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Early cognitive development and psychopathology in children at familial high risk for schizophrenia

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ABSTRACT

Schizophrenia is a neurodevelopmental disorder associated with deficits in cognitive development and childhood psychopathology. Previous studies have focused on older children and the few studies of early childhood have yielded inconsistent findings. We studied cognitive development and psychopathology in children at familial high risk (FHR) of schizophrenia and matched controls from 1 to 6 years and hypothesized that FHR children would show consistent deficits across cognitive and behavioral measures in early childhood.

Study design: Cognitive development in children at high familial risk for schizophrenia or schizoaffective disorder ($n = 33$) and matched healthy controls ($n = 66$) was assessed at 1 and 2 years with the Mullen Scales of Early Learning, and at 4 and 6 years with the Stanford Binet Intelligence Scales, BRIEF-P/BRIEF and CANTAB. Psychopathology was assessed at 4 and 6 years with the BASC-2. General linear models were used to examine differences on outcome scores, and chi-square analyses were used to explore differences in the proportion of "at risk" or "below average" score profiles.

Study results: FHR children scored significantly lower than controls on Mullen Composite at age 2, and demonstrated broad deficits in IQ, executive function and working memory and 4 and 6 years. FHR children were also rated as significantly worse on most items of the BASC-2 at ages 4 and 6.

Conclusions: Children at FHR for schizophrenia demonstrate abnormal cognitive development and psychopathology at younger ages than previously detected, suggesting that early detection and intervention needs to be targeted to very early childhood.

1. Introduction

Schizophrenia has origins in early brain development, with research establishing a number of genetic and environmental risk factors that can disrupt typical patterns of development within the prenatal and perinatal windows of development (Birnbaum and Weinberger, 2017; Cannon et al., 2002a; Estes and McAllister, 2016). As such, children who ultimately develop schizophrenia, as well as those at higher risk for schizophrenia, are likely to display subtle behaviors or deficits consistent with the disorder years before the onset of psychosis (Owen et al., 2011; Rapoport et al., 2012). Children at high familial risk (FHR) of schizophrenia have atypical development of motor skills in the first year of life (Filatova et al., 2017; Sørensen et al., 2010; Hameed and Lewis, 2016). Cognitive development has been less well studied, though some earlier studies found inconsistent reductions in Bayley Scales of Infant Development in early childhood (Sameroff et al., 1987; Goodman, 1987) or in IQ at 7 years of age (Rieder et al., 1977). More recent studies found that FHR children had lower IQ scores between the ages of 3 and 7 years (Goldstein et al., 2000; Cannon et al., 2002b; Agnew-Blais et al., 2015; Hemager et al., 2018), as well as poorer attention, working memory, and executive function at 7 years (Hemager et al., 2018). Beyond these developmental abnormalities, the offspring of parents with schizophrenia have high rates of psychopathology (Donatelli et al., 2010; De La Serna et al., 2011; Ellersgaard et al., 2018; Spang et al., 2022) and psychiatric illness (Sandstrom et al., 2020; Sanchez-Gistau et al., 2015; Gregersen et al., 2022; Ross and Compagnon, 2001). This variety of deficit and symptom presentation is consistent with the conceptualization of schizophrenia as a heterogeneous disorder (Mohr et al., 2004; Picardi et al., 2012), with atypical patterns of behavior and development across a wide range of domains stemming from both genetic and environmental factors independently as well as interactions between the two (Cannon et al., 2002a; Estes and McAllister, 2016; Owen et al., 2011; Rapoport et al., 2012).

Additionally, there is evidence of brain structural abnormalities in

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infants at risk for schizophrenia (Shi et al., 2012; Ahn et al., 2019; Li et al., 2016; Gilmore et al., 2010a). Given that atypical development of brain structure can be detected as early as birth as well as the substantial evidence for early neurodevelopmental deficits associated with familial risk for or an eventual diagnosis of schizophrenia, a focus of research remains examining how soon we may be able to detect measurable differences in patterns of behavior. Earlier detection of atypical trajectories allows for the development of more effective intervention strategies designed to mitigate the onset of psychotic symptoms. The majority of this research, however, examines deficits or symptoms in middle childhood and adolescence, with very few studies looking at behaviors in FHR children younger than age 7. Whereas there seems to be some consensus regarding behavioral differences in high-risk children through middle childhood and adolescence, there has been less exploration of potential differences in early childhood.

The goal of the current study is to confirm and extend previous studies of cognitive development and psychopathology in FHR children between 1 and 6 years of age, a period of childhood that has not been well studied and is important for understanding how early in development abnormalities may arise and be detected. We utilized a range of well-validated task-based and parent-reported measures of multiple aspects of cognition and psychopathology. We hypothesized that the FHR children would show evidence of both cognitive abnormalities and psychopathology across early childhood.

2. Methods

2.1. Participants

Participants in this study are children and their parents enrolled in the Early Brain Development Study (EBDS) (Gilmore et al., 2010b; Knickmeyer et al., 2016; Knickmeyer et al., 2008). Women were enrolled during pregnancy and they and their children have been followed longitudinally since birth. Exclusion at enrollment included active substance abuse, serious medical illness, or significant fetal abnormality on prenatal ultrasound. A subsample of the EBDS includes

Table 1
Sample characteristics.

Variable	Full sample $N = 99$	FHR sample $n = 33$	Healthy control sample $n = 66$	Statistical test
	n (%)	*n* (%)	*n* (%)	χ^2 (*df*)
Child gender				–
Female	39 (39.4 %)	13 (39.4 %)	26 (39.4 %)	
Male	60 (60.6 %)	20 (60.6 %)	40 (60.6 %)	
Child gestation				–
Single-born	81 (81.8 %)	27 (81.8 %)	54 (81.8 %)	
Twin	18 (18.2 %)	6 (18.2 %)	12 (18.2 %)	
Maternal race				9.33 (1)**
White	60 (60.6 %)	13 (39.4 %)	47 (71.2 %)	
Black or African American	39 (39.4 %)	20 (60.6 %)	19 (28.8 %)	
Smoking status during pregnancy				30.56 (1)**
Smoker	81 (81.8 %)	16 (48.5 %)	2 (3.0 %)	
Non-smoker	18 (18.2 %)	17 (51.5 %)	64 (97.0 %)	

