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Social Cognition, Language, and Social Behavior in 7-Year-Old Children at Familial High-Risk of Developing Schizophrenia or Bipolar Disorder: The Danish High Risk and Resilience Study VIA 7—A Population-Based Cohort Study

Camilla Jerlang Christiani*[,1,2], Jens R. M. Jepsen[1,2,3,4], Anne Thorup[1,2], Nicoline Hemager[1,2,3], Ditte Ellersgaard[1,2], Katrine S. Spang[2,3], Birgitte K. Burton[2,3], Maja Gregersen[1,2], Anne Søndergaard[1,2], Aja N. Greve[2,5], Ditte L. Gantriis[2,5], Gry Poulsen[2,6], Md Jamal Uddin[2,6], Larry J. Seidman[7,†], Ole Mors[2,5], Kerstin J. Plessen[2,3,8], and Merete Nordentoft[1,2,9]

[1]Mental Health Centre, Mental Health Services in the Capital Region of Denmark, Copenhagen, Denmark; [2]The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Denmark, [3]Child and Adolescent Mental Health Centre, Mental Health Services in the Capital Region of Denmark, Copenhagen, Denmark; [4]Center for Neuropsychiatric Schizophrenia Research and Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research, Mental Health Services in the Capital Region of Denmark, Copenhagen, Denmark; [5]Psychosis Research Unit, Aarhus University Hospital, Aarhus, Denmark; [6]Department of Public Health, Section of Biostatistics, University of Copenhagen, Copenhagen, Denmark; [7]Department of Psychiatry, Harvard Medical School at Beth Israel Deaconess Medical Center, Boston, MA; [8]Services of Child and Adolescent Psychiatry, Department of Psychiatry, University Hospital of Lausanne, Lausanne, Switzerland; [9]Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

[†]These authors contributed equally to the article.

*To whom correspondence should be addressed; Mental Health Centre Copenhagen, Research Unit, The Danish High Risk and Resilience Study VIA 7; Kildegaardsvej 28, 15., 1., 2900 Hellerup, Denmark; tel: +4520220285; e-mail: camilla.austa.christiani@regionh.dk

Objective: **To characterize social cognition, language, and social behavior as potentially shared vulnerability markers in children at familial high-risk of schizophrenia (FHR-SZ) and bipolar disorder (FHR-BP).** ***Methods:*** **The Danish High-Risk and Resilience Study VIA7 is a multisite population-based cohort of 522 7-year-old children extracted from the Danish registries. The population-based controls were matched to the FHR-SZ children on age, sex, and municipality. The FHR-BP group followed same inclusion criteria. Data were collected blinded to familial high-risk status. Outcomes were social cognition, language, and social behavior.** ***Results:*** **The analysis included 202 FHR-SZ children (girls: 46%), 120 FHR-BP children (girls: 46.7%), and 200 controls (girls: 46.5%). FHR-SZ children displayed significant deficits in language (receptive: $d = -0.27$, $P = .006$; pragmatic: $d = -0.51$, $P < .001$), social responsiveness ($d = -0.54$, $P < .001$), and adaptive social functioning ($d = -0.47$, $P < .001$) compared to controls after Bonferroni correction. Compared to FHR-BP children, FHR-SZ children performed significantly poorer on adaptive social functioning ($d = -0.29$, $P = .007$) after Bonferroni correction. FHR-BP and FHR-SZ children showed no significant social cognitive impairments compared to controls after Bonferroni correction.** ***Conclusion:*** **Language, social responsiveness, and adaptive social functioning deficits seem associated with FHR-SZ but not FHR-BP in this developmental phase. The pattern of results suggests adaptive social functioning impairments may not be shared between FHR-BP and FHR-SZ in this developmental phase and thus not reflective of the shared risk factors for schizophrenia and bipolar disorder.**

Key words: neurodevelopment/theory of mind, facial affect identification/language/social functioning/offspring

Introduction

Schizophrenia and bipolar disorder are severe mental diseases with a high hereditability and a partly shared genetic susceptibility.[1,2] Both schizophrenia and bipolar disorder are conceptualized as neurodevelopmental disorders,[3] and a substantial body of studies has supported the neurodevelopmental model of schizophrenia, whereas it is less well validated for bipolar disorder.[4] Vulnerability markers characterizing the aberrant developmental path of schizophrenia are present in domains of psychopathology, cognition, motor, and social behavior with abnormal development commencing in the childhood and adolescent years.[5–9] The domains of psychopathology and cognition have been suggested as possible vulnerability markers in individuals at-risk of bipolar disorder, although studies are fewer and results more divergent than for studies of at-risk populations of schizophrenia.[10–12] Thus, the characterization of shared or distinct vulnerability markers associated to later development of schizophrenia or bipolar disorder is important as it provides a window into the etiopathology and pathophysiology of these severe mental diseases. Furthermore, it might contribute to the early identification of individuals at high-risk, and also, specify relevant domains to target in intervention programs in the premorbid phase.[13,14]

