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Sex differences across developmental domains among children with a familial risk of severe mental disorders

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Abstract

Background. Sex differences in brain structure and neurodevelopment occur in non-clinical populations. We investigated whether sex had a similar effect on developmental domains amongst boys and girls with a familial risk of schizophrenia (FHR-SZ), bipolar disorder (FHR-BP), and controls.

Methods. Through Danish registries, we identified 522 7-year-old children (242 girls) with FHR-SZ, FHR-BP, and controls. We assessed their performance within the domains of neurocognition, motor function, language, social cognition, social behavior, psychopathology, and home environment.

Results. FHR-SZ boys compared with FHR-SZ girls had a higher proportion of disruptive behavior and attention-deficit hyperactivity disorder (ADHD) and exhibited lower performance in manual dexterity, balance, and emotion recognition. No sex differences were found between boys and girls within FHR-BP group. Compared with controls, both FHR-SZ boys and FHR-SZ girls showed impaired processing speed and working memory, had lower levels of global functioning, and were more likely to live in an inadequate home environment. Compared with control boys, FHR-SZ boys showed impaired manual dexterity, social behavior, and social responsiveness, and had a higher proportion of ADHD and disruptive behavior disorder diagnoses. Stress and adjustment disorders were more common in FHR-BP boys compared with control boys. We found no differences between FHR-BP girls and control girls.

Conclusions. Impairment within neurodevelopmental domains associated within FHR-SZ boys *v.* FHR-SZ girls was most evident among boys, whereas no sex differences were found within the FHR-BP group (FHR-BP boys *v.* FHR-BP girls). FHR-SZ boys exhibited the highest proportion of early developmental impairments.

Original Article

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Introduction

Developmental sex differences during normal development

From the prenatal period to adulthood, the human brain undergoes extensive development including progressive and regressive neuroanatomical changes (Giedd & Rapoport, 2010; Gilmore et al., 2012; Gogtay et al., 2004; Raznahan et al., 2011, 2014). Sex-based differences have been documented in the volume of the hippocampus, cerebellum, thalamus, and the basal ganglia, as well as cortical thickness, demonstrating the impact of sex on neuroanatomical structures during normal development (Sowell et al., 2007; Sussman, Leung, Chakravarty, Lerch, & Taylor, 2016). Accumulating evidence suggests that multiple factors contribute to the

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effects of sex differences on brain maturation (Giedd, Castellanos, Rajapakse, Vaituzis, & Rapoport, 1997; Gur & Gur, 2017; Ruigrok et al., 2014), including genetic, environmental, cultural, and hormonal influences (Gogos, Ney, Seymour, Van Rheenen, & Felmingham, 2019). Estradiol and progesterone contribute to sex differences in brain development according to their effects at receptors implicated in neurogenesis, microglial expression, inflammation, and bioenergetics (Gogos et al., 2015; Rettberg, Yao, & Brinton, 2014; Sun, Walker, Dean, Van Den Buuse, & Gogos, 2016) and contribute to the modulation and regulation of neurotransmitter activity within dopaminergic, serotonergic, glutamatergic, and GABAergic systems (Gogos et al., 2015; Kokras et al., 2018; Sun et al., 2016). Beyond the biological factors influencing brain development, culture and social environmental factors, such as distinct gender roles and cultural expectations toward boys and girls play an important role (Andermann, 2010).

Sex differences in neuropsychiatric conditions

The influence of sex on the brain is evident in neuropsychiatric conditions and neurodevelopmental disorders (Biederman et al., 2002; Jacobs et al., 2019; Kaczkurkin, Raznahan, & Satterthwaite, 2019; May, Adesina, McGillivray, & Rinehart, 2019; Pinares-Garcia, Stratikopoulos, Zagato, Loke, & Lee, 2018; Rutter, Caspi, & Moffitt, 2003) with male preponderance in childhood-onset disorders and female preponderance in adolescent-onset disorders (Dalsgaard et al., 2020; Rutter et al., 2003). Attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder, intellectual disability, and conduct disorder occur more frequently in boys than in girls (Biederman et al., 2002; Dalsgaard et al., 2020; Pedersen et al., 2014; Thapar & Cooper, 2016); whereas, anxiety disorder, obsessive-compulsive disorder, mood disorder, and eating disorders are more commonly seen among girls, emerging in adolescence (Altemus, Sarvaiya, & Neill Epperson, 2014; Biederman et al., 2002; Dalsgaard et al., 2020; Lewinsohn, Rohde, & Seeley, 1998). Register studies show conflicting results, a study reported a higher incidence of schizophrenia amongst adolescent girls *v.* boys (Dalsgaard et al., 2020), whereas an earlier register-based study reported a similar incidence of schizophrenia in childhood and adolescence among both sexes (Pedersen et al., 2014). In adulthood, men have a higher incidence of schizophrenia (Kühl, Laursen, Thorup, & Nordentoft, 2016; Pedersen et al., 2014; Thorup, Waltoft, Pedersen, Mortensen, & Nordentoft, 2007) whereas after 50 years of age, women have a higher incidence of schizophrenia than men (Pedersen et al., 2014; Thorup et al., 2007). The cumulative incidence of bipolar disorder is higher for girls in childhood and adolescence than for boys (Dalsgaard et al., 2020) and higher for women compared with men (Pedersen et al., 2014).

Although individuals who develop schizophrenia in adulthood may exhibit cognitive, social, and motor problems in childhood (Cannon et al., 2002; Howes & Murray, 2014; Murray, Bhavsar, Tripoli, & Howes, 2017; Niemi, Suvisaari, Tuulio-Henriksson, & Lonnqvist, 2003; Walker, Savoie, & Davis, 1994), few studies have examined whether these developmental problems differ according to sex (Marcus, 1985*a*; Weiser et al., 2000). Similarly, although children of parents with bipolar disorder were found to display sleep difficulties and anxiety during childhood (Duffy et al., 2014), sex differences were not examined. However, one of the risk factors, specifically for boys when developing bipolar disorder was excellent school performance (Maccabe et al., 2010).

Because of the neuroanatomical, genetic, hormonal, and cultural effects of sex during brain development and the influence of sex differences in neuropsychiatric conditions, establishing whether sex differences manifest early in development in at-risk children could facilitate early detection.

Aims of the study

The overarching objective of the Danish High Risk and Resilience Study was to assess the influences of familial risk and environmental factors in children with a familial high risk of schizophrenia (FHR-SZ) or bipolar disorder (FHR-BP). Furthermore, to identify early risk markers of schizophrenia and bipolar disorder to establish a basis for future primary preventive interventions in the premorbid phase. The purpose of this sub-study was to investigate whether groups of boys and girls with a FHR-SZ, FHR-BP, and controls differed in terms of neurocognition, language, motor function, psychopathology, social cognition, social behavior, home environment, and global functioning before puberty. Moreover, we assessed potential sex differences in symptomatology and function amongst children with FHR-SZ, FHR-BP, and controls. Given the existing sex-based differences in the incidence of schizophrenia, we hypothesized that we would find sex-based differences between the familial high-risk groups (sex-by-group interaction), and specifically, that we would observe poorer function and outcome in boys in the FHR-SZ group compared with girls in the FHR-SZ group and control boys. Because females have a higher cumulative incidence than males of bipolar disorder, we hypothesized that we would observe poorer function and outcome in FHR-BP girls compared with FHR-BP boys and control girls.

Methods and materials

The Danish Data Protection Agency approved the study protocol. We obtained authorization to draw data from registers from the Danish Ministry of Health. The Danish National Committee on Health Research Ethics received the protocol. Because of the non-interventional study design, ethical approval was not considered necessary by the authority. The legal guardians of the participating children provided written informed consent.

Study design and participants

The Danish High Risk and Resilience Study-VIA7 took place in Denmark between 1 January 2013 and 31 January 2016 (Thorup et al., 2015). This stratified cohort consisted of 522 Danish children aged 7 years with either one parent, two parents, or neither parent diagnosed with schizophrenia spectrum disorder or bipolar disorder. We chose to assess the children at age 7 because in Denmark most children have started school at age 7. Beginning school denotes an important developmental step for a child, implying increased demands, cognitive and academic, as well as socially. We identified the cohort using The Danish Civil Registration System (DCRS) (Pedersen, Gotzsche, Moller, & Mortensen, 2006) and The Danish Psychiatric Central Research Register (DPCR) (Mors, Perto, & Mortensen, 2011). Families were contacted to participate in the study by letter and subsequently by telephone (Fig. 1). Schizophrenia spectrum disorder was defined as schizophrenia, delusional disorder, or schizoaffective disorder, and was reflected by International Classification of Disease (ICD) 10-codes (F20, F22, and F25) or