	M (*SD*)	Range	*M* (*SD*)	Range	*M* (*SD*)	Range	*t* (*df*)
Maternal education (years)[a]	14.6 (3.7)	3–28	11.0 (2.3)	3–15	16.3 (2.9)	9–28	−9.18 (95)**
Gestational age at birth (days)	265.1 (17.9)	221–290	260.8 (20.6)	221–289	267.3 (16.1)	225–290	−1.73 (97)
Birthweight (g)	3054.5 (678.1)	1230–4730	2888.7 (769.2)	1230–4730	3137.3 (617.4)	1550–4701	−1.74 (97)
Maternal age at birth (years)[b]	29.8 (6.1)	16–44	27.7 (6.7)	18–41	30.9 (5.5)	16–44	−2.56 (96)*

	$n = 82$		$n = 29$		$n = 53$		
Age at 1-year test (months)	12.8 (0.8)	11.5–16.1	12.9 (1.0)	11.6–16.1	12.7 (0.7)	11.5–14.5	1.31 (80)
Absolute time at 1-year test (months)	68.3 (29.6)	8.6–126.3	54.4 (27.5)	8.6–101.6	75.8 (28.2)	12.5–126.3	−3.32 (80)**

	$n = 85$		$n = 30$		$n = 55$		
Age at 2-year test (months)	24.9 (1.0)	23.3–28.5	25.2 (1.2)	23.4–28.5	24.7 (0.8)	23.3–26.3	1.96 (83)
Absolute time at 2-year test (months)	75.6 (30.6)	18.5–139.7	62.1 (29.2)	21.2–113.5	83.0 (28.9)	18.5–139.7	−3.16 (83)**

	$n = 84$		$n = 28$		$n = 56$		
Age at 4-year test (months)	49.4 (1.6)	47.6–56.7	50.2 (2.4)	48.0–56.7	49.1 (0.9)	47.6–51.5	3.15 (82)**
Absolute time at 4-year test (months)	102.2 (30.9)	48.8–162.7	85.8 (27.3)	51.3–134.2	110.4 (29.6)	48.8–162.7	−3.69 (82)**

	$n = 87$		$n = 29$		$n = 58$		
Age at 6-year test (months)	73.2 (1.5)	71.0–79.8	73.3 (1.6)	71.0–76.7	73.2 (1.5)	71.3–79.8	0.53 (85)
Absolute time at 6-year test (months)	125.3 (30.9)	68.2–187.8	111.6 (29.7)	68.2–161.6	132.2 (29.4)	68.7–187.8	−3.08 (85)**

* $p < 0.05$.
** $p < 0.01$.
[a] Two FHR participants do not have data regarding maternal education.
[b] One FHR participant does not have data regarding maternal age.

mothers with a history of a serious psychiatric disorder including schizophrenia and schizoaffective disorder. At enrollment, mothers were interviewed using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) (First, 1994), and a consensus diagnosis based on the SCID and available psychiatric records was assigned by two psychiatrists (JHG and LFJ). Based on initial enrollment, the parent study included 1134 mother-child dyads, including 133 children of mothers with a serious psychiatric disorder, 54 of which had mothers diagnosed with schizophrenia or schizoaffective disorder. For the current study, children of mothers with schizophrenia or schizoaffective disorder (the FHR sample) were matched 1:2 with children of healthy controls (see statistical analysis section for matching details). Participants were excluded from the healthy control pool of potential matches if either parent reported a history of psychiatric illness or if the mother reported drug or alcohol use during pregnancy. In both the FHR and control matched group, participants were included only if they had valid behavioral data at either or both of the 4- and 6-year study visits. The final FHR sample included 33 children, with 66 children in the healthy control group. Sample characteristics for the full sample as well as broken down by sub-sample (FHR and healthy control) can be found in Table 1.

2.2. Measures

All assessments took place in a laboratory setting, at the UNC Frank Porter Graham Child Development Institute, in Chapel Hill, NC. While children were completing the assessments, parents completed questionnaires. In the vast majority of cases, the mother was the parent filling out questionnaires, though occasionally the reporter was a father, grandparent, adoptive parent, or someone else.

2.2.1. Mullen Scales of Early Learning (MSEL) (Mullen, 1995)

The MSEL is a measure of general cognitive functioning that is used with children from birth through 5 years of age. In the current study, the measure was administered when children were 1 and 2 years old. The MSEL provides five separate Scales across the following domains: gross motor (GM), fine motor (FM), visual reception (VR), receptive language (RL), and expressive language (EL). Age-normed T-scores of all scales aside from GM combine to generate an Early Learning Composite (ELC). Although the ELC is the most commonly used outcome score from the MSEL, outcome scores have also been explored by separating into verbal and nonverbal components (DiStefano et al., 2016; Stephens et al., 2018; Short et al., 2013; Wetherby et al., 2004). Developmental quotients (DQs) are calculated by averaging the age equivalent (AE) scores of the components, dividing by chronological age, and multiplying by 100 (see equations below). The nonverbal developmental quotient (NVDQ) includes scales of VR and FM abilities, whereas the verbal developmental quotient (VDQ) includes EL and RL. The GM scale is not included in either DQ.

$$\text{NVDQ} = \frac{\text{average (of } VR_{ae} \text{ and } FM_{ae})}{\text{chronological age (months)}} * 100 \quad \text{VDQ} = \frac{\text{average (of } RL_{ae} \text{ and } EL_{ae})}{\text{chronological age (months)}} * 100$$

In the current study, we utilized the ELC, VDQ, and NVDQ scores.

2.2.2. Stanford-Binet Intelligence Scales — 5th edition (S-B) (Roid, 2003)

The S-B is a standardized set of assessments widely used to assess intelligence (IQ) across the lifespan, specifically focusing on five major domains. The current study utilizes the Abbreviated IQ (ABIQ) score, as well as Fluid Reasoning (FR) and Working Memory (WM) factor index scores. The S-B composite scores have strong inter-rater reliability (ranging from 0.74 to 0.97 with a median of 0.90 across all scales) and test-test reliability, with correlations in the .80s and .90s across scales. For all scales, a score of 89 or lower is considered "below average."

ABIQ is calculated from two subscales: Nonverbal Fluid Reasoning and Verbal Knowledge. The ABIQ score provides a quick yet reliable estimate of general cognitive ability. It is based on performance on two tests, one verbal ("vocabulary") and one nonverbal ("object series/matrices"), and these tests represent two major cognitive factors: fluid reasoning and crystallized ability.

FR is calculated from two subscales: Nonverbal Fluid Reasoning and Verbal Fluid Reasoning. The FR tests measure a child's ability to solve novel problems using different reasoning strategies. FR abilities are relevant for a variety of tasks across academic and daily life situations (Roid, 2003). The S-B includes tests of verbal ("early reasoning," "verbal absurdities," and "verbal analogies") and nonverbal ("object series/matrices") FR.