In later decades, the domains of social cognition, language, and social behavior have been studied more

intensively in individuals at genetic risk, in at-risk populations in the prodromal phase, and in first-episode psychosis and later phases of schizophrenia.[15–19] In the domain of social cognition,[20,21] especially in aspects of Theory of Mind and emotion recognition, impairments have been found in offspring at-risk of schizophrenia and in at-risk individuals who later transitioned into psychosis, although some studies found no differences compared to typically developing individuals.[15,16,22,23] The developmental path for the different aspects of social cognition, including whether deficits follow a developmental lag or are static over time is less clear but important considering that social cognitive functioning continues to develop into early adulthood.[24] Thus, divergent trajectories for social cognitive functioning could explain differences in results. Studies of individuals at clinical high-risk of psychosis also found that the developmental trajectory for Theory of Mind and emotion perception followed a different trajectory than in healthy controls.[23,25] In the language domain, verbal ability deficits have been reported for offspring at-risk of schizophrenia,[26,27] and Cannon and colleagues[17] found that receptive language deficits in children predicted later transition into psychosis. Also, polygenic risk scores of psychoses have been associated to language intelligibility deficits and poorer social understanding in the childhood years.[28] Social behavior impairments have been described in children who later developed schizophrenia, and in young offspring at familial high-risk of schizophrenia.[19,29] In a 20-year follow-up study on social functioning, Velthorst and colleagues[30] found that children who later developed psychosis already presented with subclinical social functioning deficits in late childhood, which further declined in early adolescence. The decline and severity of social functioning deficits predicted later psychosis, rendering Velthorst and colleagues[30] to propose social functioning deficits as a potential endophenotype for psychosis.

Several meta-analytic studies have reported social cognitive impairments in offspring at familial high-risk of bipolar disorder (FHR-BP) with small and medium effect-sizes for emotion recognition and Theory of Mind deficits, respectively.[31,32] Other studies reported nonsignificant differences between healthy controls and offspring at genetic risk of bipolar disorder.[33,34] Studies of social behavior in offspring at FHR-BP are relatively few. One study found that young offspring at-risk of bipolar disorder presented with a level of social behavior comparable with healthy controls,[35] whereas another study reported mild-to-moderate deficits in psychosocial behavior, including relations to family and friends.[36] For offspring at genetic high-risk of bipolar disorder, the support for language deficits in the early maturational phase is sparse.[34]

Thus, studies of social cognition, language, and social behavior in young offspring at-risk of schizophrenia and bipolar disorder report divergent results with effect-sizes ranging from zero over small to medium, with more pronounced deficits for offspring schizophrenia, and offspring bipolar disorder performing more like typically developing children.[15,32] Divergent findings may reflect differences in the at-risk samples studied, including heterogeneity of bipolar disorder, in assessment methodologies, in small sample sizes, and wide age-ranges, which often do not consider the developmental perspective of these functions.[37] Furthermore, the question of whether these potential vulnerability markers are shared between young children at familial high-risk of schizophrenia (FHR-SZ) and bipolar are inconclusive.[9]

The aim of our study was, thus, to characterize potential impairments in aspects of social cognition, language, and social behavior in a cohort of 522 7-year-old children at FHR-SZ or FHR-BP compared to a population-based control (PBC) group without a familial high-risk of these two mental disorders. We hypothesized that the children at FHR-SZ would show significant deficits in aspects of social cognition, language, and social behavior compared to the PBC group, with the children at FHR-BP performing at an intermediate level between the children at FHR-SZ and the PBC group.

Methods

Participants

The Danish High-Risk and Resilience Study VIA 7 is a prospective cohort study with a stratified sample of 522 children, aged 7 years, with one or two biological parents diagnosed with a schizophrenia spectrum psychosis (*International Classification of Diseases, Tenth Revision* [*ICD 10*]-codes: F20, F22, F25 or *ICD 8*-codes: 295, 297, 298.29, 298.39, 298.99) or a bipolar disorder (*ICD 10*-codes: F30, F31 or ICD 8-codes: 296.19, 296.39), and with biological parents not diagnosed with any of the two disorders. The cohort was established through the Danish Psychiatric Central Research Register[38] and the Central Person Register.[39] Exclusion criteria were individuals not born in Denmark.

