function	Variable	Odds Ratio (95% CI)	*P* Value
Verbal intelligence	Guess What	0.94 (0.73–1.21)	.61
Nonverbal intelligence	Odd Item Out	0.86 (0.66–1.16)	.36
Processing speed	Coding	1.00 (0.74–1.35)	.99
Sustained attention	RVP A′	1.22 (0.95–1.56)	.12
Visuospatial memory	RCFT	0.88 (0.67–1.17)	.38
Verbal memory	Verbal Selective Reminding, IR	0.95 (0.74–1.21)	.66
Working memory	Letter-Number Sequencing	0.87 (0.64–1.17)	.35
Set-shifting	Verbal fluency switching	0.75 (0.58–0.98)	.035

Note: A′, A prime; IR, immediate recall; RCFT, Rey Complex Figure Test and Recognition Trial; RVP, Rapid Visual Information Processing. Analyses were adjusted for sex, FHR status, and psychotic experiences from age 0 to 7 years. Cluster robust variance estimation was used to adjust for dependent observations between siblings.
[a]No findings were considered statistically significant after correcting for multiple comparisons with Benjamini–Hochberg false discovery rate procedure (*P* values ≤ .030).

as a risk factor for psychotic experiences in middle childhood in these children, even after adjusting for the presence of early childhood psychotic experiences. Whether the association between set-shifting and later psychotic experiences may be explained by a third factor independently associated with the 2 cannot, however, be ruled out.

The finding that poorer working memory in early childhood was associated with a greater risk of middle childhood psychotic experiences in the entire sample aligns with existing evidence emphasizing working memory as one of the core deficits associated with psychosis.[70–72] This adds to evidence of concurrent working memory impairments and greater risk of psychotic experiences during childhood and adolescence found in general population studies[26,28] by showing that impairments in this particular neurocognitive function predict a greater risk of later psychotic experiences. Thus, as suggested by others,[73,74] working memory impairments may represent an early marker of psychosis vulnerability irrespective of familial liability.

Like working memory impairments, visuospatial memory impairments at age 7 were associated with an increased risk of psychotic experiences from age 7 to 11in the entire cohort. Visuospatial memory impairments are observed in children at FHR-SZ,[33,34] and adolescents at FHR-BP.[75,76] A prior study has addressed potential associations between psychotic experiences and visuospatial learning and memory in a community-based sample of adolescents, and this study did not find a link.[26] In contrast, a FHR study of adolescents of individuals with schizophrenia, bipolar disorder, or major depressive disorder found that poorer visuospatial memory was associated with a greater risk of concurrent psychotic symptoms.[77] The inconsistencies in findings may be due to differences in samples such as FHR sample vs community-based sample but may also reflect the use of diverse neurocognitive measures. In our study as well as the study by Vallis et al., the Rey Complex Figure Test and Recognition Trial immediate recall was applied, and besides assessing visuospatial memory,[58] it has been argued that the copy trial of this test also measures executive functioning abilities owing to the complex nature of the figure.[78,79] Hence, the immediate recall of this test probably also relies on abilities related to visuospatial memory as well as aspects of executive function.

No association between psychotic experiences and a given neurocognitive function remained significant when adjusting for all other neurocognitive functions, indicating that no neurocognitive function assessed at age 7 was uniquely associated with psychotic experiences from age 7 to 11. This finding is most likely due to a high degree of shared variance between the neurocognitive functions. Moreover, for the associations between impaired visuospatial memory and working memory and greater risk of psychotic experiences, odds ratios were significant, yet relatively small, indicating that middle childhood psychotic experiences may be attributed to factors other than early neurocognitive impairments. Such factors may include environmental adversities,[80,81] sleep disturbances,[82,83] the jumping to conclusions reasoning bias[84] as well as mental disorders.[35,36,85] Indeed, adjusting for psychopathology in the current study, attenuated all associations somewhat, and rendered the association between poor visuospatial memory and elevated risk of psychotic experiences insignificant, suggesting that the presence of middle childhood psychotic experiences was better explained by concurrent psychopathology than early visuospatial memory impairments. Similarly, when adjusting for psychopathology, children at FHR-SZ no longer displayed a significantly increased risk of psychotic experiences compared with PBC with equal level of neurocognitive functioning. A large body of research has shown that psychotic experiences are associated with concurrent mental disorders in children and adolescents,[8,9,86,87] and it has previously been shown within the current cohort that by age 11 children at FHR-SZ have a 3-fold increased risk of having met criteria for any Axis 1 disorder,[63] which may very well explain why children at FHR-SZ did not show an increased risk of psychotic experiences compared with PBC when we adjusted for psychopathology.

Somewhat surprisingly, our results did not imply associations between impaired processing speed nor lower intelligence, and greater risk of psychotic experiences, which have previously been demonstrated in general population samples of children and adolescents.[26,27,30,31] Processing speed, in particular, has been described as a core dysfunction associated with psychosis,[88,89] and processing speed impairments are also displayed by children at FHR-SZ,[33,34] albeit with considerably smaller effect sizes than those observed in schizophrenia. Although speculatively, the finding that processing speed was not associated with psychotic experiences in the current study may, at least partly, be explained by the children's young age in the current study, as developmental lags (ie, slower neurocognitive growth, whereby impairments increase with age) in processing speed before psychosis onset have previously been described.[44,90] Nevertheless, this study supports the existing literature by showing that psychotic experiences and psychotic disorder share some of the same risk factors, thus supporting the notion of a psychosis continuum.[4]

Strengths and Limitations

Strengths include the longitudinal assessment of same-aged children using an extensive neurocognitive test battery. Psychotic experiences were assessed by trained mental health professionals with a gold standard interview including information from both child and primary caregiver. Moreover, the study design allowed for the adjustment of other potential predictors, including early childhood psychotic experiences.

Some limitations should also be noted. Analyses of missing data suggested that children, who participated in the assessment of psychotic experiences at age 11, outperformed nonparticipating children in some neurocognitive measures. Thus, this may have introduced a bias towards a less heterogeneous sample and weakened the strengths of the observed associations. Moreover, restrictions to psychotic experiences causing distress and impairment, or cases with multiple types of experiences could potentially have yielded further insights into neurocognitive impairments associated with the more severe cases. Moreover, despite limitations in terms of reliability, the RIST[54] was chosen as a measure of general intelligence owing to its ability to cover a wide age range (3–99 years), thereby allowing for the use of the same instrument throughout this prospective study.

Conclusions

Poor set-shifting in early childhood appears to place children at FHR-SZ at greater risk for developing psychotic experiences during middle childhood. Furthermore, working memory impairments may constitute early markers of vulnerability to psychotic experiences in both children with and without an increased familial risk of schizophrenia or bipolar disorder. Whether such associations during childhood have implications for conversion to psychosis in adolescence and adulthood requires further research.

Supplementary Material

Supplementary material is available at https://academic.oup.com/schizophreniabulletin/.

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