WM is calculated from two subscales: Nonverbal Working Memory and Verbal Working Memory. These tests measure a child's ability to inspect, sort, and/or transform diverse information held in short-term memory. The S-B includes tests of verbal ("memory for sentences" and "last word") and nonverbal ("block span") WM.

2.2.3. Cambridge Neuropsychological Test Automated Battery (CANTAB) (Cambridge Cognition, 2019)

CANTAB is a commonly used tool to measure cognitive function as it relates to underlying neurological networks. Three specific tasks from the CANTAB were administered when children were 6 years of age and were analyzed as outcome variables for this analysis: Rapid Visual Processing (RVP), Spatial Span (SSP), and Stockings of Cambridge (SOC).

Rapid Visual Processing is a measure of sustained attention, requiring children to watch single digits appearing on a screen for 4 min. They are instructed to watch for and identify specific sequences of digits, pressing a button when that sequence appears. The outcome measure used in this study, A' is a signal detection measure of sensitivity to the target sequence. Higher values indicate better task performance.

Spatial Span is a computerized version of the Corsi Block Tapping Test (Milner, 1971), a widely used measure of working memory. This task was selected for use by our research team over other CANTAB working memory tasks task because the simplicity of instructions makes it more appropriate for 6-year-old children. Spatial Span requires participants to remember visuospatial patterns of increasing length. Participants are given three tries at each span length, and when all three attempts are incorrect, the test ends. The outcome variable used in the current study was the highest span length successfully completed.

Stockings of Cambridge is a computerized version of the Tower of London (Shallice, 1982) and is primarily a measure of planning, as participants are presented with sets of problems that require two to five moves to complete. Additionally, completion requires the use of working memory, as success depends on participants' ability to not only plan out a sequence of moves but to also remember that sequence and apply it to the problem. The outcome variable from SOC used in this study was the number of problems solved in the minimum number of moves.

2.2.4. Behavior Rating Inventory of Executive Function — Preschool version (BRIEF-P) (Gioia et al., 2003) and Behavior Rating Inventory of Executive Function (BRIEF) (Gioia et al., 2000)

Parents of 4-year-old children completed the BRIEF-P, which is designed to measure executive function behaviors in children aged 2 to 5 years. The BRIEF-P includes 63 items based on a three-point scale (never, sometimes, often). Scores are summed to generate five subscales that are combined to create three indices and a global composite. Parents of 6-year-old children completed the BRIEF, which measures executive function behaviors in children aged 5 to 18 years. The BRIEF includes 86 items based on a three-point scale (never, sometimes, often). Scores are summed to generate eight subscales that are combined to create three indices and a global composite. For all subscales, indices, and composite, scores are converted to T-scores standardized by age and gender. A T score of 65 or higher is considered indicative of potential

clinical significance. BRIEF-P & BRIEF composites, indices, and subscales have been shown to have strong internal consistency, with alpha correlations in the .80s and .90s. Similarly, test-retest reliabilities are also high, with correlations in the .70s through the .90s. Analyses for the current study include the global executive composite (GEC) and the working memory (WM) subscale at each age, as well as the emergent metacognition index (EMI) from the BRIEF-P and the metacognitive index (MI) from the BRIEF.

The GEC raw score is computed by adding the raw scores of all of the individual subscales and is designed to represent a summary that is an accurate reflection of a child's overall executive dysfunction. The WM subscale includes 17 items in the BRIEF-P and 10 items in the BRIEF and is designed to measure a child's capacity to mentally hold information for the purpose of completing a particular task. The EMI from the BRIEF-P includes items from two subscales (WM — 17 items, and Plan/Organize — 10 items). The MI from the BRIEF includes items from five subscales (WM — 10 items, Initiate — 8 items, Plan/Organize — 12 items, Organization of Materials — 6 items, and Monitor — 8 items). These indices reflect a child's ability to solve problems, using working memory to guide behavior and to implement and monitor their plans in a range of contexts. Across all scales, higher scores represent more difficulties or problematic behaviors.

2.2.5. *Behavior Assessment System for Children (BASC-2) (Reynolds and Kamphaus, 2004)*

Behaviors related to clinical outcomes in early childhood were assessed using the BASC-2. Parents of 4-year-old children completed the preschool version of the BASC-2, which is designed for use with children aged 2 to 5 years. The BASC-2 preschool version includes 134 items based on a four-point scale (never, sometimes, often, almost always) and generates scores on 12 clinical scales and 7 content scales. Similarly, parents of 6-year-old children completed the child version of the BASC-2, which is designed for use with children aged 6 to 11 years. The BASC-2 child version includes 160 items based on the same four-point scale as the preschool version and generates scores on 14 clinical scales and 7 content scales. For each scale, item scores are summed and converted to T scores standardized by age and gender. T scores of 60 and greater represent clinical risk, with scores of 60–69 categorized as "at risk" and 70+ considered "clinically significant."

For the current study, we utilized the following clinical scales: anxiety, depression, somatization, atypicality, attention problems, hyperactivity, and withdrawal. We also included content scales of developmental social disorders and executive function. Lastly, we analyzed composite scores of internalizing problems (comprised of scores on anxiety, depression, and somatization), externalizing problems (scores on hyperactivity, aggression, and conduct problems; note that the conduct problems scale is only included in the child version), and the behavior symptom index, a score reflecting more global problems with behavior (includes scales of depression, atypicality, attention problems, hyperactivity, withdrawal, and aggression). Across all scales, higher scores reflect more problems or difficulties. BASC-2 scales have strong test-retest reliability (*r*'s in the .70s through .90s for composite scores and in the .70s and .80s for individual clinical and content scales) and internal consistency (α's in the .80s and 90s for composite scales and in the .70s and .80s for individual scales).

2.3. *Statistical analysis*

All analyses were performed using SAS Statistical Software, version 9.4. To compare FHR children with healthy controls, we employed a 2:1 matching (2 control children for every 1 high risk child). We matched 2:1 to increase statistical power. Potential matches were identified by data availability (control not missing data the FHR participant had), gestation number (accounting for zygosity when possible), child sex, maternal and paternal race and ethnicity (when possible), gestational age at birth, and birthweight. Final controls who best matched on these criteria were identified by two authors (RLS and EC). After matching, we examined demographic differences between groups (see Table 1), including a variable we call "absolute time." This is a value, in months, reflecting the amount of time elapsed since the start of the study, and this variable allows us to account for the effects of any factors that may have fluctuated during the course of the study, such as different testers over time. There were statistically significant group differences in maternal race, smoking status during pregnancy, education, and age at birth. FHR children were also significantly older at the age 4 assessment, and healthy controls were tested significantly later in the study (longer absolute time). General linear models examined group differences in least squared means (LS means) on study variables, with covariates of maternal race, child sex, gestational age at birth, age at assessment, and absolute time. The last set of models included the same covariates as well as maternal education. Maternal education is often utilized as a covariate that reflects family socioeconomic status. However, it can also be considered part of the schizophrenia phenotype and therefore likely has different types of effects on outcome variables. The group variable in all models underwent FDR correction for multiple comparisons (Benjamini and Hochberg, 1995) within age and assessment type groups.