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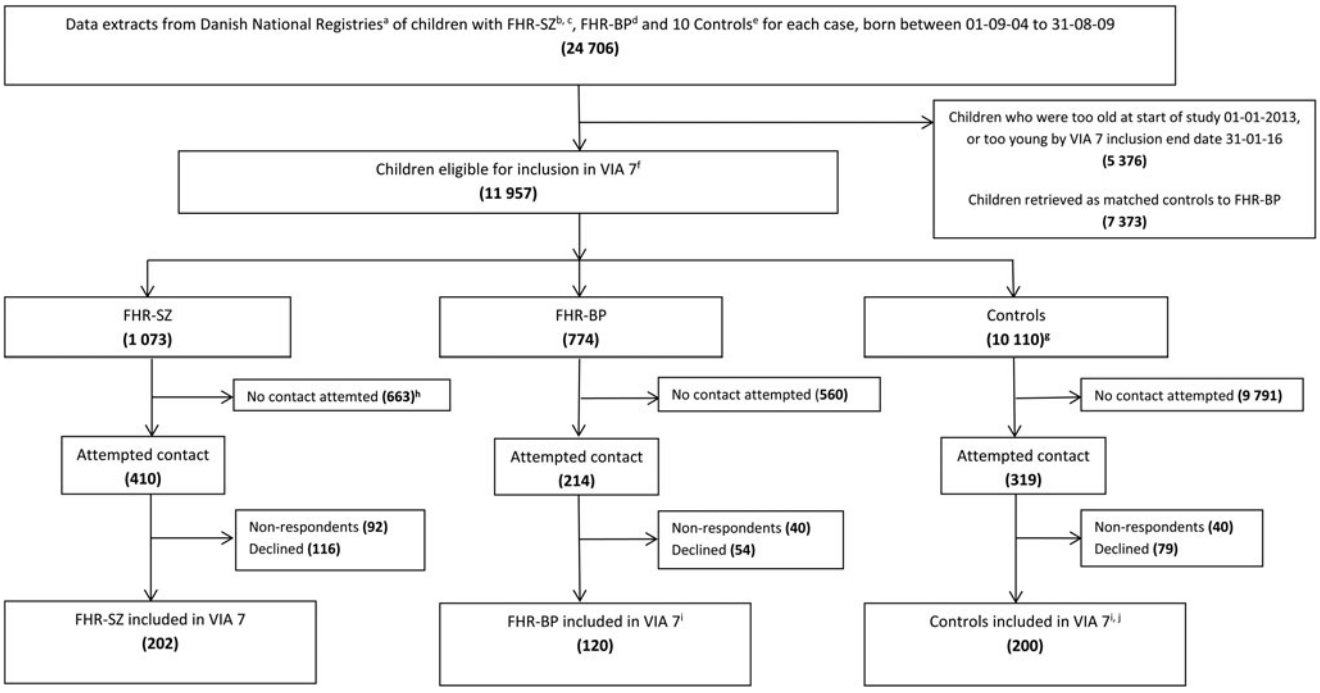

Fig. 1. Recruitment of participating children in The Danish High Risk and Resilience Study. [a]Danish National Registries: Danish Civil Registration System and Danish Psychiatric Central Research Register. [b]FHR-SZ: Children of parents with schizophrenia spectrum disorders. [c]Double diagnosed parents: 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 of parents with bipolar disorder. [e]Controls: Population-based control children of parents with no diagnoses of schizophrenia spectrum disorders or bipolar disorder. [f]Research protection: As of May 2011, legislation was enacted to protect individuals phone numbers from being called for participation in scientific research. Therefore, there were eligible children who were not contacted and enrolled in VIA 7. [g]Controls selection: Up to 10 controls were retrieved for each child in the schizophrenia spectrum disorder group and the bipolar disorder group. Controls were matched to cases on sex, municipality and exact age. Control cases were matched to children in the schizophrenia familial high-risk group. [h]Definition of contact: First through letters sent to the child´s address. If the family did not respond, contact by telephone was attempted (calls and text messages), if a phone number could be found. [i]Re-assigned control parent: One control parent was found to have a diagnosis of bipolar disorder made by a private doctor, therefore the diagnosis was not present/visible in the National Registry extract, as private doctors do not report to the National Registry. This family/parent was therefore reassigned to the bipolar disorder familial high-risk group. Therefore, the $N = 201$ for controls is now $N = 200$. [j]Control children not in the extract: Two younger siblings were included to VIA 7 by request of the parents. They were not in the original extract.

ICD 8-codes (295, 297, 298.29, 298.39, 298.89, and 298.99). Bipolar disorder was associated with ICD 10-codes (F30, F31) and ICD 8-codes (296.19 and 296.39). Controls were defined as population-based control children of parents with no diagnoses of schizophrenia spectrum disorders or bipolar disorder. The control children were matched to the FHR-SZ children according to sex, age, and municipality. The FHR-BP children were included as a non-matched group that was comparable to the other groups in terms of age and sex. The children underwent a battery of tests to assess neurocognition (Hemager et al., 2018), social cognition and language (Christiani et al., 2019), motor function (Burton et al., 2017), psychopathology (Ellersgaard et al., 2018), and the home environment (Gantriis et al., 2019), with group differences described elsewhere.

Outcome and procedure

The instruments selected were validated and specifically developed and selected for the age group, sensitive to small changes and suitable for later follow-up. Domain characteristics and outcomes are illustrated in Table 1.

Neurocognition

Reynold's Intellectual Screening test (Reynolds & Kamphaus, 2003) was used to measure general intelligence. Neurocognitive function was assessed using subtests from the Wechsler Intelligence Scale for Children – fourth edition (Wechsler, 2003), Delis-Kaplan Executive Function System (Delis, Kaplan, & Kramer, 2001), Test of Memory and Learning – Second Edition (Reynolds & Voress, 2007), Cambridge Neuropsychological Test Automated Battery (Sahakian & Owen, 1992), and Rey Complex Figure Test and Recognition Trial (Meyers & Meyers, 1995) and scores were converted to z-scores based on the control group with both sexes included. To reduce the number of variables, we derived four neurocognitive components (Processing speed and working memory, Verbal function, Executive and visuospatial functions, and Declarative memory and attention) after conducting principal component analysis [described elsewhere (Hemager et al., 2018)].

Language

Receptive language was evaluated using the Test for Reception of Grammar-2 (Bishop, 2010).

Motor

Motor function was assessed using the Movement Assessment Battery for Children – second edition (Henderson, Sugden, & Barnett, 2007). Raw scores were converted to standard scores using the normative data from the Movement ABC-2 manual, as described elsewhere (Burton et al., 2017).

Psychiatric diagnosis

The psychiatric diagnoses were established using the Schedule for Affective Disorders and Schizophrenia for School-Age Children –

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Table 1. Characteristics and performance of 7- year old children with familial risk of schizophrenia, bipolar disorder or controls presented by sex and familial risk status within specified domains of function

	Boys FHR-SZ	Girls FHR-SZ	Boys FHR-BP	Girls FHR-BP	Boys control	Girls control	*p* Value across all six groups
Children, *N* (% within each familial risk group)	109 (54%)	93 (46%)	64 (53.3%)	56 (46.7%)	107 (53.5%)	93 (46.5%)	0.993
Age at inclusion (years) mean (S.D.)	7.85 (0.23)	7.84 (0.20)	7.83 (0.24)	7.91 (0.13)	7.82 (0.18)	7.81 (0.22)	0.094
Primary caregiver to the child[a]							0.01
Biological mother, *N* (% within each familial risk group)	85 (42%)	81 (40%)	57 (47.5%)	54 (45%)	95 (47.5%)	85 (42.5%)	
Biological father, *N* (% within each familial risk group)	15 (7.4%)	9 (4.5%)	7 (5.8%)	<5	11 (5.5%)	8 (4%)	
Maternal grandmother, *N*	<5	0	0	0	0	0	
Foster mother, *N* (% within each familial risk group)	7 (3.5%)	<5	0	0	0	0	
Foster father, *N*	0	0	0	0	<5	0	
Other, *N*	<5	0	0	0	0	0	
Language							
Receptive language mean (S.D.) (Test for reception of grammar-2)	13.37 (3.47)	14.52 (3.33)	14.62 (2.80)	14.46 (2.74)	14.38 (3.18)	15.29 (2.40)	0.001
Cognition							
Intelligence IQ mean (S.D.) (RIST)	100.36 (10.67)	104.28(11.76)	104.44 (9.28)	103.85 (9.38)	104.62 (9.91)	105.34 (9.80)	0.011
Processing speed and working memory[b] mean (S.D.) (z-scores)	−2.01 (3.80)	−1.32 (3.09)	−0.60 (3.94)	0.10 (2.90)	−0.45 (3.39)	0.52 (3.03)	<0.001
Verbal functions[c] mean (S.D.) (z-scores)	−0.99 (2.76)	−0.22 (2.87)	0.22 (2.61)	−0.09 (2.67)	−0.17 (2.23)	0.19 (2.60)	0.021
Executive and visuospatial functions[d] mean (S.D.) (z-scores)	−0.56 (1.54)	−0.19 (1.40)	0.09 (1.73)	0.20 (1.42)	−0.16 (1.36)	0.19 (1.37)	0.003
Declarative memory and attention[e] mean (S.D.) (z-scores)	−0.56 (1.54)	−0.20 (1.36)	0.01 (1.41)	0.07 (1.34)	−0.26 (1.19)	0.30 (1.31)	<0.001
Social cognition							
Theory of mind (accuracy) mean (S.D.) (Strange Stories-Revised)	6.92 (2.58)	7.59 (2.59)	7.65 (2.52)	8.00 (2.42)	7.80 (2.46)	7.99 (2.44)	0.033
Theory of mind response latency mean (S.D.) (Strange Stories-Revised)	0.21 (0.20)	0.33 (0.80)	0.19 (0.12)	0.19 (0.14)	0.22 (0.16)	0.21 (0.22)	0.124
Emotion recognition (accuracy) mean (S.D.) (Cambridge Automated Neuropsychological Test Battery)	45.85 (10.76)	52.53 (8.97)	49.35 (8.23)	51.35 (10.44)	48.23 (10.34)	52.14 (8.98)	<0.001
Emotion recognition response latency mean (S.D.) (Cambridge Automated Neuropsychological Test Battery)	2848.55 (1040.13)	2914.08 (1160.26)	2729.33 (700.89)	2782.09 (854.42)	2768.52 (847.95)	2747.55 (873.31)	0.795
Social behavior							
Social responsiveness mean (S.D.) (Social Responsiveness Scale, SRS, raw scores)	44.52 (28.79)	32.97 (26.03)	36.38 (32.68)	29.20 (29.37)	26.40 (21.63)	23.18 (18.86)	<0.001
Social Behavior – interpersonal relations mean (S.D.) (Vineland-II-subdomain Socialization, raw score)	35.03 (10.07)	35.58 (8.66)	36.50 (8.01)	38.75 (6.98)	39.17 (5.13)	38.14 (6.02)	0.001
Social Behavior – play and leisure mean (S.D.) (Vineland-II-subdomain Socialization, raw scores)	30.04 (8.68)	30.23 (7.09)	31.55 (5.83)	32.89 (7.03)	33.64 (5.11)	32.65 (5.63)	0.001
Social Behavior –coping skills mean (S.D.) (Vineland-II-subdomain Socialization, raw scores)	33.55 (9.73)	34.64 (8.32)	36.09 (7.42)	37.39 (7.96)	38.48 (6.02)	36.96 (6.02)	<0.001

