



Development of social responsiveness and theory of mind in children of parents with schizophrenia or bipolar disorder

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ABSTRACT

Social impairments are suggested as vulnerability markers for schizophrenia and bipolar disorder. Therefore, we investigated the development of social responsiveness and theory of mind (ToM) in children at familial high-risk of schizophrenia (FHR-SZ) or bipolar disorder (FHR-BP).

This study is part of The Danish High Risk and Resilience Study, a longitudinal cohort study of children at FHR-SZ or FHR-BP and population-based controls (PBC). Social responsiveness was measured with the Social Responsiveness Scale (SRS-2), completed by teachers and primary caregivers. ToM was measured using The Animated Triangles Task (ATT). Both SRS-2 and ATT were applied at age 7 and 11. A total of 520 children participated (FHR-SZ, $n = 201$; FHR-BP, $n = 119$; PBC, $n = 200$).

Results showed no significant time by group interactions. At follow-up, children at FHR-SZ exhibited impaired social responsiveness compared with PBC regardless of the informant. At both timepoints, a higher proportion of children at FHR-SZ were rated at a clinically significant level, implying inference in everyday social interactions. Compared with PBC, primary caregivers reported impairments in social responsiveness in children at FHR-BP at follow-up. The three groups did not differ in ToM at follow-up.

Social responsiveness and ToM do not develop differently in children at FHR-SZ, FHR-BP and PBC from age 7 to 11, but impairments in social responsiveness remain stable and may constitute a vulnerability marker particularly in children at FHR-SZ, but also FHR-BP. ToM abilities seem to improve and remain intact, but ToM development and ToM task properties should be taken into consideration.

1. Introduction

Social impairments are core features of schizophrenia (Green et al., 2015; Burns and Patrick, 2007), and are also well established in bipolar disorder, albeit to a lesser extent (Samamé, 2013; Bora and Pantelis,

2016). Social impairments associated with schizophrenia and bipolar disorder have been examined in various ways focusing on a wide range of different aspects. However, the literature unequivocally suggests that social dysfunction in a broad sense is apparent in both disorders and may serve as a potential vulnerability marker (Burns and Patrick, 2007; Lavoie

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et al., 2013; Bora and Özerdem, 2017; Sanchez-Moreno et al., 2009).

Social abilities are crucial in almost all settings of daily functioning and various social abilities evolve from infancy or childhood, and then develop and change throughout life with adolescence as an essential developmental period (Kilford et al., 2016; Legerstee, 1992; Blakemore, 2008). Results from retrospective and longitudinal studies of adults with schizophrenia or bipolar disorder indicate that social impairments are present during childhood and adolescence before illness onset (Schenkel and Silverstein, 2004; Schiffman et al., 2004; Cannon et al., 1997; Parellada et al., 2017; Payá et al., 2013). Moreover, children and adolescents born to parents with schizophrenia or bipolar disorder, who are at increased risk of developing severe mental disorders due to high heritability rates (Rasic et al., 2013), likewise exhibit impaired social functioning (Gibson et al., 2010; Gkintoni et al., 2017; Shim et al., 2008; Bella et al., 2011).

Taken together, the above-mentioned findings emphasize the importance of examining different social abilities in children at familial high-risk of schizophrenia or bipolar disorder as such research is an effective way of studying potential vulnerability markers (Sandstrom et al., 2019; Stone et al., 2005). Additionally, such research has both functional and clinical importance as it may facilitate early detection by assisting in identification of children at elevated risk (Cotter et al., 2018).

Social responsiveness, often also referred to as social reciprocity, refers to the ability to understand and engage in social interactions with others, which more specifically involves processing social information, comprehending the message being conveyed, and responding appropriately in interpersonal interactions (Constantino et al., 2000). Impaired reciprocal social behavior is typically linked to autism, but is also essential when characterizing the behavior of children whose social deficits fall below the threshold for a diagnosis of autism, but may need support anyway (Constantino et al., 2000; Constantino, 2011). Studies of social responsiveness in individuals with schizophrenia or bipolar disorder as well as in familial high-risk samples are sparse. A prior study documented poorer social responsiveness in adults with schizophrenia and bipolar disorder compared with controls (Matsuo et al., 2015). This is in line with the results from a study of adolescent offspring of parents with bipolar disorder (Whitney et al., 2013). Additionally, in our baseline study, the Danish High Risk and Resilience Study - VIA 7, impairments in social responsiveness were observed at age seven in children at familial high-risk of schizophrenia (FHR-SZ), but not in children at familial high-risk of bipolar disorder (FHR-BP) (Christiani et al., 2019).