In an exploratory analysis, we considered what proportion of each group (FHR vs. control) was considered "clinically significant" or below average, per cut-offs established by the respective measures. We then ran Chi-square analyses to determine whether there were group differences (FHR vs. control) in proportions of children who fell into the range of scores indicating some kind of deficit. Significance was determined through use of the Fisher's exact test. Lastly, we converted scores on cognitive measures (Mullen composite and S-B ABIQ) to sample z-scores to look at patterns over time. Linear mixed models were fit to examine group differences in z-scores at each age as well as changes in z-scores within each group between time points. The model included age, group, and the interaction (age x group), with an autoregressive covariance structure, AR(1). This allowed us to examine overall patterns between groups, specifically whether cognitive deficits in the FHR group remained stable over time.

3. Results

3.1. *Cognitive development 1 to 6 years*

Group differences in Mullen scores are presented in Table 2. FHR children had significantly lower composite, verbal, and non-verbal developmental quotients scores at age 2 as well as non-significant lower composite scores at age 1. Controlling for maternal education yielded a similar pattern of results at age 2, with a significant reduction in composite score at age 1 as well (Supplemental Table 1). Scores from the Stanford Binet, BRIEF(-P), and CANTAB are presented in Table 2. Broadly, FHR children demonstrated broad deficits in IQ, executive function and working memory and 4 and 6 years. FHR children scored significantly lower than controls on the abbreviated IQ and the working memory and fluid reasoning scales of the Stanford-Binet and at both 4 and 6 years. FHR children also scored significantly lower on the SSP, SOC and RVP items of the CANTAB at 6 years. Finally, FHR children were rated by parents as significantly higher (i.e., worse) at ages 4 and 6 on the global executive composite, the working memory subscale, and the (emergent) metacognition index of the BRIEF-P/BRIEF. FHR children also had a significantly larger portion of children in the risk range of the Stanford-Binet and the BRIEF (Table 4). When controlling for maternal education, the significance was lost for some measures, though the direction of the effect remained (Supplemental Table 1).

We explored whether the cognitive deficits observed in FHR children were stable, between 1 and 6 years. *Z*-scores for each participant using sample means and standard deviations on the Mullen composite and S-B ABIQ are plotted in Fig. 1. As evidenced in both the figure and Supplemental Table 3, there is a significant and consistent difference between scores in the FHR and healthy control participants across all ages.

Table 2
Scores and general linear models of group comparisons on cognitive outcomes.

	FHR		Control		GLM results	
	N	LSM (SE)	N	LSM (SE)	Est (SE)	*p*-Value
1-year Mullen scores						
Verbal developmental quotient	29	101.4 (2.4)	53	107.6 (1.9)	−6.18 (3.28)	0.063
Nonverbal developmental quotient	29	116.7 (2.5)	53	119.7 (1.9)	−3.02 (3.40)	0.376
Mullen composite	29	113.5 (2.3)	53	119.1 (1.8)	−5.58 (3.17)	0.082
2-year Mullen scores						
Verbal developmental quotient	29	98.0 (2.6)	54	111.2 (2.0)	−13.20 (3.52)	**<0.001**
Nonverbal developmental quotient	30	93.9 (1.9)	55	103.9 (1.4)	−10.03 (2.50)	**<0.001**
Mullen composite	29	97.5 (2.4)	54	112.7 (1.9)	−15.18 (3.30)	**<0.001**
4-year cognitive scores						
Stanford-Binet						
Abbreviated IQ	21	99.7 (2.8)	55	109.9 (1.8)	−10.21 (3.48)	**0.005**
Fluid reasoning	20	104.4 (3.7)	56	114.5 (2.2)	−10.11 (4.42)	**0.025**
Working memory	18	97.6 (3.1)	48	115.9 (1.8)	−18.24 (3.77)	**<0.001**
BRIEF-P						
Working memory	26	65.6 (2.3)	56	51.3 (1.5)	14.23 (2.94)	**<0.001**
Emergent metacognition index	26	63.5 (2.3)	56	50.2 (1.6)	13.29 (2.99)	**<0.001**
Global executive composite	26	60.5 (2.4)	56	48.7 (1.6)	11.81 (3.07)	**<0.001**
6-year cognitive scores						
Stanford-Binet						
Abbreviated IQ	29	99.9 (2.5)	58	109.2 (1.8)	−9.32 (3.29)	**0.006**
Fluid reasoning	28	105.2 (2.6)	58	115.5 (1.8)	−10.24 (3.38)	**0.003**
Working memory	12	102.9 (3.9)	43	114.5 (2.0)	−11.59 (4.51)	**0.013**
BRIEF						
Working memory	27	60.6 (2.5)	58	50.8 (1.7)	9.79 (3.15)	**0.003**
Metacognition index	26	58.3 (2.0)	57	48.7 (1.3)	9.64 (2.54)	**<0.001**
Global executive composite	26	59.2 (2.0)	57	48.8 (1.4)	10.32 (2.57)	**<0.001**
CANTAB						
RVP A′	27	0.9 (0.0)	58	0.9 (0.0)	−0.04 (0.01)	**0.001**
SOC	25	4.4 (0.4)	56	5.6 (0.3)	−1.15 (0.48)	**0.020**
SSP	28	3.1 (0.2)	57	3.8 (0.1)	−0.70 (0.24)	**0.004**

Note. LSM = LS Means. *p*-Values in **bold** reflect statistical significance after FDR correction for multiple comparison. General linear models include the following covariates: maternal race, child sex, gestational age at birth, age at assessment, and absolute time.

Z-scores were relatively stable from 1 to 6 years, with no significant changes except a small but significant change from 1 to 2 years in the FHR group (Supplemental Table 4).