(*Continued*)

Table 1. (*Continued.*)

	Boys FHR-SZ	Girls FHR-SZ	Boys FHR-BP	Girls FHR-BP	Boys control	Girls control	*p* Value across all six groups
Motor function							
Manual dexterity mean (s.d.) (Movement ABC-2), standard scores	6.84 (2.95)	9.30 (3.51)	7.86 (3.51)	9.62 (3.42)	8.36 (3.26)	10.73 (3.51)	<0.001
Balance mean (s.d.) (Movement ABC-2), standard scores)	6.65 (2.74)	8.76 (3.37)	7.44 (2.83)	9.29 (3.80)	7.93 (3.32)	10.36 (3.83)	<0.001
Aiming and catching mean (s.d.) (Movement ABC-2), standard scores)	8.89 (2.98)	7.88 (2.76)	8.71 (3.27)	8.05 (2.79)	9.21 (3.02)	8.47 (2.92)	0.024
Psychopathology & functioning							
Inattention, hyperactivity and impulsivity, mean (s.d.) (mADHD-RS) (raw scores)	16.03 (14.40)	7.10 (7.73)	10.81 (12.73)	5.98 (9.62)	9.07 (9.90)	5.26 (8.00)	<0.001
Oppositional defiant mean (s.d.) (mADHD-RS) (raw scores)	4.18 (5.62)	1.74 (3.04)	2.69 (4.04)	1.30 (2.70)	1.39 (2.73)	1.33 (3.17)	<0.001
CBCL Externalizing mean (s.d.) (The Child behavior Checklist) (raw scores)	8.49 (7.93)	6.98 (6.76)	6.82 (7.07)	5.41 (6.17)	3.62 (4.28)	4.63 (5.16)	<0.001
CBCL Internalizing mean (s.d.) (The Child behavior Checklist) (raw scores)	6.05 (6.05)	7.18 (5.65)	5.73 (5.45)	7.64 (8.12)	4.71 (4.36)	4.99 (4.62)	0.006
CGAS mean (s.d.) (Children's Global Assessment Scale)	65.49 (15.39)	71.08 (14.95)	70.90 (15.37)	76.58 (13.88)	75.58 (12.98)	80.23 (13.67)	<0.001
TRF Externalizing mean (s.d.) (Teacher's Report Form)	10.34 (12.19)	4.04 (5.56)	5.74 (8.21)	3.47 (5.58)	3.03 (4.93)	3.03 (5.71)	<0.001
TRF Internalizing mean (s.d.) (Teacher's Report Form)	5.92 (5.61)	5.44 (5.60)	5.19 (5.89)	5.89 (8.26)	3.37 (4.19)	4.00 (4.66)	0.015
TOF Internalizing mean (s.d.) (The Test Observation Form)	7.50 (8.61)	7.76 (8.62)	6.51 (8.54)	4.81 (7.47)	5.17 (6.81)	4.73 (6.98)	0.025
TOF Externalizing mean (s.d.) (The Test Observation Form)	16.80 (20.10)	10.29(14.35)	10.37 (12.54)	5.94 (8.62)	10.41 (13.11)	8.03 (12.29)	<0.001
Psychiatric diagnosis							
ADHD, *N* (%) (K-SADS-PL)	30 (28)	11 (12.0)	8 (12.7)	3 (5.5)	7 (6.5)	7 (7.8)	<0.001
Anxiety disorders, *N* (%) (K-SADS-PL)	9 (8.4)	14 (15.2)	3 (4.8)	11 (20.0)	4 (3.7)	5 (5.6)	0.002
Elimination disorders, *N* (%) (K-SADS-PL)	34 (31.8)	19 (20.7)	24 (38.1)	14 (25.5)	37 (34.6)	17 (18.9)	0.028
Pervasive developmental disorders, *N*, (%) (K-SADS-PL)	9 (8.4)	3 (3.3)	7 (11.1)	2 (3.6)	3 (2.8)	2 (2.2)	0.055
Stress and adjustment disorders, *N*, (%) (K-SADS-PL)	4 (3.7)	7 (7.6)	7 (11.1)	3 (5.5)	0 (0)	3 (3.3)	0.019
Disruptive behavior disorders, *N*, (%) (K-SADS-PL)	11 (10.3)	1 (1.1)	4 (6.3)	0 (0)	0 (0)	2 (2.2)	<0.001
Home Environment							
Living in a sufficient home *N*, (%) (The Middle Childhood-HOME Inventory)	80 (76.2)	70 (76.9)	58 (93.5)	47 (87.0)	103 (96.3)	84 (94.4)	<0.001
Living with the index parents *N*, (%)	63 (57.8)	61 (65.6)	47 (73.4)	37 (66.1)	102 (95.3)	87 (93.5)	<0.001

FHR-SZ: children with familial risk of schizophrenia, FHR-BP: children with familial risk of bipolar disorder, controls: Population-based controls. Index parents refer to the biological parents with a diagnosis of schizophrenia spectrum psychosis or bipolar disorder. Higher scores in the social responsiveness domain indicate more problematic social behavior. RIST: The Reynold's Intellectual Screening test. Movement ABC-2: Movement Assessment Battery for Children – second edition. mADHD-RS: A modified version of the Attention Deficit Hyperactivity Disorder Rating Scale. RS K-SADS-PL: Schedule for Affective Disorders and Schizophrenia for School-Age Children- present and Lifetime Version.

[a]The primary caregiver to the child, is the legal guardian who spent the most time with the child. The primary caregiver completed CBCL and Vineland-II.

[b]Includes Trail-Making Test Number Sequencing, Trail-Making Test Letter Sequencing, Trail-Making Test Letter-Number Switching, Symbol Search, Coding, Arithmetic, Letter-Number Sequencing, and Spatial Working Memory; total errors.

[c]Includes Memory for Stories immediate recall, Memory for Stories delayed recall, Guess What, Verbal Fluency phonemic, Verbal Fluency semantic, and Verbal Fluency switching.

[d]Includes Stockings of Cambridge Problems Solved in Minimum Moves, Spatial Span length, Odd-Item Out, Intra-Extra Dimensional Set Shift extra-dimensional stage errors, and Spatial Recognition Memory percentage correct.

[e]Includes Rey Complex Figure Test and Recognition Recall, Word Selective Reminding Immediate Recall, Word Selective Reminding Delayed Recall, and Rapid Visual Information Processing.

Present and Lifetime Version (K-SADS-PL) (Kaufman et al., 1997).

Psychopathology and functioning

A modified version of the ADHD Rating Scale (Barkley, Gwenyth, & Arthur, 1999; Dupaul, Power, & Anastopoulos, 1998; Makransky & Bilenberg, 2014) was used to assess symptoms of ADHD and oppositional defiant disorder. These were completed by the teacher of each child. The Child Behavior Checklist (Achenbach & Rescorla, 2001) was used to assess the severity of various dimensions of psychopathology; this was completed by the caregiver of each child (defined as the parent/legal guardian who spent the most time with the child). Each child's teacher filled out the Teacher's Report Form (Achenbach & Rescorla, 2001). An interviewer evaluated the current level of functioning of each child using the Children's Global Assessment Scale (Shaffer et al., 1983), as part of the K-SADS-PL interview. The Test Observation Form, which assesses behavioral and emotional problems observed during an assessment session (Mcconaughy & Achenbach, 2004), was also completed. Psychiatric diagnoses and psychopathology are described elsewhere (Ellersgaard et al., 2018).