Theory of mind (ToM) refers to the ability to infer and predict other people's behavior, intentions, thoughts, beliefs, plans, and desires with an awareness of that these might differ from one's own (Frith and Frith, 2011; Green et al., 2008). Although evident in both schizophrenia and bipolar disorder, findings from a recent meta-analysis indicate that the ToM deficits associated with schizophrenia are more severe (Bora and Pantelis, 2016). Nevertheless, ToM deficits have been considered a candidate endophenotype for both disorders (Bora et al., 2009; Mitchell and Young, 2016), and results from meta-analyses indicate that ToM deficits are also evident in unaffected relatives, although to a lesser extent (Bora and Özerdem, 2017; Bora and Pantelis, 2013; Lavoie et al., 2013). Notably, these meta-analyses primarily rely on studies including adult first-degree relatives and studies of children or adolescents are sparse. A prospective study of children and adolescents with familial high-risk of schizophrenia found that those who later developed schizophrenia had ToM deficits before illness onset compared to those who did not (Schiffman et al., 2004). Similarly, a study of children born to mothers with schizophrenia observed ToM deficits compared with controls (Maróthi and Kéri, 2014). Contrary, another study found no ToM deficits in adolescent first-degree relatives of individuals with schizophrenia (Gibson et al., 2010). Two studies of offspring of parents with bipolar disorder neither observed any ToM deficits (Whitney et al., 2013; Maróthi and Kéri, 2014), which is in line with the results from the VIA 7 study where children at FHR-SZ or FHR-BP exhibited intact ToM abilities at age seven (Christiani et al., 2019). Nevertheless, prospective research implies that lower premorbid social functioning during childhood is associated with more severe ToM

impairment and more pronounced autistic traits after illness onset in individuals with schizophrenia (Schenkel et al., 2005; Bechi et al., 2020).

Notably, the abovementioned familial high-risk studies used a cross-sectional design and relied on children and adolescents with wide age ranges. This challenges the interpretation of results as ToM in particular is a developmental construct involving a progression of insights that unfold and changes through the different phases of childhood (Wellman et al., 2001). Results from newer studies of typically developing children suggest that the simplest aspects of ToM develop in infancy and the pre-school years, whereas developmental onset of more complex aspects occurs in middle childhood and adolescence (Weimer et al., 2021; Peterson and Wellman, 2019).

In the current study, we intended to elucidate whether social responsiveness and ToM constitute potential vulnerability markers. Our main aim was to compare the development of social responsiveness and ToM from age 7 to 11 in children at FHR-SZ, FHR-BP, and population-based controls (PBC). Additionally, we intended to investigate between-group differences in social responsiveness and ToM at age 11.

2. Methods and materials

The data presented in the present paper constitute as part of The Danish High Risk and Resilience Study – VIA, which is a longitudinal, nationwide familial high-risk study (Thorup et al., 2018; Thorup et al., 2015). Baseline data collection took place from January 1st, 2013 to January 31st, 2016 (the VIA 7 study) and follow-up assessment from March 1st, 2016 to June 30th, 2020 (the VIA 11 study). Data collection was primarily carried out in research facilities in Aarhus or Copenhagen, Denmark, and sometimes in the children's homes. Teacher questionnaires were sent to the child's school. Study data was collected and stored using Research Electronic Data Capture tools hosted at the Capital Region of Denmark (Harris et al., 2009; Harris et al., 2019). The assessors were psychologists, medical doctors, or research nurses, all carefully trained and supervised in the applied instruments. Child assessors were blind to familial high-risk status.

2.1. Participants

Initially, 522 seven-year-old children born to parents diagnosed with schizophrenia spectrum psychosis (FHR-SZ, $n = 202$), bipolar disorder (FHR-BP, $n = 120$) or neither of these disorders ($n = 200$) were recruited. Participants were extracted from The Danish Civil Registration System and The Danish Psychiatric Central Research Register (Mors et al., 2011; Pedersen et al., 2006). The PBC were matched one-to-one to the FHR-SZ sample based on age, sex, and municipality. The FHR-BP sample was a non-matched sample, but the children did not differ from the others in terms of sex and age. At four-year follow-up at age 11, a total number of 465 families participated (FHR-SZ, $n = 179$; FHR-BP, $n = 105$; PBC, $n = 181$) corresponding to a retention rate of 89%. At both assessments the primary caregiver was chosen to be the adult knowing the child the best. The primary caregiver selected the teacher who knew the child the best in school settings. Both the primary caregiver and teacher were not necessarily the same at baseline and follow-up. The primary caregiver completed questionnaires concurrently with child participation, whereas teachers received questionnaires by mail.

2.2. Measurements

We applied the same measures at both assessments. However, at baseline we only collected information about social responsiveness from teachers, but primary caregiver ratings were added at follow-up to obtain information from more than one social environment.

2.3. Descriptive and clinical measures

Children's level of functioning was measured with the Children's Global Assessment Scale. Each participating child was rated on a scale ranging from zero to 100, with lower scores reflecting poorer levels of daily functioning (Shaffer et al., 1983). Emotional and behavioral problems were assessed with the Child Behavior Checklist, School-Age version (CBCL), filled out by

the primary caregiver. A higher CBCL total score indicate more problem behavior (Achenbach and Rescorla, 2001). The Personal and Social Performance Scale (PSP) was applied to measure the primary caregivers' daily level of functioning. The PSP global score range from zero to 100 with higher scores indicating better functioning (Morosini et al., 2000).

2.4. Social responsiveness

We used the Social Responsiveness Scale, Second Edition, School-Age Form (SRS-2) to assess the children's social responsiveness in their natural social contexts. SRS-2 is a well-validated 65-item rating scale designed to identify the presence and severity of social impairments associated with autism spectrum disorders (Constantino and Gruber, 2012). The questionnaire is based on the child's behavior for the last 6 months and each question is answered on a four-point Likert-scale (1 = not true; 2 = sometimes true; 3 = often true; 4 = almost always true). SRS-2 provides a global score where the maximum raw score is 195, with higher scores reflecting greater severity of social responsiveness impairment. Scores from 60 to 80 indicate deficiencies that are clinically significant and result in mild to moderate interference in everyday social interactions (Constantino and Gruber, 2012, Constantino and Todd, 2005). The scale can be divided into two well-validated and highly correlated subscales; Social Communication and Interaction (SCI) and Restricted Interests and Repetitive Behavior (RIRB) (Frazier et al., 2014).