3.2. Psychopathology at 4 and 6 years

FHR children exhibited broad psychopathology compared to controls, having significantly higher (i.e., worse) scores on most items of the BASC-2 at ages 4 and 6, including anxiety, atypicality, attention problems, hyperactivity executive functioning and externalizing symptoms (Table 3). At 6 years, FHR children also exhibited higher scores for depression and externalizing problems. Most findings remained significant when controlling for maternal education (Supplemental Table 2). Finally, a significantly larger portion of the FHR children had "clinically significant" scores on most BASC-2 items at both 4 and 6 years (Table 4).

4. Discussion

We found that children at familial risk of schizophrenia had altered cognitive development compared to healthy control children as early as 2 years of age, with significantly lower 2-year Mullen composite scores, as well as lower IQ and executive function scores at 4 and 6 years. In addition, FHR children showed evidence of broad psychopathology at 4 and 6 years. These findings confirm and extend previous studies of cognitive deficits and psychopathology related to risk for schizophrenia, indicating that these abnormalities arise very early in childhood, at younger ages than had been previously examined.

Previous studies of FHR children found delays in motor development in the first year of life (Filatova et al., 2017; Sørensen et al., 2010; Hameed and Lewis, 2016). Decreased IQ has been observed as early as age 3 (Cannon et al., 2002b) and 4 years (Agnew-Blais et al., 2015), while specific abnormalities of attention, working memory and executive function have been documented as early as 7 years (Hemager et al., 2018). We found significantly lower Mullen scores (composite, VDQ, and NVDQ), in 2-year-olds and abnormalities of attention, working memory and executive function in 4-year-olds, indicating that abnormalities in these aspects of cognitive function are evident earlier in childhood than previously documented.

There is inconsistent evidence about the progression of cognitive deficits during childhood. In FHR children, Mollon et al. (2018) found progression between 18 months and 20 years, though this large age range makes it difficult to understand progression in early childhood. In contrast, other studies found no progression of deficits between the ages of 6 and 15 years (Ross et al., 2008) or between 7 and 11 years (Knudsen et al., 2022). In children who went on to develop schizophrenia (not FHR), Cannon et al. (2000) found that cognitive deficits scores were stable between 4 and 7 years. Our study is consistent with those studies finding developmentally stable cognitive deficits in childhood and indicates that these deficits are detectable by 2 years of age.

We found that FHR children exhibited psychopathology across multiple domains consistent with studies that find high rates of psychopathology (Donatelli et al., 2010; De La Serna et al., 2011; Ellersgaard et al., 2018; Spang et al., 2022) and psychiatric illness (Sandstrom et al., 2020; Sanchez-Gistau et al., 2015; Gregersen et al., 2022; Ross and Compagnon, 2001) in the offspring of parents with schizophrenia. This broad psychopathology is also consistent with the high comorbidity of schizophrenia with other psychiatric disorders (Kessler et al., 2005; Plana-Ripoll et al., 2019; Williams et al., 2023), the transdiagnostic nature of psychopathology domains in psychiatric disorders, including a common psychopathology or P factor (Grotzinger et al., 2022; Caspi et al., 2014; Caspi and Moffitt, 2018), and the pleiotropy of genetic risk across psychiatric disorders (Grotzinger et al., 2022; Lee et al., 2019; Owen et al., 2023). Childhood psychopathology is common in FHR children, with broad increases in psychopathology detected as early as 7 years (Ellersgaard et al., 2018; Spang et al., 2022). Donatelli et al. (2010) found increased internalizing and externalizing symptoms at age

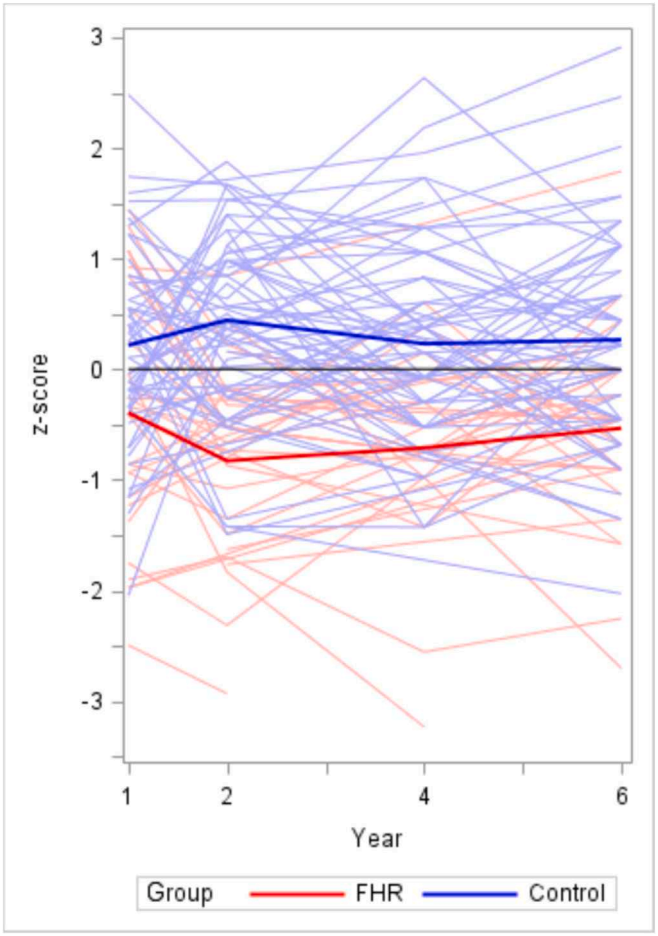

Fig. 1. z-Scores for FHR and healthy control participants on cognitive measures (Mullen Composite and S-B ABIQ) over time. FHR = familial high risk participants; each line represents individual participants, with healthy control in blue and FHR in red. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

7, but not at age 4. Our study found broad psychopathology as early as 4 years, indicating that problem behaviors are evident earlier than previously reported.

An important consideration when designing analyses involving risk for schizophrenia is how to account for differences in maternal education (Resnick, 1992). In many areas of research, maternal education is utilized as a proxy for socioeconomic status (SES). However, there is consistent evidence for stark differences in educational attainment for those individuals diagnosed with schizophrenia (Dickson et al., 2020), so controlling for maternal education likely controls for risk status as well. The polygenic risk score for schizophrenia is associated with intelligence in the general population, but not consistently in patients with schizophrenia, indicating that cognitive deficits in schizophrenia are due mainly to genes important for intelligence and not for the disorder itself (Mallet et al., 2020; Legge et al., 2021; Richards et al., 2020). Schizophrenia PGRS has been associated with premorbid intelligence in adults with schizophrenia and in healthy controls (Legge et al., 2021; Ohi et al., 2021) and in 7–9-year-olds in the general population (Riglin et al., 2017). Interestingly, GWAS studies have found overlap and genetic dependence between schizophrenia and educational attainment loci (Bansal et al., 2018; Le et al., 2017). Education therefore may not be cleanly representative of a largely environmental factor such as SES and may also be considered part of the schizophrenia genotype and phenotype. Given that it would be nearly impossible to untangle the effects of both SES and schizophrenia on maternal education, we elected to run

Table 3
Scores and general linear models of group comparisons on BASC-2 outcomes.