Sample and Matching

The VIA7 cohort consists of 202 children at FHR-SZ, 120 children at FHR-BP, and 200 population-based controls. The FHR-SZ group was individually matched with the control group on the child's age, sex, and municipality as well as on the sex of the ill parent. The latter was used to define the index-parent in the control group. The FHR-BP was a non-matched sample although the inclusion criteria for the matched samples were followed (supplementary material: flowchart).

Procedure

Approval from The Danish Data Protection Agency was obtained (RHP-2012-06). Following the guidelines

from the Danish Committee on Health Research Ethics, all adult participants received verbal and written information and signed a written informed content before enrollment. Families were assessed from January 1, 2013 to January 31, 2016. The assessment took place at the research facilities and in the family's home environment. Families were assessed with a comprehensive assessment battery reported elsewhere.[40] Examiners received training and supervision from a child and adolescent psychiatrist and a clinical child neuropsychologist. Child examiners were blind to the family's high-risk status.

Measures

Information about the child was obtained from the child, the primary caregiver, and the teachers, applying well-validated tests and questionnaires commonly used in studies of schizophrenia, bipolar disorder, and autism spectrum disorders. Several outcome measures on each domain were included to reflect the multidimensionality of the functions studied. The outcomes for the social cognitive domain included facial affect identification, Theory of Mind, and ideational generativity. Facial affect recognition, including response latency, was assessed with the computerized Emotion Recognition Task from the Cambridge Automated Neuropsychological Test Battery, Cambridge Cognition.[41] Theory of Mind was assessed with the Strange Stories-Revised, including response latency[42] and the Animated Triangles Test.[43–45] Ideational generativity was measured with Pattern Meanings test.[46] Language functioning was measured as receptive language, using the Test for Reception of Grammar-2,[47] and as pragmatic language with the Children's Communication Checklist-2,[48] filled out by the teacher. Social behavior was conceptualized as social responsiveness and adaptive social functioning,[49] measured with the Social Responsiveness Scale, filled out by the teacher,[50] and the Vineland-II subdomain Socialization, reported by the primary caregiver[51] (supplementary material: method and outcomes).

Interrater Reliability

Interrater-reliabilities were carried out on the Strange Stories-Revised, the Animated Triangles, and the Pattern Meanings. All interrater-reliabilities reached excellent interclass correlation coefficients: 0.914–0.988 (supplementary material: interrater-reliability).

Statistical Analyses

Statistical analyses were carried out with STATA version 13[52] and IBM SPSS Statistics Version 22.[53] Demographic data (table 1) were analyzed with chi-square tests and analyses of variance when relevant, followed by post hoc pairwise comparisons with the least significance difference.

Missing value analyses (2.1%–17.8%) implied the choice of multiple imputations to prevent reducing power and selection bias (see supplementary material: missing value analyses and multiple imputation). Multiple imputations were followed by a standardizing into z-scores, using the controls as the reference group with a mean of 0 and a standard deviation of 1. For all variables, z-scores were generated so that higher scores indicated better performance. To control for the Type I error probability and correlation between multiple outcome variables, data were analyzed with multivariate analyses of variance (MANOVA): first, on total outcome variables within each domain, social cognition, language, and social functioning and second, on subscales outcome variables within the three domains studied. For the social cognitive domain, the overall multivariate analysis of covariance (MANCOVA) using subscale variables were nonsignificant; hence, further analysis was not indicated. The MANOVAs were followed by MANCOVAs with high-risk status entered as fixed factor and age and sex as covariates. Parent's socioeconomic status or levels of education were not entered in the model as covariates because these factors are intrinsically associated with schizophrenia and bipolar disorder. Each MANCOVA were followed by pairwise comparisons. To control for multiple testing, and to prevent a too conservative Bonferroni correction, the following formula was applied on each MANOVA: 0.05/(three groups × number of tests). Thus, the social cognitive domain reached an alpha-level of .002 and both the language and social behavior domains reached an alpha-level of .008. Effect-sizes, including 95% confidence intervals, were calculated following Cohen's interpretation of effects-sizes: small, 0.20; medium, 0.5; and large, 0.8[54–57] (supplementary material: raw data).