2.5. Theory of mind

We assessed ToM with the Animated Triangles Task (ATT) consisting of short movie clips with two animated triangles moving around either in an intentionally or arbitrary manner. There are four movies of each type of animation lasting from 38 to 41 s (Abell et al., 2000; Castelli et al., 2000). After each movie clip, the children were asked to give a free description of what they thought was happening. The children's descriptions were recorded and transcribed. Their answers were rated according to the published set of scoring criteria (Castelli et al., 2002; Castelli et al., 2000; Abell et al., 2000), that is regarding intentionality, referring to the degree of mental state attribution (ranging from 0 to 5, with a score of 4 or 5 indicating ToM) and appropriateness, referring to how well the intended script was captured (ranging from 0 to 3, where 3 reflects a perfect description). Afterwards, these ratings were summarized to calculate the total scores (ToM intentionality, ToM appropriateness, random intentionality, and random appropriateness). See Supplementary 1 and Table

S1 for a detailed description of the scoring process including intra-class correlation analyses of inter-rater agreements.

2.6. Statistical analyses

One-way ANOVA or chi-square tests were used in analyses of descriptive and clinical characteristics followed by pairwise comparisons, when relevant. As advised in the manual, missing items on SRS-2 were assigned with the particular item's median score with a maximum of six missing responses for each respondent (Constantino and Gruber, 2012). Dropout analyses were performed using *t*-tests and chi-square tests.

Developmental differences and between-group differences at each assessment point on the outcome variables from ATT and SRS-2 teacher ratings were examined with multilevel mixed-effects linear regression models with a random intercept at id-level including the outcome of interest, time, high-risk group, and time x group. Missing data was handled in the analyses by the maximum-likelihood method. For the SRS-2 primary caregiver ratings, where data only was available at follow-up, between-group differences were examined using multiple linear regression analyses with each SRS-2 outcome as the dependent variable and high-risk status as the independent variable. Due to evidence that social responsiveness and ToM abilities are sex dependent (Devine and Hughes, 2013; Hus et al., 2013; Ibanez et al., 2013), all models were adjusted for sex.

A clinical cutoff score of or above 70 raw score points on the total scale was established based on the recommendations in the SRS-2 manual (Constantino and Gruber, 2012). Between-group differences in the proportion of children rated at a clinically significant level were ascertained with chi-square tests. For exploratory analyses of ToM, where the groups were defined based on the SRS-2 clinically cutoff score, between-group differences were examined using *t*-tests.

Effect sizes were calculated cross-sectionally using Cohen's *d* (small, 0.2; medium, 0.5; and large, 0.7) (Cohen, 1988). Alpha level was set to 0.05 for all statistical analyses and the false discovery rate in the multiple comparisons were calculated according to the Benjamini-Hochberg correction procedure with the *q*-value set to 0.05 (Benjamini and Hochberg, 1995). All analyses were conducted using Stata IC software, version 16.1 (StataCorp, 2019).

3. Results

3.1. Sample characteristics

Data from 458 children (FHR-SZ, *n* = 175; FHR-BP, *n* = 104; PBC, *n*

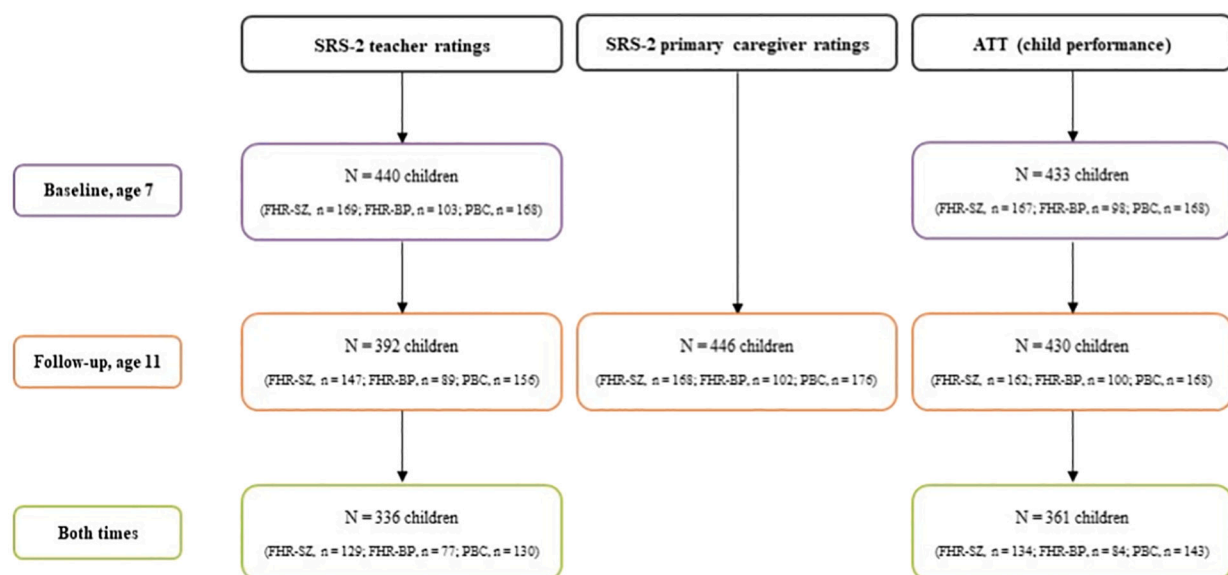


Fig. 1. Flowchart illustrating available data on each measurement at each assessment point.