	FHR, n = 26	Control, n = 56	GLM results	
	LSM (SE)	LSM (SE)	Est (SE)	p-Value
4-year BASC-2 scores				
Anxiety	53.9 (2.4)	47.1 (1.6)	6.83 (3.11)	**0.031**
Depression	50.7 (2.4)	47.9 (1.6)	2.85 (3.06)	0.355
Somatization	51.2 (2.5)	46.5 (1.7)	4.66 (3.24)	0.155
Atypicality	60.4 (2.1)	49.5 (1.4)	10.95 (2.74)	**<0.001**
Attention problems	54.9 (1.9)	49.6 (1.2)	5.35 (2.40)	**0.029**
Hyperactivity	58.4 (2.1)	48.8 (1.4)	9.55 (2.73)	**<0.001**
Withdrawal	51.1 (2.3)	46.4 (1.5)	4.73 (2.96)	0.114
Developmental social disorders	56.8 (2.0)	46.6 (1.4)	10.23 (2.64)	**<0.001**
Executive functioning	55.9 (2.3)	48.5 (1.5)	7.39 (2.97)	**0.015**
Externalizing problems	55.0 (2.1)	48.1 (1.4)	6.94 (2.71)	**0.012**
Internalizing problems	52.6 (2.6)	46.2 (1.7)	6.36 (3.35)	0.062
Behavioral symptoms index	55.9 (2.1)	47.8 (1.4)	8.17 (2.70)	**0.003**

	FHR, n = 27	Control, n = 58	GLM results	
	LSM (SE)	LSM (SE)	Est (SE)	p-Value
6-year BASC-2 scores				
Anxiety	52.2 (2.1)	46.1 (1.4)	6.16 (2.70)	**0.025**
Depression	53.3 (1.6)	45.7 (1.1)	7.60 (2.09)	**<0.001**
Somatization	48.7 (2.1)	45.6 (1.4)	3.12 (2.74)	0.257
Atypicality	56.0 (2.0)	47.7 (1.3)	8.36 (2.53)	**0.001**
Attention problems	57.3 (1.9)	47.3 (1.3)	9.99 (2.44)	**<0.001**
Hyperactivity	57.1 (2.0)	49.0 (1.4)	8.15 (2.62)	**0.003**
Withdrawal	52.6 (2.3)	47.4 (1.6)	5.18 (3.00)	0.088
Developmental social disorders	55.4 (1.9)	45.4 (1.3)	9.93 (2.42)	**<0.001**
Executive functioning	55.9 (1.9)	46.6 (1.3)	9.28 (2.48)	**<0.001**
Externalizing problems	55.9 (1.8)	47.9 (1.2)	8.05 (2.33)	**<0.001**
Internalizing problems	51.8 (1.8)	44.7 (1.3)	7.06 (2.37)	**0.004**
Behavioral symptoms index	56.2 (1.8)	46.4 (1.2)	9.77 (2.34)	**<0.001**

Note. LSM = LS Means. p-Values in **bold** reflect statistical significance after FDR correction for multiple comparison. General linear models include the following covariates: maternal race, child sex, gestational age at birth, age at assessment, and absolute time.

models both with and without this variable as a covariate. Controlling for maternal education resulted in generally modest changes in the significance of our findings, suggesting that our findings are related to familial risk status.

Across outcomes, results of models that included performance-based measures as outcome variables (i.e., S-B and CANTAB) were more likely than outcomes from parent-report measures to show different patterns when including maternal education as a covariate. Given that these are both measures of cognitive abilities, the impact of including maternal education as a covariate in the model is consistent with prior research examining associations between maternal education and cognitive performance in children (Hackman et al., 2015; Rahu et al., 2010; Montroy et al., 2019). Group differences in scores from the parent-report measures (BRIEF(-P) and BASC-2) were less likely to change when adding maternal education as a covariate. This difference could be related to the multidimensional nature of a variable such as maternal education and could reflect how mothers with varying levels of education interpret items and subsequently rate their children. Further analysis utilizing alternative measures of SES, for example, could begin to examine the specific role that maternal education plays in early development of children at high familial risk for schizophrenia.

The study sample also had significant group differences in maternal race, with a higher proportion of Black or African American mothers of FHR children compared to healthy controls. Although some research

Table 4
Chi-square models examining group differences in proportions of children scoring in the "at risk" ranges on outcome variables.