Results

Demographic and Clinical Characteristics

The children at FHR-SZ, FHR-BP, and the PBC differed nonsignificantly regarding sex or age. Groups differed significantly regarding the primary caregivers' psychosocial functioning: The primary caregivers in the FHR-SZ and FHR-BP group presented with lower psychosocial functioning than controls. There was a significantly higher percentage of controls living with two parents (84.5%) compared to children at FHR-SZ (40.6%) and FHR-BP (52.2%). Significantly, more parents in the FHR-BP and PBC group were educated than in the FHR-SZ group (see table 1).

Social Cognitive Domain

FHR-SZ children differed on the Strange Stories-Revised mentalizing ($d = -0.26$, $P = .013$) and nonmentalizing stories ($d = -0.24$, $P = .02$) compared to PBCs, but these results did not remain significant after Bonferroni

Table 1. Demographic Data on the 522 Children at Familial High Risk of Schizophrenia (FHR-SZ), Bipolar Disorder (FHR-BP), and a Population-Based Control (PBC) Group and on the Children's Parents Participating in the Danish High Risk and Resilience Study VIA 7

										FHR-SZ vs PBC	FHR-BP vs PBC	FHR-SZ vs FHR-BP
	FHR-SZ			FHR-BP			PBC			*P* Values	Pairwise Comparisons *P* Values		
Children, *N*	202			120			200						
Female, *N* (%)	93	46.0		56	46.7		93	46.5		.993[a]	.926[a]	.977[a]	.913[a]
Age for inclusion, Mean (SD)	7.84	0.22		7.86	0.20		7.81	0.20		.097[c]	.177[c]	.035[c]	.345[c]
Two biological parents with SZ and/or BP, *N* (%)	8	4.0		1	0.8		—	—	—	—	—	—	—
CBCL[e] score mean (SD) *N* (*N* = 494)	27.20	21.1	192	23.41	19.7	111	17.01	14.7	191	.000[b]	.000[b]	.009[b]	.062[b]
CGAS[f], mean (SD) *N*	68.07	15.4	199	73.6	14.91	118	77.71	13.47	197	.000[c]	.000[c]	.015[c]	.001[c]
Child's home environment													
Living with both parents, *N* (%)	82	40.6		63	52.5		169	84.5		.000[a]	.000[a]	.000[a]	.038[a]
Living out of home, *N* (%)	11	5.4		0	0.0		1	0.5		.001[a]	.004[a]	.438[a]	.009[a]
Living with a single parent, *N* (%)	75	37.1		39	32.5		21	10.6		.000[a]	.000[a]	.000[a]	.401[a]
Living with an index parent, *N* (%)	124	61.4		84	70.0		189	94.5		.000[a]	.000[a]	.000[a]	.118[a]
PSP[g] primary caregiver, mean (SD) (*N* = 512)	73.1	14.0	197	74.5	14.1	118	84.4	9.1	197	.000[c]	.000[c]	.000[c]	.346[c]
Index parent[h], *N*	200[i]			116			204						
Female, *N* (%)	111	55.5		64	55.2		115		56.4	.974[a]	.860[a]	.835[a]	.955[a]
Age at child's birth, mean (SD)	30.20	6.07		33.12	7.01		32.83		4.78	.000[c]	.000[c]	.668[c]	.000[c]
PSP, mean (SD) *N* = 454	66.1	15.7	158	68.9	14.1	102	84.3	9.9	194	.000[c]	.000[c]	.000[c]	.095[c]
Employed, or studying, *N* (%) (*N* = 497)	93	49.7		61	56.0		185		92.0	.000[c]	.000[c]	.000[c]	.301[c]
Education, *N* (*N* = 484)	178			109			197						
Primary/lower secondary, *N* (%)	54	30.3		10	9.2		8		4.1	.000[d]	.000[d]	.985[d]	.000[d]
Upper secondary, vocational, short-cycle tertiary, *N* (%)	76	42.7		45	41.3		95		48.2				
Bachelor degree, equivalent or higher, *N* (%)	48	27.0		54	49.5		94		47.7				
Biological nonindex parents, *N* (*N* = 492)	186			114			192						
Female, *N* (%)	82	44.1		51	44.7		83	43.2		.966[a]	.867[a]	.797[a]	.912[a]
Age at child's birth, mean (SD)	30.92	6.37		33.10	5.39		32.97	4.28		.000[c]	.000[c]	.841[c]	.001[c]
PSP, mean (SD) *N* (*N* = 437)	76.4	14.3	163	81.8	13.1	94	85.5	8.4	180	.000[c]	.000[c]	.013[c]	.001[c]
Employed or studying, *N* (%) (*N* = 474)	133	75.1		93	85.3		179	95.2		.000[a]	.000[a]	.003[a]	.040[a]
Education, *N* (*N* = 469)	176			106			187						