Social cognition

Theory of mind was assessed using Strange Stories-Revised (White, Hill, Happé, & Frith, 2009), and facial affect recognition was assessed via the computerized emotion recognition task from the Cambridge Automated Neuropsychological Test Battery (Sahakian & Owen, 1992).

Social behavior

Social behavior was conceptualized as social responsiveness and adaptive social functioning, as assessed by the child's teacher via the Social Responsiveness Scale (Constantino et al., 2003). The primary caregiver completed the Vineland-II Socialization subdomain (Sparrow, Cincchetti, & Balla, 2006). The tests of social cognition, social behavior, and language are described elsewhere (Christiani et al., 2019).

Home environment

The quality of the home environment was assessed with the Middle Childhood-HOME Inventory (Caldwell & Bradley, 2003) evaluating the level of stimulation and support in the home, which is described elsewhere (Gantriis et al., 2019). Sex differences among children living with an index parent (defined as a parent with a diagnosis of either schizophrenia spectrum disorder or bipolar disorder, or a matched control parent) were assessed.

Statistical analyses

Summary statistics for demographic, clinical and domain characteristics were calculated by sex and familial risk group (FHR-SZ, FHR-BP or control). Differences in mean values were analyzed bivariately by means of an analysis of variance for continuous outcomes and by chi-square test for categorical outcomes (Table 1). All variables listed in Table 1 were used for statistical analyses separately and all the outcomes from Table 1 are illustrated in Figs 2 and 3. We tested the influences of sex and familial-risk status as well as the effect modification of sex and familial-risk group on each of the continuous dependent variables in each domain (language, neurocognition, social cognition, social behavior, motor function, psychopathology and general functioning). This was done by fitting regression models including main effects of sex and familial-risk group and their interaction followed by a hierarchical F-test. All continuous outcomes were standardized to z-scores. For binary outcomes, logistic regression models were fitted using the same dependent variables to the following domains: psychiatric diagnosis (present/absent), home environment (having an insufficient home environment was defined as an MC-HOME Inventory total score ≤40) (Gantriis et al., 2019) and (living with index parent or not), regression on sex, group and the interaction sex-by-familial-risk-group. For all outcomes, pairwise comparisons between sexes and group were performed post hoc and visualized graphically (Figs 2 and 3 and Table 2). For continuous outcomes the pairwise comparison is the difference in Cohen's delta, where $d = 0.2$ is considered a 'small' effect size, 0.5 represents a 'medium' effect size and 0.8 a 'large' effect size (Cohen, 1988), while for binary outcomes the difference is in proportions. We applied a hierarchical testing principle to reduce the risk of type I error. First, for overall testing, the significance was set at 0.05. For all pairwise comparisons, a Bonferroni correction significance level of 0.001 was applied (i.e. 0.05/50 tests). Because of the small number of sibling pairs ($n = 16$ of which 6 pairs were twins), we did not consider the effect of a sibling or high genetic loading (nine children had two parents with schizophrenia or bipolar disorder) in the statistical model. All statistical analyses were conducted using R version 3.5.1 (2018-07-02).

Results

The VIA-7 cohort included 522 children aged 7 years; 202 (39%) with FHR-SZ [93 girls (46%)], 120 (23%) with FHR-BP [56 girls (46.7%)] and 200 (38%) controls [93 girls (46.5%)]. No significant difference between sexes ($p = 0.99$) nor age at inclusion ($p = 0.09$) were observed across all groups. Demographic characteristics and the various domains are reported in Table 1.

Sex differences modified by familial-risk groups

Significant effect modifications (sex had different implications in different groups) were seen for four domains: oppositional defiant (ADHD-RS), teacher report form externalizing, disruptive behavior disorders (K-SADS) and stress & adjustment disorders (K-SADS). The significant interaction between group and sex for the domain of oppositional defiant (ADHD-RS), rated by the teacher ($F = 4.11$, df = 2, $p = 0.017$) denoted that the sex difference was greater in the FHR-SZ group compared with the sex difference in the other groups with a medium effect (Cohen's $d = 0.622$, $p < 0.0001$). Furthermore, the effect modification between group and sex for teacher-rated externalizing behavior ($F = 7.13$, df = 2, $p < 0.001$) signified the sex difference was greater in the FHR-SZ group compared with the sex difference in the other groups with a medium effect (Cohen's $d = 0.776$, $p < 0.0001$) (Table 2).

The significant effect modification between group and sex for the domains of K-SADS diagnosis disruptive disorders (Residual dev. = 130.8, df = 2, $p = 0.008$) revealed the sex difference was greater in the FHR-SZ group compared with the other groups; denoting the FHR-SZ boys had 9.19% higher proportion of disruptive behavior disorders, ($p = 0.0004$) compared with FHR-SZ girls (Fig. 2), whereas no sex difference were evident within the FHR-BP ($p = 0.057$) or the control group ($p = 0.39$) (Table 2). For stress and adjustment disorders (Residual dev = 177.2, df = 2, $p = 0.033$), the sex difference was larger in the FHR-BP group

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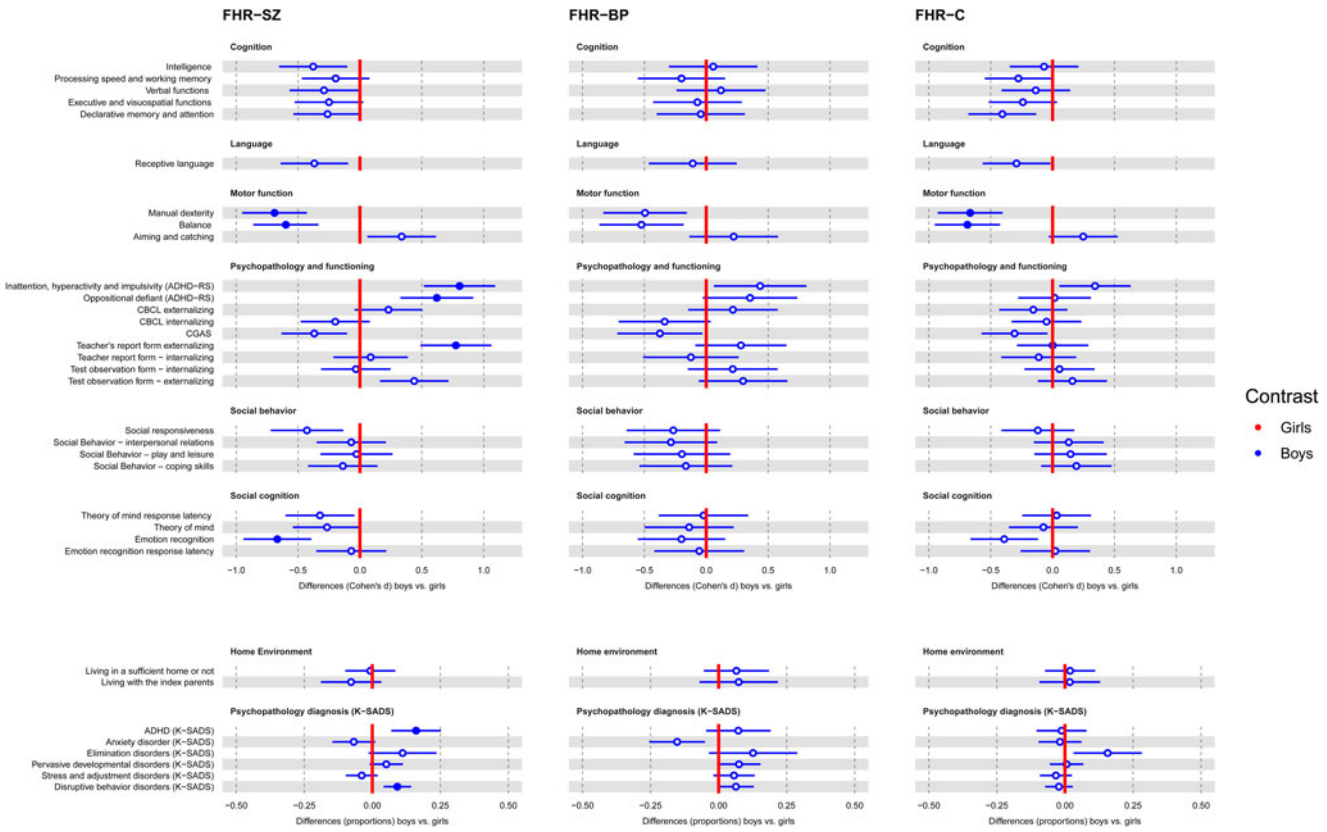

Fig. 2. Sex differences within familial-risk groups; FHR-SZ boys compared with FHR-SZ girls, FHR-BP boys compared with FHR-BP girls and control boys compared with control girls. Boys are illustrated in blue and girls in red as the contrast group. Differences are illustrated by effect size Cohen's *d*. For the domains of the home environment and psychopathology diagnoses differences are illustrated in proportions. Error bars indicate 95% confidence interval. Marked dots represent significant Bonferroni correction ($p = 0.001$). Estimates with clear dots and 95% confidence intervals which do not cross the red vertical contrast line represent a significance level of 5%. The direction of performance (worse/better) follows the instrument.

compared with controls. FHR-BP boys had an 11.11% higher proportion of stress and adjustment disorder compared with control boys ($p = 0.0009$), whereas there was no difference between FHR-BP girls compared with control girls ($p = 0.55$) (Fig. 3). For the remaining domains (described in Table 2, Figs 2 and 3) no significant modifications between sex and group were evident.