Abbreviations: Familial high-risk of schizophrenia (FHR-SZ), Familial high-risk of bipolar disorder (FHR-BP), Population-based controls (PBC), Social Responsiveness Scale, Second Edition (SRS-2), The Animated Triangles Task (ATT).

Table 1
Demographic and clinical characteristics of the participants at follow-up assessment at age 11.

	FHR-SZ	FHR-BP	PBC	p-Value	Pairwise comparisons		
					FHR-SZ vs PBC	FHR-BP vs PBC	FHR-SZ vs FHR-BP
					p-Value		
Children, N*	175	104	179	–	–	–	–
Female, N (%)	83 (47.43)	46 (44.23)	83 (46.37)	0.874 ^C	–	–	–
Age at inclusion, mean (SD)	11.96 (0.27)	11.94 (0.22)	11.93 (0.22)	0.676 ^A	–	–	–
C-GAS ^a , mean (SD)	64.55 (15.65)	68.12 (14.94)	75.17 (13.97)	<0.001^A	<0.001^A	<0.001^A	0.063 ^A
CBCL ^b , mean (SD)	23.70 (20.55)	21.61 (21.24)	12.75 (12.66)	<0.001^A	<0.001^A	<0.001^A	0.426 ^A
Primary caregivers, N	168	102	176	–	–	–	–
PSP total score ^c , mean (SD)	70.44 (16.49)	71.76 (15.53)	83.21 (10.22)	<0.001^A	<0.001^A	<0.001^A	0.513 ^A
Educational level^d:							
Primary/lower secondary, N (%)	43 (25.60)	18 (17.82)	26 (14.86)	0.057 ^C	–	–	–
Upper secondary, vocational, short-cycle tertiary, N (%)	50 (29.76)	24 (23.76)	52 (29.71)				
Bachelor degree, equivalent or higher, N (%)	75 (44.64)	59 (58.42)	97 (55.43)				
Lived with the child for the past 6 months^e:							
All the time, N (%)	152 (91.02)	90 (87.82)	165 (94.83)	0.175 ^C	–	–	–
Less than all the time, but at least half of the time, N (%)	11 (6.59)	10 (9.80)	9 (5.17)				
Less than half of the time or not at all, N (%)	4 (2.40)	2 (1.96)	0 (0)				
Primary caregiver is index ^f (%)	78 (58.65)	55 (41.35)	0 (0)	<0.001^C	<0.001^C	<0.001^C	0.232 ^C
Teachers, N	147	89	156	–	–	–	–
Known the child^g:							
Below 6 months, N (%)	9 (6.29)	9 (10.47)	8 (5.26)	0.653 ^C	–	–	–
6–12 months, N (%)	17 (11.89)	10 (11.63)	19 (12.5)				
More than 12 months, N (%)	117 (81.82)	67 (77.91)	125 (82.24)				

Abbreviations: Familial high-risk of schizophrenia (FHR-SZ), Familial high-risk of bipolar disorder (FHR-BP), Population-based controls (PBC), Children's Global Assessment Scale (C-GAS), Child Behavior Checklist School-Age version (CBCL), Personal and Social Performance Scale (PSP).

* Includes participating children on ATT and children rated on SRS-2 by either primary caregiver and/or teacher.

^a Ranging from zero to 100, with lower scores reflection poorer global functioning. C-GAS scores in this sample range from 33 to 98 (FHR-SZ, $n = 171$; FHR-BP, $n = 104$; PBC, $n = 175$).

^b Completed by the primary caregiver. Ranging from zero to 266, with higher scores reflecting more problem behavior. CBCL scores in this sample range from 0 to 126 (FHR-SZ, $n = 165$; FHR-BP, $n = 102$; PBC, $n = 173$).

^c Global score ranging from zero to 100, with higher scores reflecting better functioning. PSP scores in this sample range from 29 to 99 (FHR-SZ, $n = 167$; FHR-BP, $n = 102$; PBC, $n = 173$).

^d Based on data from $N = 444$ primary caregivers (FHR-SZ, $n = 168$; FHR-BP, $n = 101$; PBC, $n = 175$).

^e Based on data from $N = 443$ primary caregivers (FHR-SZ, $n = 167$; FHR-BP, $n = 102$; PBC, $n = 174$).

^f Index refers to whether the primary caregiver is the parent diagnosed with schizophrenia or bipolar disorder, but is not a measure of current illness severity.

^g Based on data from $N = 381$ teachers (FHR-SZ, $n = 143$; FHR-BP, $n = 86$; PBC, $n = 152$).

^A One-way ANOVA, significance level $p < .05$. Significant findings are marked with bold typing in the table.

^C Chi-square test, significance level $p < .05$. Significant findings are marked with bold typing in the table.