	FHR sample		Control sample		Fisher's exact test	FHR sample		Control sample		Fisher's exact test
	N	*n* (%)[a]	*N*	*n* (%)[a]	*p*-Value	*N*	*n* (%)[a]	*N*	*n* (%)[a]	*p*-Value
	1-year-olds					2-year-olds				
Mullen										
Verbal developmental quotient	29	4 (4.88 %)	53	3 (3.66 %)	0.237	29	3 (3.61 %)	54	0 (0.00 %)	**0.040**
Nonverbal developmental quotient	29	0 (0.00 %)	53	0 (0.00 %)	n/a	30	5 (5.88 %)	55	2 (2.35 %)	0.091
Mullen composite	29	1 (1.22 %)	53	0 (0.00 %)	0.354	29	6 (7.23 %)	54	0 (0.00 %)	**0.001**
	4-year-olds					6-year-olds				
Stanford-Binet										
Abbreviated IQ	21	3 (14.3 %)	55	2 (3.6 %)	0.126	29	5 (17.2 %)	58	3 (5.2 %)	0.111
Fluid reasoning	20	5 (25.0 %)	56	3 (5.4 %)	**0.026**	28	3 (10.7 %)	58	1 (1.7 %)	0.099
Working memory	18	4 (22.2 %)	48	1 (2.1 %)	**0.017**	12	1 (8.3 %)	43	1 (2.3 %)	0.392
BRIEF-P/BRIEF										
Working memory	26	14 (53.9 %)	56	8 (14.3 %)	**<0.001**	27	8 (29.6 %)	58	8 (13.8 %)	0.134
(Emergent) metacognition index	26	16 (61.5 %)	56	5 (8.9 %)	**<0.001**	26	6 (23.1 %)	57	4 (7.0 %)	0.064
Global executive composite	26	9 (34.6 %)	56	5 (8.9 %)	**0.009**	26	8 (30.8 %)	57	5 (8.8 %)	**0.020**
BASC-2										
Anxiety	26	6 (23.1 %)	56	7 (12.5 %)	0.329	27	5 (18.5 %)	58	8 (13.8 %)	0.747
Depression	26	6 (23.1 %)	56	2 (3.6 %)	**0.011**	27	7 (25.9 %)	58	2 (3.5 %)	**0.004**
Somatization	26	7 (26.9 %)	56	9 (16.1 %)	0.369	27	5 (18.5 %)	58	5 (8.6 %)	0.277
Atypicality	26	16 (61.5 %)	56	7 (12.5 %)	**<0.001**	27	9 (33.3 %)	58	3 (5.2 %)	**0.001**
Attention problems	26	10 (38.5 %)	56	4 (7.1 %)	**0.001**	27	16 (59.3 %)	58	5 (8.6 %)	**<0.001**
Hyperactivity	26	13 (50.0 %)	56	5 (8.9 %)	**<0.001**	27	12 (44.4 %)	58	7 (12.1 %)	**0.002**
Withdrawal	26	5 (19.2 %)	56	5 (8.9 %)	0.275	27	3 (11.1 %)	58	7 (12.1 %)	0.999
Developmental social disorders	26	12 (46.2 %)	56	4 (7.1 %)	**<0.001**	27	8 (29.6 %)	58	4 (6.9 %)	**0.015**
Executive functioning	26	11 (42.3 %)	56	4 (7.1 %)	**<0.001**	27	9 (33.3 %)	58	5 (8.6 %)	**0.009**
Externalizing problems	26	10 (38.5 %)	56	3 (5.4 %)	**<0.001**	27	9 (33.3 %)	58	4 (6.9 %)	**0.003**
Internalizing problems	26	8 (30.8 %)	56	5 (8.9 %)	**0.021**	27	5 (18.5 %)	58	3 (5.2 %)	0.103
Behavioral symptoms index	26	13 (50.0 %)	56	2 (3.6 %)	**<0.001**	27	12 (44.4 %)	58	3 (5.2 %)	**<0.001**

Note. *p*-Values in **bold** represent those that remain significant after FDR correction for multiple comparisons.
[a] For Mullen scores, this is the number of children <85 is "below average" or Stanford-Binet scores, this is the number of children scoring "below average" (below a score of 89). For the BRIEF-P/BRIEF, this is the number of children with a score of 65 or higher, which indicates "potential clinical significance." For BASC-2 scores, this is the number of children with a score of 60 or higher, which indicates "at risk.

suggests racial differences in diagnostic patterns across races, this is not thought to reflect actual epidemiological differences and may be more indicative of systemic biases and widespread lack of appreciation of cultural differences in symptom expression (Schwartz et al., 2019; Schwartz and Blankenship, 2014; Olbert et al., 2018). In our sample specifically, these group differences can also be attributed to our matching protocols, in which we prioritized data availability. Had we emphasized matching based on race, it is likely that differences may not have been as striking.

The primary limitation of the current study is the sample size, with only 33 FHR children and 66 matched controls. Given the strength of study findings across multiple measures, types of analyses, and ages, we believe that findings would likely generalize to the larger population. Future studies with larger, more representative samples are needed. Additionally, this study does not include a consideration of mothers' mental health status at the time of study visits, paternal or sibling mental health, or any measure of environmental stimulation or support, information which could potentially enhance interpretability and generalizability of study results. Lastly, the FHR group had a high rate of smoking during pregnancy, compared to the healthy control group. Although we did not find evidence for differences in cognitive or psychopathological outcomes based on smoking status in the FHR group, further exploration is warranted to confirm how this may interact with FHR status to impact development.

In summary, children at high familial risk for schizophrenia demonstrate cognitive deficits and psychopathology in early childhood. These findings indicate that research on the early detection of behaviors associated with FHR status and a potential later diagnosis of schizophrenia may need to be focused on the first few years of life. These have the potential to guide intervention studies with a goal of improving long-term outcomes for those individuals eventually diagnosed with schizophrenia by targeting factors such as environmental support and stimulation, parenting behaviors, and stress and trauma prevention. Given that results of this study are consistent with existing research supporting differences in brain structure that can be detected as early as birth (Shi et al., 2012; Ahn et al., 2019; Li et al., 2016; Gilmore et al., 2010a), a logical next step is to examine brain-behavior relationships in high-risk samples along with a consideration of environmental or sociodemographic factors that may moderate the relationship between brain structure and behavior. Finally, we are following this cohort into adolescence to study not only trajectories of behavior but to also to track which children ultimately develop psychotic symptoms.

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CRediT authorship contribution statement

Rebecca L. Stephens: Writing – review & editing, Writing – original draft, Project administration. **Isabel Leavitt:** Writing – review & editing, Writing – original draft, Investigation. **Emil Cornea:** Writing – review & editing, Formal analysis, Data curation. **L. Fredrik Jarskog:** Writing – review & editing, Investigation. **John H. Gilmore:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

All authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2024.07.034.

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Supplemental Table 1. Scores and general linear models of group comparisons on cognitive outcomes, controlling for maternal education