Sex differences within the familial-risk group

Sex differences within familial risk groups is shown in Fig. 2 and Table 2. Overall, sex had a significant impact on various domains among FHR-SZ children, whereas sex did not affect the tested domains in FHR-BP children (Fig. 2).

FHR-SZ boys v. *FHR-SZ girls*

Figure 2. FHR-SZ boys compared with FHR-SZ girls exhibited poorer social cognition in relation to emotion recognition with a medium effect (Cohen's $d = -0.667$, $p < 0.0001$), poorer motor skills with regard to manual dexterity (Cohen's $d = -0.690$, $p < 0.0001$) and balance with a medium effect (Cohen's $d = -0.598$, $p < 0.0001$). FHR-SZ boys had a 16.08% higher proportion of ADHD diagnoses ($p = 0.0006$) and a 9.19% higher proportion of disruptive behavior disorders ($p = 0.0004$) compared with FHR-SZ girls. The teachers of the children rated higher levels of inattention, hyperactivity and impulsivity with a large effect (Cohen's $d = 0.805$, $p < 0.0001$). We detected no differences in the home environment between boys or girls having a parent diagnosed with schizophrenia (difference in proportion = −0.007, $p = 0.876$). Furthermore, we found no sex differences between FHR-SZ boys and FHR-SZ girls in the domains of cognition, language, social behavior and home environment (FHR-SZ in Fig. 2) and Table 2.

FHR-BP boys v. *FHR-BP girls*

We detected no significant effects of sex after Bonferroni corrections between boys of parents with bipolar disorder compared with girls of parents with bipolar disorder, (FHR-BP in Fig. 2).

Control boys v. *control girls*

We found sex-based differences in motor function among the control children after Bonferroni correction. Boys displayed poorer manual dexterity (Cohen's $d = -0.666$, $p < 0.0001$) and balance (Cohen's $d = -0.688$, $p < 0.0001$) both with a medium effect compared with the girls from the control group.

Sex differences between familial-risk groups and controls

FHR-SZ boys compared with control boys

Figure 3. FHR-SZ boys showed impaired processing speed and working memory with a medium effect (Cohen's $d = -0.448$,

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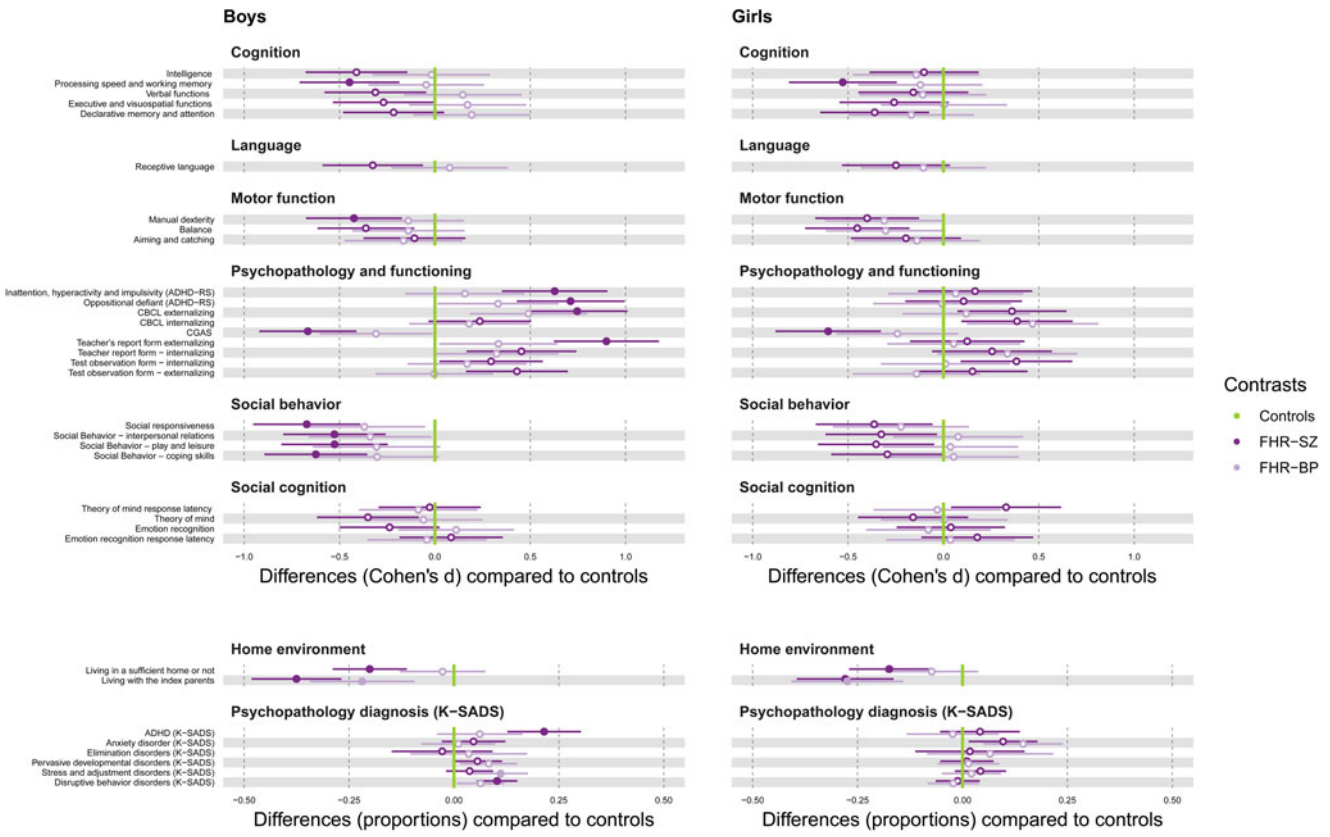

Fig. 3. Sex differences between familial-risk groups compared with controls. On the left FHR-SZ boys *v.* control boys and FHR-BP boys *v.* control boys. On the right FHR-SZ girls *v.* control girls and FHR-BP girls *v.* control girls. FHR-SZ are illustrated in dark purple, FHR-BP in light purple and controls in the green vertical line. Differences are illustrated by effect size Cohen's *d*. For the domains of the home environment and psychopathology diagnoses differences are illustrated in proportions. Error bars indicate 95% confidence interval. Marked dots represent significant Bonferroni correction ($p = 0.001$). Estimates with clear dots and 95% confidence intervals which do not cross the green vertical control line represent a significance level of 5%. The direction of performance (worse/better) follows the instrument.

$p < 0.001$), and poorer manual dexterity with a small to medium effect (Cohen's $d = -0424$, $p < 0.001$) compared with control boys (Boys in Fig. 3). FHR-SZ boys had a higher proportion (21.5%) of ADHD diagnoses ($p < 0.0001$) and a higher proportion (10.28%) of disruptive behavior disorders ($p < 0.0001$) compared with boys from the control group. Teachers reported a higher degree of externalizing behavior problems among FHR-SZ boys (Cohen's $d = 0.8995$, $p < 0.0001$) compared with control boys with a large effect. Teachers reported higher levels of inattention, hyperactivity and impulsivity symptoms in FHR-SZ boys (Cohen's $d = 0.628$, $p < 0.0001$), as well as oppositional defiant behavior (Cohen's $d = 0.711$, $p < 0.0001$) compared with control boys with a medium effect. FHR-SZ boys showed less social responsiveness (Cohen's $d = -0.672$, $p < 0.0001$) and poorer adaptive social functioning: interpersonal relations (Cohen's $d = -0527$, $p = 0.0001$), play and leisure (Cohen's $d = -0.526$, $p = 0.0002$) and coping skills (Cohen's $d = -0.624$, $p < 0.0001$) with a medium effect compared with control boys. FHR-SZ boys demonstrated lower global functioning than the control boys with a medium effect (Cohen's $d = -0.666$, $p < 0.0001$). Furthermore, 20.07% of FHR-SZ boys lived in insufficient home environments compared with boys from the control group ($p < 0.0001$). A higher proportion (37.53%) of FHR-SZ boys did not live with the index parent (i.e. the parent diagnosed with schizophrenia spectrum disorder) compared with boys from the control group who lived with the control index parent (the parent that was matched to the index parent) ($p < 0.0001$), Fig. 3. No group differences were detected after Bonferroni correction between FHR-SZ boys compared with control boys in the domain of language and social cognition.

FHR-SZ girls compared with control girls

FHR-SZ girls showed impaired processing speed and working memory (Cohen's $d = -0.528$, $p = 0.0003$), and lower global functioning (Cohen's $d = -0.604$, $p < 0.0001$) compared with control girls with a medium effect. A higher proportion (27.96%) of FHR-SZ girls did not live with the index parent compared with control girls who lived with the control index parent ($p < 0.0001$). A higher proportion (17.46%) of FHR-SZ girls lived in an inadequate home environment compared with control girls ($p = 0.0004$), (girls in Fig. 3). No group differences were detected between FHR-SZ girls compared with control girls in the domains of language, motor function, social behavior, social cognition and psychopathology.