= 179) were available at follow-up on ATT and/or SRS-2 primary caregiver and/or teacher ratings (see Fig. 1). Demographics and clinical characteristics of the participants at the follow-up assessment are detailed in Table 1.

Results from dropout analyses comparing baseline SRS-2 teacher global scores and ATT total scores for those children participating at both assessments with those children solely participating at age seven showed no essential differences (see Supplementary 2). Main reasons for dropout were serious illness in the family and lack of time or energy to participate in the study.

3.2. Social responsiveness

No time by group interactions were observed on the SRS-2 teacher ratings between FHR-SZ and PBC (Global score, $p = .552$; SCI, $p = .733$; RIRB, $p = .130$), FHR-BP and PBC (Global score, $p = .991$; SCI, $p = .994$; RIRB, $p = .968$), or FHR-SZ and FHR-BP (Global score, $p = .600$; SCI, $p = .763$; RIRB, $p = .178$) (see Fig. S1). At age 11, children at FHR-SZ

exhibited impairments regarding social responsiveness compared with PBC regardless of the informant, primarily with medium effect sizes. Primary caregivers rated children at FHR-BP higher on all SRS-2 measures compared with PBC (with small effect sizes). The two familial high-risk groups differed solely on the teacher-rated RIRB subscale at age 11 with children at FHR-SZ having a higher score than children at FHR-BP (see Table 2).

At baseline, 41 children were rated at a clinically relevant level on SRS-2 (FHR-SZ, $n = 22$; FHR-BP, $n = 12$; PBC = 7) revealing that significantly more children at FHR-SZ and FHR-BP were rated at a clinically significant level by their teacher compared with PBC. At follow-up, 38 children were rated at a clinically relevant level by their teacher (FHR-SZ, $n = 24$; FHR-BP, $n = 8$; PBC, $n = 6$) with significantly more children at FHR-SZ compared with PBC. Finally, 34 children were rated at a clinically relevant level by their primary caregiver (FHR-SZ, $n = 20$; FHR-BP, $n = 9$; PBC, $n = 5$) with significantly more children at FHR-SZ compared with PBC (see Fig. 2 and Table S2).

Table 2
Ratings on The Social Responsiveness Scale, second edition, presented with raw scores.

	FHR-SZ	FHR-BP	PBC	Pairwise comparisons		
				FHR-SZ vs PBC	FHR-BP vs PBC	FHR-SZ vs FHR-BP
	Mean (95% CI)			p-Value (d)		
Baseline, age 7, teacher^a						
Global score	37.77 (34.00–41.54)	31.85 (27.03–36.68)	23.96 (20.19–27.73)	<0.001 (0.58)	0.012 (0.33)	0.058 (0.20)
Social Communication and Interaction (SCI) ^c	33.14 (30.05–36.87)	28.50 (24.10–32.00)	21.42 (18.33–24.51)	<0.001 (0.59)	0.010 (0.34)	0.047 (0.21)
Restricted Interests and Repetitive Behavior (RIRB) ^c	4.64 (3.86–5.43)	3.81 (2.80–4.81)	2.53 (1.75–3.32)	<0.001 (0.44)	0.050 (0.26)	0.197 (0.14)
Follow-up, age 11, teacher^a						
Global score	40.64 (36.63–44.65)	32.69 (27.53–37.85)	24.84 (20.94–28.74)	<0.001 (0.64)	0.017 (0.35)	0.017 (0.30)
Social Communication and Interaction (SCI) ^c	34.82 (31.53–38.11)	28.77 (24.54–32.99)	22.61 (18.97–25.36)	<0.001 (0.63)	0.015 (0.36)	0.028 (0.29)
Restricted Interests and Repetitive Behavior (RIRB) ^c	5.82 (4.98–6.65)	3.92 (2.84–4.99)	2.67 (1.86–3.84)	<0.001 (0.61)	0.070 (0.27)	0.006 (0.33)
Follow-up, age 11, primary caregiver^b						
Global score	35.20 (31.54–38.87)	30.94 (26.25–35.36)	21.23 (17.66–24.80)	<0.001 (0.59)	0.001 (0.46)	0.160 (0.14)
Social Communication and Interaction (SCI) ^c	30.26 (27.33–33.19)	26.04 (22.27–29.80)	18.71 (15.86–21.57)	<0.001 (0.60)	0.002 (0.44)	0.083 (0.18)
Restricted Interests and Repetitive Behavior (RIRB) ^c	4.94 (4.11–5.77)	4.76 (3.69–5.82)	2.52 (1.71–3.33)	<0.001 (0.45)	0.001 (0.27)	0.793 (0.23)

Abbreviations: Familial high-risk of schizophrenia (FHR-SZ), Familial high-risk of bipolar disorder (FHR-BP), Population-based controls (PBC), Social Responsiveness Scale, Second Edition (SRS-2), Confidence Intervals (CI), *d* = Cohens *d*, p-value = significance level $p < .010$ after correction according to the Benjamini-Hochberg procedure.