Table 1. Continued

	FHR-SZ		FHR-BP		PBC	*P* Values	FHR-SZ vs PBC	FHR-BP vs PBC	FHR-SZ vs FHR-BP
							Pairwise Comparisons *P* Values		
Primary/lower secondary, *N* (%)	31	17.6	5	4.7	10	5.3	.002[d]	.002[d]	.276[d]	.000[d]
Upper secondary, vocational, short-cycle tertiary, *N* (%)	86	48.9	44	41.5	89	47.6				
Bachelor degree, equivalent or higher, *N* (%)	59	33.5	57	53.8	88	47.1				

[a]Chi-square test.
[b]One-way ANOVA with post hoc pairwise comparison least significance difference alpha (0.05) after log-transformation of child behavior checklist (CBCL) total sum variable.
[c]One-way ANOVA with post hoc pairwise comparison least significance difference alpha (0.05).
[d]Linear by linear association *P* value is used when an ordinal variable has more than two categories.
[e]Child Behavior Checklist.
[f]Child Global Assessment Scale.
[g]Personal and Social Behavior.
[h]Index-parent refers to the biological parent with a diagnosis of schizophrenia spectrum disorder or bipolar disorder. In the population based control group, the index parent refers to the matched biological parent without any of these two mental disorders. In case of siblings, information about the parent is only included once and from the first child included in the study in order not to count the same parent twice.
[i]One father diagnosed with a bipolar disorder is counted in the index group for parents diagnosed with schizophrenia spectrum disorder because the child belongs to the FHR-SZ group.

correction. Correcting for the nonmentalizing stories, the result was nonsignificant after Bonferroni correction (P = .043). FHR-BP children performed better than FHR-SZ children on Theory of Mind (Animated Triangles Accuracy, d = +0.25, P = .045; Strange Stories-Revised, d = +0.23, P = .038), and ideational generativity (d = +0.27, P = .014), but these results became nonsignificant after Bonferroni correction. No significant impairments in emotion recognition or social cognitive response latencies were found for any group (See table 2).

Language Domain

FHR-SZ children presented with significant receptive language deficits compared to PBCs (d = −0.27, P = .006) but not significantly different from FHR-BP children after Bonferroni correction (d = −0.25; P = .025). Further, FHR-SZ children showed pragmatic language impairments compared to PBCs (d = −0.51, P < .001) but not significantly different from FHR-BP children after Bonferroni correction (d = −0.24; P = .018). For FHR-SZ children, the General Communication Subscale (CCC-2 GC) reached significance compared to PBCs (d = −0.45, P < .001) but not compared to FHR-BP after Bonferroni correction (d = −0.22, P = .034). The result of the FHR-SZ children on the Social Interaction subscale was not significantly different from PBC nor FHR-BP children (PBC: d = −0.17, P = .09; FHR-BP: d = −0.03, P = .73). The FHR-BP children had neither significant receptive nor pragmatic language deficits compared to PBC children (see table 3).

Social Behavior Domain

Significant impairments in social responsiveness were found for FHR-SZ compared to PBC (d = −0.54, P < .001). Compared to PBC, the social responsivness subscales Social Communication and Interaction (SCI; d = −0.54, P < .001) and Restrictive Interest and Repetitive Behavior (RIRB; d = −0.41, P < .001) were significant for FHR-SZ children. FHR-BP children did not show any significant social responsiveness deficits compared to PBC children after Bonferroni correction (d = −0.31, P =.013; SCI: d = −0.31, P = .012; RIRB: d = −0.26, P = .043). The social responsiveness differences between FHR-SZ and FHR-BP children were nonsignificant (see table 4). In terms of adaptive social functioning (Socialization domain, Vineland II), FHR-SZ children showed significant impairments compared to FHR-BP (d = −0.29, P = .007) and PBCs (d = −0.47, P < .001). FHR-BP children did not show any significant adaptive social functioning deficits compared to PBCs. For between-group differences in Vineland-II Socialization subscales, see table 4.