FHR-BP boys or girls compared with control boys or girls respectively

A higher proportion of both FHR-BP boys (21.89%), ($p = 0.0006$) and FHR-BP girls (27.48%), ($p < 0.0001$) did not live with their parent diagnosed with bipolar disorder compared with control boys or girls respectably. For all other domains, no group differences were detected for FHR-BP boys or girls (Fig. 3).

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Table 2. Pairwise comparisons between sex and familial high-risk status

	Pairwise comparison between sex and familial high-risk group according to Bonferroni correction.													
	Sex differences within familial risk groups						Sex differences between familial risk groups and controls							
	FHR-SZ boys *v.* FHR-SZ girls		FHR-BP boys *v.* FHR-BP girls		Control boys *v.* control girls		FHR-SZ boys *v.* control boys		FHR-SZ girls *v.* control girls		FHR-BP boys *v.* control boys		FHR-BP girls *v.* control girls	
	Cohen's *d* 95% CI	*p* Value	Cohen's *d* 95% CI	*p* Value	Cohen's *d* 95% CI	*p* Value	Cohen's *d* 95% CI	*p* Value	Cohen's *d* 95% CI	*p* Value	Cohen's *d* 95% CI	*p* Value	Cohen's *d* 95% CI	*p* Value
Receptive language	−0.368 (−0.642 to −0.095)	0.008	−0.109 (−0.464 to 0.246)	0.547	−0.292 (−0.566 to −0.018)	0.037	−0.326 (−0.589 to −0.062)	0.016	−0.249 (−0.532 to 0.034)	0.085	0.078 (−0.228 to 0.383)	0.617	−0.105 (−0.434 to 0.224)	0.530
Cognition														
Intelligence	−0.378 (−0.654 to −0.102)	0.007	0.056 (−0.302 to 0.414)	0.758	−0.069 (−0.346 to 0.208)	0.626	−0.411 (−0.678 to −0.144)	0.003	−0.102 (−0.388 to 0.184)	0.485	−0.018 (−0.326 to 0.290)	0.909	−0.143 (−0.474 to 0.189)	0.398
Processing speed and working memory	−0.196 (−0.469 to 0.077)	0.160	−0.200 (−0.553 to 0.152)	0.265	−0.276 (−0.548 to −0.004)	0.046	−0.448 (−0.709 to −0.186)	**<0.001**	−0.528 (−0.810 to −0.245)	**0.0003**	−0.045 (−0.349 to 0.258)	0.769	−0.121 (−0.447 to 0.205)	0.465
Verbal function	−0.290 (−0.569 to −0.012)	0.041	0.119 (−0.241 to 0.478)	0.517	−0.136 (−0.413 to 0.141)	0.335	−0.312 (−0.579 to −0.045)	0.022	−0.158 (−0.446 to 0.130)	0.282	0.146 (−0.163 to 0.456)	0.354	−0.109 (−0.441 to 0.224)	0.521
Executive and visuospatial functions	−0.250 (−0.527 to 0.027)	0.077	−0.071 (−0.429 to 0.287)	0.697	−0.240 (−0.516 to 0.036)	0.088	−0.269 (−0.535 to −0.003)	0.047	−0.259 (−0.546 to 0.028)	0.077	0.172 (−0.137 to 0.480)	0.274	0.003 (−0.328 to 0.334)	0.986
Declarative memory and attention	−0.262 (−0.538 to 0.014)	0.063	−0.044 (−0.401 to 0.312)	0.808	−0.406 (−0.681 to −0.131)	0.004	−0.216 (−0.481 to 0.048)	0.109	−0.361 (−0.646 to −0.075)	0.013	0.193 (−0.114 to 0.500)	0.217	−0.169 (−0.498 to 0.160)	0.314
Social cognition														
Theory of mind response latency	−0.323 (−0.601 to −0.044)	0.023	−0.022 (−0.383 to 0.339)	0.906	0.033 (−0.245 to 0.311)	0.816	−0.027 (−0.295 to 0.240)	0.842	0.329 (0.040 to 0.617)	0.026	−0.087 (−0.398 to 0.224)	0.583	−0.032 (−0.366 to 0.302)	0.850
Theory of mind.	−0.266 (−0.543 to 0.012)	0.060	−0.138 (−0.498 to 0.222)	0.451	−0.074 (−0.353 to 0.205)	0.602	−0.351 (−0.618 to −0.083)	0.010	−0.159 (−0.448 to 0.129)	0.279	−0.060 (−0.370 to 0.251)	0.705	0.004 (−0.329 to 0.338)	0.980
Emotion recognition	−0.667 (−0.942 to −0.393)	**<0.0001**	−0.200 (−0.553 to 0.152)	0.265	−0.391 (−0.664 to −0.118)	0.005	−0.238 (−0.500 to 0.025)	0.076	0.039 (−0.245 to 0.323)	0.789	0.112 (−0.192 to 0.415)	0.470	−0.079 (−0.405 to 0.248)	0.635
Emotion recognition response latency	−0.070 (−0.353 to 0.213)	0.628	−0.056 (−0.420 to 0.307)	0.761	0.022 (−0.259 to 0.303)	0.876	0.085 (−0.185 to 0.356)	0.536	0.177 (−0.115 to 0.470)	0.234	−0.042 (−0.355 to 0.271)	0.793	0.037 (−0.300 to 0.373)	0.830
Social behavior														
Social responsiveness	−0.428 (−0.721 to −0.135)	0.004	−0.266 (−0.643 to 0.111)	0.166	−0.119 (−0.414 to 0.175)	0.426	−0.672 (−0.952 to −0.391)	**<0.0001**	−0.363 (−0.669 to −0.057)	0.020	−0.370 (−0.688 to −0.051)	0.023	−0.223 (−0.580 to 0.134)	0.220
Social Behavior – interpersonal relations	−0.070 (−0.350 to 0.210)	0.623	−0.286 (−0.659 to 0.088)	0.134	0.131 (−0.152 to 0.413)	0.364	−0.527 (−0.796 to −0.258)	**0.0001**	−0.326 (−0.619 to −0.033)	0.029	−0.339 (−0.660 to −0.018)	0.038	0.077 (−0.264 to 0.418)	0.657
		0.852		0.323		0.330		**0.0002**		0.023		0.073		0.841