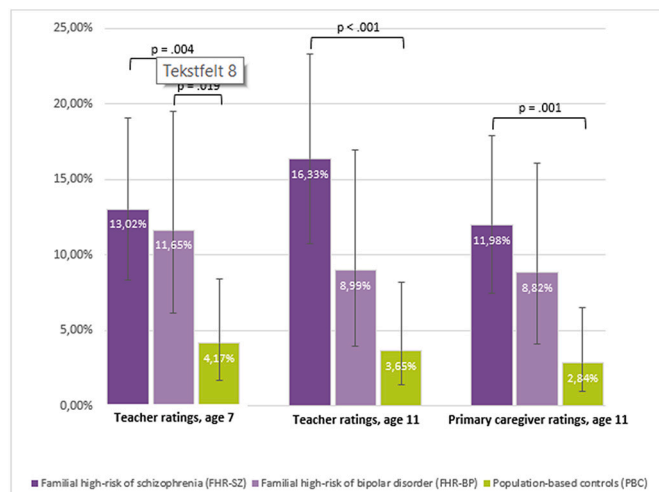
Significant findings are marked with bold typing in the table.

Note: The results from the baseline study have already been presented elsewhere (Christiani et al., 2019). Due to methodological differences, divergencies exist between the previous published results and the baseline results presented here.

^a Analyses are based on 496 children rated either at baseline (FHR-SZ, $n = 169$; FHR-BP, $n = 103$; PBC, $n = 168$) or follow-up (FHR-SZ, $n = 147$; FHR-BP, $n = 89$; PBC, $n = 156$), of whom 336 were rated by a teacher at both assessments (FHR-SZ, $n = 129$; FHR-BP, $n = 77$; PBC: 130).

^b Analyses are based on 446 children (FHR-SZ, $n = 168$; FHR-BP, $n = 102$; PBC, $n = 176$).

^c DSM-V compatible subscales.



Note: Between-group differences of the proportion of children rated above the SRS-2 clinically relevant cutoff were calculated with chi-square tests. Significance level $p < .022$ after correction according to the Benjamini-Hochberg procedure. 95% confidence intervals: Teacher ratings, age 7 (FHR-SZ, 8.34–19.04; FHR-BP, 6.17–19.47; PBC, 1.69–8.40), teacher ratings, age 11 (FHR-SZ, 10.75–23.31; FHR-BP, 3.96–16.93; PBC, 1.42–8.18), primary caregiver ratings, age 11 (FHR-SZ, 7.47–17.89; FHR-BP, 4.11–16.09; PBC, 0.93–6.50).

Fig. 2. Proportion of children rated at a clinically significant level (global score ≥ 70) on the Social Responsiveness Scale, Second Edition, by teacher or primary caregiver.

3.3. Theory of mind

No differences in ToM between the three groups were observed (see Table 3). Additionally, no time by group interactions on the measures from ATT were found between FHR-SZ and PBC (ToM intentionality, $p = .406$; ToM appropriateness, $p = .608$; random intentionality, $p = .565$; random appropriateness, $p = .721$), FHR-BP and PBC (ToM intentionality, $p = .851$; ToM appropriateness, $p = .789$; random intentionality, $p = .805$; random appropriateness, $p = .219$), or FHR-SZ and FHR-BP (ToM intentionality, $p = .589$; ToM appropriateness, $p = .857$; random intentionality, $p = .798$; random appropriateness, $p = .359$) (see Fig. S2).

Explorative analyses for the ATT follow-up data, where the children were divided into two groups based on the SRS-2 clinically relevant level, revealed that the 45 children (FHR-SZ, $n = 25$; FHR-BP, $n = 12$; PBC, $n = 8$) rated at a clinically significant level on SRS-2 at age 11 exhibited impaired ToM compared with children rated below the SRS-2 clinically relevant level (ToM intentionality, $p = .004$, $d = 0.47$; ToM appropriateness, $p = .001$, $d = 0.53$) (see Table S3).

4. Discussion

In this longitudinal, nationwide cohort study, we investigated social responsiveness and ToM as potential vulnerability markers of schizophrenia and bipolar disorder by examining the development in children born to parents diagnosed with one of these mental disorders and

Table 3
Theory of mind performance based on the Animated Triangles Task.

	FHR-SZ	FHR-BP	PBC	Pairwise comparisons		
				FHR-SZ vs PBC	FHR-BP vs PBC	FHR-SZ vs FHR-BP
	Mean (95% CI)			p-Value (<i>d</i>)		
Baseline, age 7						
ToM intentionality	11.78 (11.32–12.24)	11.96 (11.37–12.54)	11.71 (11.24–12.17)	0.828 (0.05)	0.507 (0.08)	0.636 (0.03)
ToM appropriateness	4.73 (4.50–4.96)	4.97 (4.86–5.26)	4.83 (4.60–5.06)	0.567 (0.06)	0.441 (0.15)	0.201 (0.21)
Random intentionality	5.34 (4.92–5.75)	5.18 (4.64–5.72)	4.99 (4.56–5.42)	0.267 (0.12)	0.605 (0.06)	0.655 (0.06)
Random appropriateness	6.81 (6.44–7.19)	7.19 (6.70–7.68)	6.95 (6.57–7.34)	0.601 (0.06)	0.476 (0.09)	0.234 (0.15)
Follow-up, age 11						
ToM intentionality	14.20 (13.76–14.65)	14.64 (14.07–15.21)	14.48 (14.04–14.91)	0.392 (0.10)	0.658 (0.05)	0.238 (0.14)
ToM appropriateness	6.76 (6.54–6.98)	7.04 (6.76–7.33)	6.96 (6.75–7.18)	0.193 (0.12)	0.666 (0.04)	0.120 (0.16)
Random intentionality	3.42 (3.00–3.85)	3.39 (2.87–3.92)	3.33 (2.92–3.75)	0.764 (0.04)	0.860 (0.02)	0.931 (0.01)
Random appropriateness	8.40 (8.01–8.78)	8.38 (7.90–8.85)	8.68 (8.30–9.05)	0.307 (0.12)	0.313 (0.13)	0.942 (0.02)