Discussion

FHR-SZ children showed impairments in receptive and pragmatic language, social responsiveness, and adaptive

Table 2. Social Cognitive Functions of 522 7-Year-Old Children at Familial High Risk of Schizophrenia (FHR-SZ), Bipolar Disorder (FHR-BP), and Population-Based Control (PBC) Group Presented in Z-scores, Pairwise Comparisons Between Groups, and Effect-Sizes

	FHR-SZ (n = 202)			FHR-BP (n = 120)			PBC (n = 200)			Pairwise comparison FHR-SZ vs PBC		Pairwise comparison FHR-BP vs PBC		Pairwise comparison FHR-SZ vs FHR-BP	
Domains/variables	Mean (SD) 95% CI[b,c]			Mean (SD) 95% CI[b,c]			Mean (SD) 95% CI[b,c]			P value	d[e]	P value	d[e]	P value	d[e]
Emotion processing/ (Emotion Recognition Task	−0.12	(1.08)	−0.26 to 0.03	0.02	(0.96)	−0.15 to 0.20	0.00	(1.01)	−0.14 to 0.14	.25[b]	−0.11	.85[b]	+0.02	.23[c]	−0.14
Emotion processing (Emotion Recognition Task Response Latency)	−0.14	(1.28)	−0.32 to 0.04	0.01	(0.92)	−0.16 to 0.17	0.00	(1.01)	−0.14 to 0.14	.23	−0.12	.89	+0.01	.24	−0.13
Theory of Mind (Animated Triangles Task Intentionality)	0.05	(1.10)	-0.11 – 0.20	0.16	(1.01)	−0.02 to 0.35	−0.01	(1.04)	−0.15 to 0.14	.59	−0.06	.16	+0.17	.35	-0.10
Theory of Mind (Animated Triangles Task Accuracy)	−0.02	(1.06)	−0.16 to 0.13	0.23	(0.97)	0.05 to 0.41	−0.01	(1.03)	−0.15 to 0.13	.88	−0.01	.06	+0.24	.045	−0.25
Theory of Mind (Strange Stories-Revised)	−0.27	(1.07)	−0.42 to −0.12	−0.03	(1.02)	-0.22 to 0.15	0.00	(1.00)	−0.14 to 0.14	.013[d]	−0.26	.93[b]	−0.03	.038[d]	−0.23
Theory of Mind (Strange Stories – Revised Response Latency)	−0.26	(2.92)	−0.67 to 1.14	0.12	(0.75)	−0.02 to 0.25	0.00	(1.01)	−0.14 to 0.14	.17	−0.12	.63	+0.13	.10	−0.18
Ideational Generativity (Pattern Meanings)[a]	−0.06	(1.07)	−0.21 to 0.08	0.23	(1.05)	0.04 to 0.42	0.00	(1.01)	−0.14 to 0.14	.054[d]	−0.06	.054[d]	+0.22	.014[d]	−0.27

[a]Multivariate analysis of covariance (MANCOVA) with pairwise comparisons and high-risk status entered as fixed factors and sex and age as covariate on multiple imputations data. The MANCOVA for total outcome had an overall significance of F (28; 514.5) = 2.49. P > .000.
[b]Mean and SD are presented in z-scores with the PBC children as the reference-group (mean = 0; SD =1). A negative score denotes a poorer performance.
[c]Confidence interval (95%).
[d]Sex is significant P <.05.
[e]Effect-size, Cohen d.

Table 3. Language Functioning of 522 7-Year-Old Children at Familial High-Risk of Schizophrenia (FHR-SZ), Bipolar Disorder (FHR-BP), and Population-Based Control (PBC) Group Presented in Z-scores, Pairwise Comparisons Between groups, and Effect-Sizes

	FHR-SZ (n = 202)			FHR-BP (n = 120)			PBC (n = 200)			Pairwise Comparisons FHR-SZ vs PBC		Pairwise Comparison FHR-BP vs PBC		Pairwise Comparison FHR-SZ vs FHR-BP	
Domains/variables	Mean	(SD)	95% CI[a,e]	Mean	(SD)	95% CI[a,e]	Mean	(SD)	95% CI[a,e]	P value	d[g]	P value	d[g]	P value	d[g]
Receptive Language[b] (Test for Reception of Grammar-2)	−0.29	(1.17)	−0.45 to −0.13	−0.02	(1.00)	−0.20 to 0.16	0.00	(1.00)	−0.13 to 0.17	.006[f]	−0.27	.89	−0.02	.025[f]	−0.25
Pragmatic Language[b] (Children's Communication Checklist-2)	-0.62	(1.41)	-0.81 – -0.42	-0.27	(1.45)	-0.53 – 0.00	0.02[c]	(1.07)	-0.14 – 0.14	<.001[f]	-0.51	.08	-0.23	.018[f]	-0.24
Pragmatic Language[c] (Children's Communication Checklist General Communication Subscale)	−0.55	(1.39)	−0.74 to −0.36	−0.24	(1.43)	−0.5 to 0.02	0.02[d]	(0.00)	−0.14 to 0.17	<.001[f]	−0.45	.11	−0.20	.034[f]	−0.22
Pragmatic Language[c] (Children's Communication Checklist-2 Social Interaction Subscale)	−0.23	(1.48)	−0.44 to −0.03	−0.19	(1.15)	−0.40 to 0.02	1.11	(1.13)	−0.16 to 0.16	.09	−0.17	.24	−0.17	.73[f]	−0.03