Social Behavior – play and leisure	−0.028 (−0.319 to 0.263)		−0.197 (−0.587 to 0.194)		0.145 (−0.147 to 0.438)		−0.526 (−0.805 to −0.247)		−0.353 (−0.658 to −0.048)		−0.306 (−0.640 to 0.028)		0.036 (−0.320 to 0.392)	
Social Behavior coping skills	−0.138 (−0.419 to 0.143)	0.335	−0.165 (−0.540 to 0.211)	0.389	0.192 (−0.092 to 0.476)	0.185	−0.624 (−0.894 to −0.354)	**<0.0001**	−0.294 (−0.589 to 0.001)	0.051	−0.303 (−0.626 to 0.021)	0.067	0.054 (−0.288 to 0.396)	0.755
Motor function														
Manual dexterity	−0.690 (−0.952 to −0.428)	**<0.0001**	−0.495 (−0.832 to −0.158)	0.004	−0.666 (−0.929 to −0.403)	**<0.0001**	−0.424 (−0.676 to −0.173)	0.001	−0.400 (−0.672 to −0.128)	0.004	−0.139 (−0.431 to 0.152)	0.348	−0.310 (−0.623 to 0.002)	0.052
Balance	−0.598 (−0.862 to −0.335)	**<0.0001**	−0.524 (−0.864 to −0.184)	0.003	−0.688 (−0.952 to −0.424)	**<0.0001**	−0.362 (−0.615 to −0.108)	0.005	−0.452 (−0.725 to −0.178)	0.001	−0.139 (−0.433 to 0.156)	0.356	−0.303 (−0.617 to 0.011)	0.059
Aiming and catching	0.338 (0.060 to 0.615)	0.017	0.222 (−0.136 to 0.580)	0.224	0.248 (−0.031 to 0.527)	0.081	−0.107 (−0.374 to 0.160)	0.432	−0.197 (−0.486 to 0.092)	0.182	−0.165 (−0.474 to 0.145)	0.296	−0.139 (−0.470 to 0.193)	0.412
Psychopathology & general functioning														
Inattention, hyperactivity and impulsivity (ADHD-RS)	0.805 (0.517 to 1.093)	**<0.0001**	0.436 (0.062 to 0.810)	0.022	0.343 (0.054 to 0.631)	0.020	0.628 (0.351 to 0.905)	**<0.0001**	0.166 (−0.134 to 0.465)	0.277	0.157 (−0.155 to 0.469)	0.323	0.064 (−0.290 to 0.419)	0.721
Oppositional defiant (ADHD-RS)	0.622 (0.327 to 0.916)	**<0.0001**	0.354 (−0.028 to 0.736)	0.069	0.016 (−0.278 to 0.310)	0.915	0.711 (0.429 to 0.993)	**<0.0001**	0.106 (−0.200 to 0.411)	0.497	0.331 (0.013 to 0.649)	0.041	−0.007 (−0.369 to 0.355)	0.971
CBCL externalizing	0.231 (−0.043 to 0.505)	0.099	0.215 (−0.147 to 0.577)	0.244	−0.156 (−0.432 to 0.121)	0.269	0.746 (0.482 to 1.010)	**<0.0001**	0.359 (0.073 to 0.645)	0.014	0.490 (0.182 to 0.799)	0.002	0.119 (−0.216 to 0.455)	0.484
CBCL internalizing	−0.199 (−0.479 to 0.081)	0.162	−0.336 (−0.708 to 0.036)	0.076	−0.049 (−0.331 to 0.233)	0.734	0.236 (−0.034 to 0.505)	0.086	0.386 (0.094 to 0.678)	0.010	0.180 (−0.135 to 0.495)	0.262	0.467 (0.123 to 0.812)	0.008
Global functioning (CGAS)	−0.369 (−0.634 to −0.104)	0.006	−0.375 (−0.719 to −0.031)	0.033	−0.307 (−0.574 to −0.041)	0.024	−0.666 (−0.921 to −0.411)	**<0.0001**	−0.604 (−0.881 to −0.328)	**<0.0001**	−0.309 (−0.605 to −0.012)	0.041	−0.241 (−0.560 to 0.078)	0.138
Teacher report form externalizing	0.776 (0.489 to 1.063)	**<0.0001**	0.280 (−0.089 to 0.649)	0.137	0.001 (−0.288 to 0.289)	0.996	0.899 (0.624 to 1.175)	**<0.0001**	0.124 (−0.176 to 0.425)	0.416	0.333 (0.022 to 0.644)	0.036	0.054 (−0.296 to 0.404)	0.761
Teacher report form internalizing	0.086 (−0.214 to 0.387)	0.573	−0.124 (−0.511 to 0.262)	0.528	−0.112 (−0.415 to 0.191)	0.467	0.454 (0.165 to 0.742)	0.002	0.255 (−0.059 to 0.570)	0.112	0.323 (−0.003 to 0.650)	0.052	0.336 (−0.031 to 0.702)	0.073
Test observation form – internalizing	−0.033 (−0.314 to 0.248)	0.819	0.214 (−0.149 to 0.577)	0.248	0.055 (−0.228 to 0.339)	0.701	0.295 (0.024 to 0.566)	0.033	0.383 (0.090 to 0.676)	0.011	0.169 (−0.143 to 0.481)	0.288	0.011 (−0.328 to 0.350)	0.951
Test observation form – externalizing	0.438 (0.161 to 0.715)	0.002	0.298 (−0.060 to 0.656)	0.103	0.160 (−0.120 to 0.440)	0.261	0.430 (0.163 to 0.698)	0.002	0.152 (−0.137 to 0.441)	0.302	−0.003 (−0.311 to 0.305)	0.984	−0.141 (−0.475 to 0.193)	0.408
ADHD, K-SADS[a]	0.161 (0.070 to 0.252)	**0.0006**	0.072 (−0.046 to 0.191)	0.230	−0.012 (−0.104 to 0.079)	0.791	0.215 (0.127 to 0.303)	**<0.0001**	0.042 (−0.053 to 0.137)	0.388	0.062 (−0.040 to 0.163)	0.235	−0.023 (−0.133 to 0.086)	0.678
Anxiety disorder, K-SADS[a]	−0.068 (−0.147 to 0.011)	0.090	−0.152 (−0.255 to −0.050)	0.004	−0.018 (−0.097 to 0.061)	0.652	0.047 (−0.029 to 0.122)	0.226	0.097 (0.015 to 0.179)	0.021	0.010 (−0.078 to 0.098)	0.819	0.144 (0.050 to 0.239)	0.003
		0.081		0.126		0.014		0.647		0.790		0.621		0.391

(*Continued*)

Table 2. (*Continued.*)

	Pairwise comparison between sex and familial high-risk group according to Bonferroni correction.													
	Sex differences within familial risk groups						Sex differences between familial risk groups and controls							
	FHR-SZ boys *v.* FHR-SZ girls		FHR-BP boys *v.* FHR-BP girls		Control boys *v.* control girls		FHR-SZ boys *v.* control boys		FHR-SZ girls *v.* control girls		FHR-BP boys *v.* control boys		FHR-BP girls *v.* control girls	
	Cohen's *d* 95% CI	*p* Value	Cohen's *d* 95% CI	*p* Value	Cohen's *d* 95% CI	*p* Value	Cohen's *d* 95% CI	*p* Value	Cohen's *d* 95% CI	*p* Value	Cohen's *d* 95% CI	*p* Value	Cohen's *d* 95% CI	*p* Value
Elimination disorders, K-SADS[a]	0.111 (−0.014 to 0.236)		0.126 (−0.036 to 0.289)		0.157 (0.031 to 0.283)		−0.028 (−0.148 to 0.092)		0.018 (−0.113 to 0.148)		0.035 (−0.104 to 0.175)		0.066 (−0.085 to 0.216)	
Pervasive developmental disorders, K-SADS[a]	0.052 (−0.009 to 0.112)	0.097	0.075 (−0.004 to 0.154)	0.064	0.006 (−0.055 to 0.067)	0.852	0.056 (−0.003 to 0.115)	0.061	0.010 (−0.053 to 0.074)	0.748	0.083 (0.015 to 0.151)	0.017	0.014 (−0.059 to 0.087)	0.705
Stress & adjustment disorders K-SADS[a]	−0.039 (−0.097 to 0.020)	0.194	0.057 (−0.019 to 0.132)	0.144	−0.033 (−0.092 to 0.026)	0.266	0.037 (−0.019 to 0.094)	0.192	0.043 (−0.018 to 0.104)	0.169	0.111 (0.046 to 0.176)	**0.0009**	0.021 (−0.049 to 0.092)	0.554
Disruptive behavior disorders K-SADS[a]	0.092 (0.042 to 0.142)	**0.0004**	0.063 (−0.002 to 0.129)	0.057	−0.022 (−0.073 to 0.029)	0.390	0.103 (0.054 to 0.151)	**<0.0001**	−0.011 (−0.064 to 0.041)	0.672	0.063 (0.007 to 0.120)	0.027	−0.022 (−0.083 to 0.038)	0.472
Home/domestic environment														
Living in sufficient home environment[a]	−0.007 (−0.099 to 0.085)	0.876	0.065 (−0.054 to 0.185)	0.285	0.019 (−0.073 to 0.111)	0.689	−0.201 (−0.289 to −0.113)	**<0.0001**	−0.175 (−0.270 to −0.079)	**0.0004**	−0.027 (−0.130 to 0.075)	0.603	−0.073 (−0.184 to 0.037)	0.193
Living with the index parent[a]	−0.078 (−0.189 to 0.033)	0.169	0.074 (−0.071 to 0.218)	0.316	0.018 (−0.094 to 0.129)	0.755	−0.375 (−0.483 to −0.268)	**<0.0001**	−0.280 (−0.395 to −0.164)	**<0.0001**	−0.219 (−0.343 to −0.094)	**0.0006**	−0.275 (−0.408 to −0.142)	**<0.0001**

The pairwise comparison is the difference in Cohen's delta, where $d = 0.2$ is considered a 'small' effect size, 0.5 represents a 'medium' effect size and 0.8 a 'large' effect size while for binary outcomes (marked as a) the difference is in proportions. Due to the multiple comparisons we used Bonferroni correction for the post-hoc pairwise comparisons and considered p values <0.001 (0.05/50 tests) as significant (marked in bold), to reduce the risk of type I errors when performing multiple comparisons. Index parents refer to the biological parents with either diagnosis of schizophrenia spectrum psychosis or bipolar disorder and their adult matched control.

Discussion

The findings from our register-based cohort of 522 7-year-old children showed for disruptive behavior (either assessed by semi-structural interview, by rating-scales filled out by the primary caregiver and teacher) that the sex difference was greater between boys and girls in the FHR-SZ group compared with the other groups; denoting the FHR-SZ boys had a higher proportion (or with a medium effect) of disruptive behavior compared with FHR-SZ girls. The sex difference for stress & adjustment disorders was larger for boys in the FHR-BP group compared with control boys, whereas no difference detected between FHR-BP girls *v.* control girls. No other modifications between sex and group were evident however, there were similar but large sex differences in the following domains: FHR-SZ boys performed poorer than FHR-SZ girls in manual dexterity and balance, emotion recognition, and had a higher proportion of ADHD diagnoses. We found no sex differences between FHR-BP boys and girls. Within the control group, boys showed poorer manual dexterity and balance compared with girls.

Compared with boys from the control group, FHR-SZ boys exhibited poorer processing speed and working memory, manual dexterity, and social behavior. Additionally, compared with control boys, FHR-SZ boys had a higher proportion of ADHD diagnoses and disruptive behavior disorder, as well as lower levels of general functioning. In addition, a higher proportion of FHR-SZ boys lived in inadequate homes compared with boys from the control group. Thus, impairments within neurodevelopmental domains were most frequently associated with FHR-SZ among boys.