Abbreviations: Familial high-risk of schizophrenia (FHR-SZ), Familial high-risk of bipolar disorder (FHR-BP), Population-based controls (PBC), Theory of mind (ToM), Confidence Intervals (CI), d = Cohens d , p-value = significance level $p < .010$ after correction according to the Benjamini-Hochberg procedure.

Note: The results from the baseline study have already been presented elsewhere (Christiani et al., 2019). Due to methodological differences, divergencies exist between the previous published results and the baseline results presented here.

For the ToM intentionality, ToM appropriateness, and random appropriateness scores a higher score is preferable, whereas for the random intentionality score a lower score is preferable.

Analyses are based on 502 children participating either at baseline (FHR-SZ, $n = 167$; FHR-BP, $n = 98$; PBC, $n = 168$) or follow-up (FHR-SZ, $n = 162$; FHR-BP, $n = 100$; PBC, $n = 168$), of whom 361 participated at both assessments (FHR-SZ, $n = 134$; FHR-BP, $n = 84$; PBC: 143).

controls. The results indicate that social responsiveness and ToM do not develop differently in children at FHR-SZ, FHR-BP and PBC from age 7 to 11. However, children in the two familial high-risk groups displayed impairments in social responsiveness, but not ToM.

In line with results from the baseline study (Christiani et al., 2019), children at FHR-SZ displayed impairments in social responsiveness compared to PBC at age 11. To our knowledge, no other study has examined social responsiveness in children at familial high-risk of schizophrenia, but comparable to our study, previous studies using other measurements have found impaired social functioning and poor social skills (Gibson et al., 2010; Gkintoni et al., 2017; Shim et al., 2008). Further, our results revealed no between-group differences in the development of social responsiveness, indicating that social responsiveness impairments in children at FHR-SZ remain stable from age 7 to 11 and are thereby detectable at an early age. Moreover, 12–16% of the children at FHR-SZ were rated at a clinically significant level compared to 3–4% in the PBC group. This underlines the clinical relevance of our findings and highlights the importance of designing intervention studies and supportive initiatives for children with social impairments as such interventions may serve as an important strategy for preventing further decline in social abilities and development of mental disorders. Recently, social cognitive training have been shown to improve social functioning and social cognitive abilities in young individuals at clinical high-risk of psychosis (Friedman-Yakoobian et al., 2020). Additionally, integrated psychological interventions including social skills training have been documented to prevent or delay progression into psychosis in young individuals with prodromal psychotic symptoms (Nordentoft et al., 2006; Bechdolf et al., 2012; van der Gaag et al., 2013). Likewise, individuals diagnosed with schizophrenia seem to benefit from interventions targeting social cognition and social functioning in the early stage of psychosis (Yamada et al., 2019). Nevertheless, preventative intervention studies focusing on first-degree relatives, including children at familial high-risk of schizophrenia, are still lacking.

For children at FHR-BP the results are more ambiguous as primary

caregivers report social responsiveness impairments compared with PBC at age 11, whereas teachers do not. The results based on teacher ratings are in line with results from the baseline study at age seven (Christiani et al., 2019), as well as another study examining social functioning more broadly (Reichart et al., 2007). However, these findings are incongruent to results from other studies reporting poorer social functioning in children and adolescents at familial high-risk of bipolar disorder (Bella et al., 2011; Gkintoni et al., 2017), as well as with results from the only prior study using SRS-2 to examine adolescents of parents with bipolar disorder (Whitney et al., 2013). Notably, all participants in this latter study exhibited some degree of psychopathology, but not fully symptomatic bipolar disorder. Moreover, they used SRS-2 parent ratings and so their results may be more comparable to the findings from the primary caregiver ratings in our study.

Remarkably, the SRS-2 mean scores from our study revealed that primary caregivers in all three groups in general reported less impairments than teachers. Further, differences in teacher ratings between FHR-BP and PBC at age 11 did not remain significant after correction for multiple comparisons. This discrepancy between primary caregiver and teacher ratings may be due to that children often behave differently depending on the environmental context. In other words, the results may simply be an expression of different social behaviors at home and in school. Similarly, some difficulties may be more evident in certain social situations, and primary caregivers and teachers may perceive the degree of difficulties differently (Kanne et al., 2009). This emphasizes the importance of using multiple sources of information when examining social abilities in children (De Los Reyes, 2011; Jepsen et al., 2012).