[a]Multivariate analysis of covariance (MANCOVA) with Pairwise Comparisons between Groups and High Risk Status entered as fixed factor and age and sex as covariates on multiple imputations data. Mean and SD are presented in Z Scores with the PBC children as the reference-group (mean = 0; SD =1). A negative Z score denotes a poorer performance.
[b]The MANCOVA total sum outcome had an overall significance of $F(4, 502.0) = 6.89$; $P > F = .0000$.
[c]The MANCOVA subscales had an overall significance of $F(16, 511.3) = 3.30$ $P > F = .0000$.
[d]A mean of 0.02 for the PBC group is considered acceptable close to zero.
[e]95% Confidence Interval.
[f]Sex is significant at $P < .02$.
[g]Effect-size, Cohen d.

Table 4. Social Behavior of 522 7-Year-Old Children at Familial High Risk of Schizophrenia (FHR-SZ), Bipolar Disorder (FHR-BP), and Population-Based Control (PBC) Group presented in Z-scores, Pairwise Comparisons Between Groups, and Effect-Sizes

	FHR-SZ (n = 202)			FHR-BP (n = 120)			PBC (n = 200)			Pairwise Comparison FHR-SZ vs PBC		Pairwise Comparison FHR-BP vs PBC		Pairwise Comparison FHR-SZ vs FHR-BP	
Domains/Variables	Mean (SD) 95% CI[a,d]			Mean (SD) 95% CI[a,d]			Mean (SD) 95% CI[a,d]			P value	d^g	P value	d^g	P value	d^g
Social Behavior/ Social Responsiveness Scale Total[b]	−0.68	(1.44)	−0.88 to −0.48	−0.41	(1.55)	−0.45 to 0.04	0.01	(1.10)	−0.15 to 0.16	<.001[e]	−0.54	.013[e]	−0.31	.056[e]	−0.18
Social Behavior/ Social Responsiveness Scale SCI subscale[c]	−0.69	(1.42)	−0.89 to −0.50	−0.42	(1.55)	−0.69 to −0.14	0.00	(1.10)	−0.15 to 0.16	<.001[e]	−0.54	.012[e]	−0.31	.055[e]	−0.18
Social Behavior/ Social Responsiveness Scale RIRB subscale[c]	−0.52	(1.46)	−0.72 to −0.32	−0.34	(1.58)	−0.62 to 0.05	0.01	(1.08)	−0.14 to 0.16	<.001[f]	−0.41	.043[f]	−0.26	.205[f]	−0.12
Social Behavior/ Vineland Socialization Composite[b]	−0.64	(1.62)	−0.87 to −0.42	−0.21	(1.37)	−0.45 to 0.04	0.00	(1.02)	−0.15 to 0.14	<.001	−0.47	.186	−0.17	.007	−0.29
Social Behavior/ Vineland-II Interpersonal relations Subscale[c]	−0.62	(1.70)	−0.85 to −0.38	−0.20	(1.44)	−0.44 to 0.05	−0.01	(1.04)	−0.15 to 0.14	<.001	−0.43	.202	−0.15	.015	−0.27
Social Behavior/ Vineland-II Play and leisure subscale[c]	−0.54	(1.56)	−0.75 to −0.32	−0.16	(1.31)	−0.46 to 0.08	0.04	(1.06)	−0.11 to 0.18	<.001	−0.43	.206	−0.17	.016	−0.26
Social Behavior/ Vineland Coping Skills subscale[c]	−0.66	(1.54)	−0.88 to −0.45	−0.19	(1.36)	−0.46 to 0.06	0.00	(1.04)	−0.15 to 0.14	<.001	−0.50	.200	−0.16	.003	−0.32

Note: Multivariate analysis of covariance (MANCOVA) with Pairwise Comparisons and High-Risk Status entered as fixed factors and sex and age as covariates on multiple imputations data. SCI, Social Communication and Interaction; RIRB, restrictive interest and repetitive behavior.
[a]Mean and SD are presented in z-scores with the PBC children as the reference-group (mean = 0; SD =1). A negative z-score denotes a poorer performance.
[b]The MANCOVA main outcomes had an overall significance of F (4; 503.5) = 9.63; Prob.>F = 0.0000.
[c]The MANCOVA subscales outcomes had an overall significance of F (20; 510.1) =3.46; Prob.> F = 0.000.
[d]95% confidence interval.
[e]Sex and age are significant at $P < .02$.
[f]Sex is significant at $P < .001$.
[g]Effect-size Cohen d.