	FHR		Control		GLM results	
	n	LSM (SE)	*n*	LSM (SE)	Est (SE)	*p*-value
1-year Mullen scores						
Verbal Developmental Quotient	27	99.6 (3.1)	53	108.8 (2.0)	-9.20 (4.21)	**0.032**
Nonverbal Developmental Quotient	27	113.5 (3.2)	53	121.2 (2.1)	-7.67 (4.33)	0.080
Mullen Composite	27	109.6 (2.9)	53	121.1 (1.9)	-11.51 (3.98)	**0.005**
2-year Mullen scores						
Verbal Developmental Quotient	28	100.8 (3.3)	54	109.6 (2.2)	-8.79 (4.65)	0.062
Nonverbal Developmental Quotient	29	95.0 (3.4)	55	103.1 (1.5)	-8.12 (3.27)	**0.015**
Mullen Composite	28	99.6 (3.1)	54	111.3 (2.0)	-11.78 (4.28)	**0.007**
4-year cognitive scores						
Stanford-Binet						
Abbreviated IQ	21	101.5 (3.5)	55	109.4 (1.9)	-7.87 (4.41)	0.079
Fluid Reasoning	20	108.4 (4.4)	56	113.3 (2.3)	-4.84 (5.46)	0.379
Working Memory	18	99.1 (3.9)	48	115.3 (2.0)	-16.23 (4.95)	**0.002**
BRIEF-P						
Working Memory	26	64.6 (2.8)	56	51.7 (1.7)	12.85 (3.69)	**<.001**
Emerging Metacognition Index	26	63.0 (2.9)	56	50.4 (1.7)	12.55 (3.76)	**0.001**
Global Executive Composite	26	60.6 (2.9)	56	48.6 (1.8)	11.98 (3.87)	**0.003**
6-year cognitive scores						
Stanford-Binet						
Abbreviated IQ	27	100.7 (3.3)	58	108.3 (2.0)	-7.68 (4.49)	0.091
Fluid Reasoning	26	104.6 (3.5)	58	115.4 (2.1)	-10.81 (4.69)	0.024
Working Memory	11	106.6 (5.6)	43	113.6 (2.2)	-7.01 (6.68)	0.299
BRIEF						
Working Memory	26	60.5 (3.2)	58	50.9 (1.9)	9.54 (4.25)	**0.028**
Metacognition Index	25	59.2 (2.6)	57	48.3 (1.5)	10.90 (3.41)	**0.002**
Global Executive Composite	25	60.4 (2.6)	57	48.4 (1.5)	12.02 (3.44)	**<.001**
CANTAB						
RVP A’	25	0.9 (0.0)	58	0.9 (0.0)	-0.03 (0.02)	0.119
SOC	23	4.7 (0.5)	56	5.5 (0.3)	-0.88 (0.69)	0.207
SSP	26	3.2 (0.3)	57	3.8 (0.1)	-0.68 (0.34)	0.049

Note. LSM = LS Means. *P*-values in **bold** reflect statistical significance after FDR correction for multiple comparison. General linear models include the following covariates: maternal race, child sex, gestational age at birth, age at assessment, absolute time, and maternal education.

Supplemental Table 2. Scores and general linear models of group comparisons on BASC-2 outcomes, controlling for maternal education

	FHR, *n* = 26	Control, *n* = 56	GLM results	
	LSM (SE)	LSM (SE)	Est (SE)	*p*-value
4-year BASC-2 scores				
Anxiety	55.9 (2.9)	46.3 (1.7)	9.56 (3.84)	**0.015**
Depression	52.7 (2.8)	47.0 (1.7)	5.71 (3.77)	0.134
Somatization	51.2 (3.0)	46.5 (1.8)	4.64 (4.04)	0.254
Atypicality	60.7 (2.6)	49.4 (1.5)	11.33 (3.41)	**0.001**
Attention Problems	54.8 (2.3)	49.6 (1.4)	5.24 (2.99)	0.084
Hyperactivity	58.9 (2.6)	48.6 (1.5)	10.28 (3.40)	**0.003**
Withdrawal	51.5 (2.8)	46.2 (1.7)	5.25 (3.68)	0.157
Developmental Social Disorders	57.1 (2.5)	46.4 (1.5)	10.65 (3.28)	**0.002**
Executive Functioning	57.5 (2.8)	47.9 (1.7)	9.62 (3.66)	**0.011**
Externalizing Problems	56.8 (2.5)	47.3 (1.5)	9.44 (3.33)	**0.006**
Internalizing Problems	54.3 (3.1)	45.5 (1.9)	8.77 (4.14)	0.038
Behavioral Symptoms Index	57.2 (2.5)	47.2 (1.5)	9.92 (3.34)	**0.004**
	FHR, *n* = 26	Control, *n* = 58	GLM results	
	LSM (SE)	LSM (SE)	Est (SE)	*p*-value
6-year BASC-2 scores				
Anxiety	52.5 (2.7)	45.7 (1.6)	6.80 (3.56)	0.060
Depression	53.7 (2.0)	45.2 (1.2)	8.46 (2.72)	**0.003**
Somatization	48.6 (2.8)	45.6 (1.6)	3.03 (3.70)	0.415
Atypicality	56.0 (2.6)	47.7 (1.5)	8.32 (3.42)	**0.017**
Attention Problems	57.7 (2.5)	47.1 (1.5)	10.63 (3.31)	**0.002**
Hyperactivity	57.4 (2.7)	48.8 (1.6)	8.62 (3.54)	**0.017**
Withdrawal	52.8 (3.0)	47.4 (1.8)	5.39 (4.06)	0.188
Developmental Social Disorders	56.1 (2.5)	45.0 (1.4)	11.06 (3.27)	**0.001**
Executive Functioning	56.6 (2.5)	46.2 (1.5)	10.41 (3.33)	**0.003**
Externalizing Problems	56.3 (2.4)	47.7 (1.4)	8.64 (3.15)	**0.008**
Internalizing Problems	52.1 (2.3)	44.4 (1.4)	7.75 (3.12)	**0.015**
Behavioral Symptoms Index	56.7 (2.4	46.1 (1.4)	10.53 (3.15)	**0.001**

Note. LSM = LS Means. *P*-values in **bold** reflect statistical significance after FDR correction for multiple comparison. General linear models include the following covariates: maternal race, child sex, gestational age at birth, age at assessment, and absolute time.

Supplemental Table 3. Comparison of z-scores on cognitive measures between groups at different ages

Scores	FHR sample LSM (SE)	Control sample LSM (SE)	Difference (SE)	*p*-value
1-year Mullen Composite	-0.39 (0.17)	0.22 (0.12)	0.61 (0.21)	.003
2-year Mullen composite	-0.83 (0.17)	0.44 (0.12)	-1.27 (0.21)	<.0001
4-year Abbreviated IQ	-0.71 (0.19)	0.23 (0.12)	-0.94 (0.22)	<.0001
6-year Abbreviated IQ	-0.54 (0.17)	0.27 (0.12)	-0.79 (0.20)	.0001

Supplemental Table 4. Change in z-scores on cognitive measures over time

Time period	FHR sample		Control sample	
	Difference (SE)	*t*-score (*p*-value)	Difference (SE)	*t*-score (*p*-value)
1 to 2 years	-0.43 (0.18)	-2.40 (.02)	0.23 (0.13)	1.68 (.09)
2 to 4 years	0.12 (0.20)	0.60 (.55)	-0.21 (0.13)	-1.64 (.10)
4 to 6 years	0.18 (0.20)	0.89 (.37)	0.04 (0.13)	0.27 (.79)
1 to 6 years	-0.14 (0.22)	-0.64 (.52)	0.05 (0.16)	0.30 (.77)