Surprisingly, children across the three groups did not differentiate in their ToM abilities at age 11, which thus is in line with the results from the baseline study (Christiani et al., 2019). Contrary, this finding is inconsistent with results from previous meta-analyses of ToM in first-degree relatives of schizophrenia or bipolar disorder (Bora and Özerdem, 2017; Bora and Pantelis, 2013; Lavoie et al., 2013). As previously mentioned, these meta-analyses primarily relied on studies of

adults, thereby missing the developmental aspect. In comparison with studies of children or adolescents of parents with schizophrenia or bipolar disorder our results are equivalent to some (Gibson et al., 2010; Whitney et al., 2013; Maróthi and Kéri, 2014), but incongruent with others (Schiffman et al., 2004; Maróthi and Kéri, 2014). One possible explanation of divergent results in this field is the appliance of different ToM tasks. To our knowledge, we are the first to study ToM in children at FHR-SZ or FHR-BP using ATT, which is an example of a more advanced ToM test (compared to e.g. false-belief tests) suggested to be a relatively pure measure of ToM not influenced by other demands (Wilson, 2021), and without ceiling effects (Bundsgaard and Bliksted, 2019). Nevertheless, our results indicate that 11-year-old children at FHR-SZ or FHR-BP display intact ToM at this stage. However, it is possible that ToM impairments will emerge later as recent research indicate that adolescence is a crucial period for the development of more complex ToM components (Meinhardt-Injac et al., 2020). Even though the children across all three groups showed improvement in ToM from age 7 to 11, their mean values do not attain the same level as in healthy adults (Bundsgaard and Bliksted, 2019). Non-differentiation between groups may also be due to ATT being a task proper for detection of severe ToM deficits, as results from explorative analyses indicated that children rated at a clinically relevant level on SRS-2 exhibited ToM deficits compared to children not rated at a clinically relevant level. Thereby, ATT may not be a suitable task to detect subtle ToM deficits as one would expect to see in children at FHR-SZ or FHR-BP (Bora and Özerdem, 2017; Bora and Pantelis, 2013; Lavoie et al., 2013).

The current study has several strengths. It is one of the largest familial high-risk studies to date examining social impairments in both FHR-SZ, FHR-BP, and PBC. The longitudinal design enables developmental investigation, and the narrow age-range makes the findings less likely to be obscured by age-related differences. Capturing both teacher and primary caregiver ratings enabled us to examine social responsiveness in multiple contexts strengthening and nuancing the interpretation of our results. However, some limitations should also be noted. The FHR-BP group is smaller than the two other groups diminishing the possibility of capturing subtle differences. We only collected SRS-2 ratings from primary caregivers at follow-up, precluding us to examine the development for this measure. Likewise, we only applied a single (advanced) ToM task, conceivably not appropriate to capture subtle ToM deficits. Nevertheless, ATT enables appliance of the same ToM task in future follow-up studies in this cohort as it is also a suitable task for assessment beyond childhood (Wilson, 2021).

5. Conclusion

Social responsiveness impairments are detectable early in development and remain stable from age 7 to 11 in children at FHR-SZ, while children at FHR-BP solely exhibit impairments at age 11, and only according to primary caregivers. These findings indicate that social responsiveness impairments may constitute a vulnerability marker and emphasize the importance of designing preventative intervention strategies targeting children with poor social abilities. Contrary, ToM appear to remain intact in children at FHR-SZ or FHR-BP at age 11, but developmental aspects and ToM task properties should be considered. More prospective research is warranted, and future studies should apply various ToM tasks.

Ethical statement

The Danish High Risk and Resilience Study – VIA 11 was approved by the Danish Data Protection Agency (dispensation from 1st of March 2017). The National Committee on Health Research Ethics deemed ethical approval unnecessary due to the observational nature of the study (ref. H16043682). The study complies with the principles in the Declaration of Helsinki. All participants received written and verbal information about the study and written informed consent was obtained

from the legal guardians of the participating children and from the participating adults themselves.

Role of funding source

The study sponsors solely provided financial support and had no additional involvement in the study design, data collection, or preparation of the manuscript.

CRediT authorship contribution statement

Lotte Veddem: Conceptualization, Methodology, Formal analysis, Investigation, Visualization, Writing – original draft. **Aja Neergaard Greve:** Conceptualization, Project administration, Writing – review & editing. **Anna Krogh Andreassen:** Investigation, Writing – review & editing. **Christina Bruun Knudsen:** Investigation, Writing – review & editing. **Julie Marie Brandt:** Investigation, Writing – review & editing. **Maja Gregersen:** Investigation, Writing – review & editing. **Mette Falkenberg Krantz:** Investigation, Writing – review & editing. **Anne Søndergaard:** Investigation, Writing – review & editing. **Jessica Ohland:** Data curation, Writing – review & editing. **Birgitte Klee Burton:** Writing – review & editing. **Jens Richardt Møllegaard Jepsen:** Writing – review & editing. **Nicoline Hemager:** Project administration, Writing – review & editing. **Anne Amalie Elgaard Thorup:** Project administration, Writing – review & editing. **Merete Nordentoft:** Funding acquisition, Project administration, Writing – review & editing. **Ole Mors:** Funding acquisition, Project administration, Writing – review & editing. **Vibeke Bliksted:** Conceptualization, Project administration, Writing – review & editing.

Declaration of competing interest

All authors on the manuscript entitled ‘Development of social responsiveness and theory of mind in children of parents with schizophrenia or bipolar disorder’ submitted to the special issue ‘**The Evolution of Cognitive Impairment in Schizophrenia**’ to be published in *Schizophrenia Research – Cognition* declare no conflicts of interest.

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Appendix A. Supplementary data

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