Previous studies examining sex differences in children with a familial risk of schizophrenia or premorbid schizophrenia characteristics have shown that boys display more neurocognitive (Aylward, Walker, & Bettes, 1984; Hans, 1999), motor (Hans, 1999; Marcus, 1985*b*), and behavioral (Watt & Lubensky, 1976) impairments than girls.

Sex differences in motor abilities

Our motor ability findings, which reflect coordination skills, demonstrated sex-based differences both within the FHR-SZ group and within the control group, where boys performed worse than girls in manual dexterity and balance, signifying a possible stereotype sex pattern of motor function. Furthermore, we found that FHR-SZ boys exhibited poorer manual dexterity than control boys. Our results are consistent with evidence from previous studies of high-risk populations. The Copenhagen High-Risk Study, which assessed children of parents with schizophrenia, reported that Danish boys exhibited poorer performance than girls in terms of motor coordination and motor overflow at age 11–13 year (Marcus, 1985*b*). When the children from the Copenhagen High-Risk Study were assessed again at age 31–33 years, the offspring who developed schizophrenia exhibited significantly poorer premorbid coordination skills compared with those who did not develop a mental illness (Schiffman et al., 2009). The Northern Finland Birth Cohort reported that boys who learned to stand without support after 12 months of age had a significantly higher risk of developing schizophrenia, and this was not the case for girls. The earlier the child stood unsupported, the lower the subsequent risk of schizophrenia (Isohanni et al., 2001). Furthermore, the Israeli High-Risk Study assessing 7–14 years old children of a parent with schizophrenia, showed that boys compared with girls exhibited impaired motor coordination and motor overflow/associated movement, but the effect of sex was no longer evident 5 years later (Marcus, 1985*a*). Future studies may evaluate whether motor sex differences are early childhood manifestations, which are transitory and disappear in adolescent/adulthood or whether they persist.

Sex differences in cognition

A cohort study examining premorbid cognitive sex differences at age 16–18 years showed that global cognitive performance/general intelligence was poorer in girls *v.* boys before they developed schizophrenia (Weiser et al., 2000), whereas a meta-analysis showed premorbid IQ deficits were more prevalent among males than females (Aylward et al., 1984). When controlling for multiple comparisons in the present study, we found that FHR-SZ boys and girls at age 7 years exhibited poorer processing speed and working memory compared with controls, but there were no sex-based differences in general intelligence, declarative memory and attention, verbal function, or executive and visuo-spatial function. Although children of parents with schizophrenia have been found to exhibit deficits in neurocognitive functioning compared with controls (Agnew-Blais & Seidman, 2013; Cornblatt, Obuchowski, Roberts, Pollack, & Erlenmeyer-Kimling, 1999; Erlenmeyer-Kimling et al., 2000; Hameed & Lewis, 2016; Ozan et al., 2010), studies examining children and adolescents with a familial risk of bipolar disorder have produced contrasting results. For instance, these children were found to exhibit deficient (Diwadkar et al., 2011; Hemager et al., 2019; Klimes-Dougan, Ronsaville, Wiggs, & Martinez, 2006) and non-deficient attention capacities (Burton et al., 2018; Goetz et al., 2019). Furthermore, none of the mentioned studies reported sex-based differences. Indeed, the heterogeneity of study methods in relation to age and neurocognitive function hinders the comparison of our results with previous data.

Neuropsychiatric and behavioral sex differences

Compared with FHR-SZ girls and controls boys, the FHR-SZ boys in our study showed more behaviors associated with conduct disorder and externalizing behavior problems. This finding is consistent with a previous report that teacher ratings of social maladjustment were higher in 7-year-old children who developed schizophrenia in adulthood (Done, Crow, Johnstone, & Sacker, 1994). Furthermore, teacher ratings of over-reactive social maladjustment behavior (anxiety regarding acceptance, hostility, inconsequential behavior) were higher in boys *v.* girls who developed schizophrenia in adulthood, as well as typically developing children (Done et al., 1994). Furthermore, studies documenting incidence rates derived from register-based nationwide cohorts of children have reported that ADHD and conduct disorder are more common among boys than girls in the general population (Dalsgaard et al., 2020). This supports our finding that FHR-SZ boys had a significantly higher proportion of ADHD diagnoses and disruptive behavior disorders compared with FHR-SZ girls. Moreover, children of parents with severe mental illness are known to have a higher risk of any mental disorder (Rasic, Hajek, Alda, & Uher, 2014). However, the sex-based differences for these disorders were not evident among our control group. This may be due to the relatively low incidence of mental disorders in the general population at this early age, as well as our relatively small control group ($n = 200$), which may have contributed to a lack of power to detect sex-based differences.

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The genetic and environmental exposure

Considering the home environment, our study showed no sex differences within the FHR-SZ group (FHR-SZ boys *v.* FHR-SZ girls), or within the FHR-BP group (FHR-BP boys *v.* FHR-BP girls) or within the control group (Fig. 2). However, a group difference between FHR-SZ and controls was evident showing a higher proportion of boys or girls with FHR-SZ compared with control boys or control girls respectively, lived in insufficient homes (Fig. 3). This was not evident for FHR-BP children compared with controls (Fig. 3). Even though we have tried to avoid environmental confounding by having a matched control group, where we controlled for municipality, sex and age, we could not control for the within family exposure. It would be unethical and impossible to randomized children to be exposed to poor environmental conditions to investigate the interaction between environmental and genetic risk factors.

We know that despite the considerable genetic risk, environmental factors also contribute to the risk of developing severe mental disorders (Van, Kenis, & Rutten, 2010). These environmental exposures range from prenatal factors such as maternal intrauterine infections (Borglum et al., 2014; Brown, 2006; Mednick, Machon, Huttunen & Bonett, 1988; Mortensen et al., 2007) preterm birth and obstetric complications (Byrne, Agerbo, Bennedsen, Eaton & Mortensen, 2007), neonatal vitamin D status (McGrath et al., 2010), childhood maltreatment (Varese et al., 2012) and childhood trauma (Daruy-Filho, Brietzke, Lafer & Grassi-Oliveira, 2011; Morgan & Fisher, 2007), to urbanicity (Vassos, Pedersen, Murray, Collier & Lewis, 2012) and cannabis consumption (Hjorthøj, Posselt & Nordentoft, 2021; Moore et al., 2007). Familial high risk of severe mental disorders may be further explained by the environment in which children of parents with severe mental disorders are raised. Research suggests that a secure attachment between children and their caregivers is a protective factor against mental disorders (Rutter, 1985). However, little is known about the impact of environmental factors associated with being reared by a parent with a severe mental disorder.

It has proven difficult to differentiate between the environmental and genetic contribution to the familial high risk of severe mental disorders, one of the reasons being the presence of gene-environment interactions (Uher, 2014). Individuals with a genetic risk are more vulnerable to environmental risk factors than those without a genetic risk (Uher, 2014). Evidence suggests that individual differences, such as factors fostering resilience, influence the impact and sensitivity of environmental exposure (Collishaw et al., 2007), which may be mediated through genetic factors to some degree (Uher, 2009). However, not all individuals who either carry a genetic risk variant or are exposed to environmental risk factors or both will develop a severe mental disorder in adulthood (Van et al., 2014). Symptoms of vulnerability during childhood can be transitory (Gogtay et al., 2007) but importantly we need to know more about which factors contributing to resilience.

Strengths and limitations

Our study has several major strengths, including the novelty of assessing sex-based differences in a large, same-aged, pre-pubertal sample with a familial risk of severe mental disorders. An advantage of assessing 7-year-old children before puberty is the limited influence of changing levels of hormones, which can contribute to sex differences (Kaczkurkin, Raznahan & Satterthwaite, 2019). Despite the difficulty in disentangling biological sex-based differences from those resulting from environmental and cultural influences, our study included both biological and environmental measures. A limitation of our study is that even though the assessors were blinded to group affiliation, they were not blinded to the sex of the child because the assessments were conducted face-to-face. Thus, scores could have been influenced by social expectations regarding the behavior of boys and girls. However, this influence would have been similar for the FHR groups and controls. Additionally, the cross-sectional nature of the study does not address the effect of development over time. We thus cannot dismiss the possibility that the effect of sex is transitorily and moreover, that girls might show impairments in domains which we have not assessed in this study. Since we did not assess the teacher-pupil relationship, we cannot rule out the possibility that the teachers knew about the familial high-risk disposition of the child, which potentially could have biased their ratings. Furthermore, the parents in the control group had no diagnoses of schizophrenia spectrum disorder or bipolar disorder but could potentially have other somatic and mental health disorders like in the general population. However, the advantage of this method, is the higher generalizability of the findings, in contrast to a more selected population.

To the best of our knowledge, this age-specific study is the first to assess sex-based differences among multiple domains in children with a familial risk of schizophrenia or bipolar disorder. We found that impairments within neurodevelopmental domains associated within FHR-SZ boys *v.* FHR-SZ girls were most evident among boys at age 7. Our results suggest heterogeneity in the development of FHR-children, with distinct sex characteristics among boys and girls with FHR-SZ and not children with FHR-BP. On a group level, boys with FHR-SZ had the highest proportion of neurodevelopmental impairments.

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