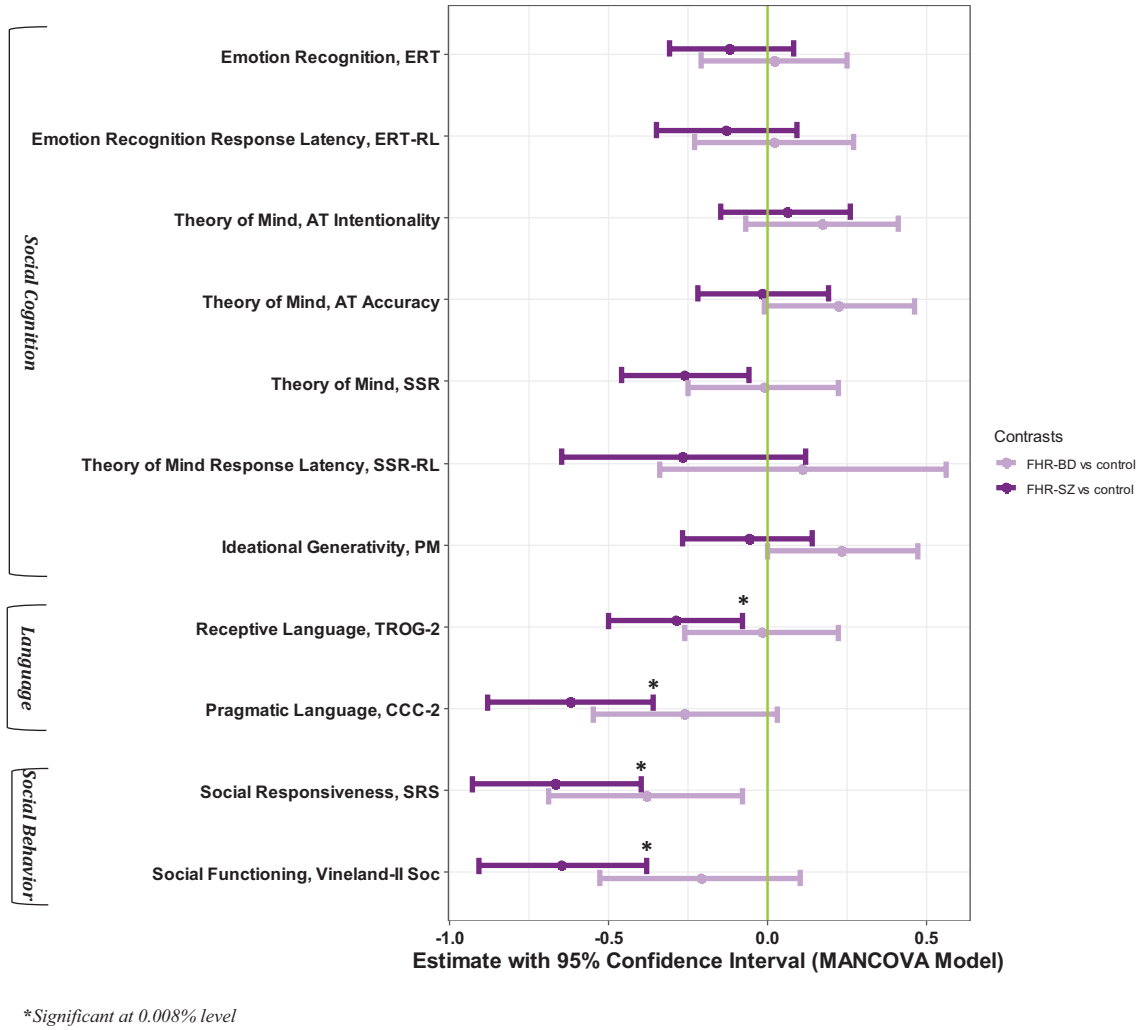

Fig. 1. Social cognition, language, and social behavior of children at familial high-risk of schizophrenia or bipolar disorder. ERT, Emotion Recognition Task, ERT-RL, Emotion Recognition Task Response Latency; AT, Animated Triangles; SSR, Strange Stories-Revised; SSR-RL, Strange Stories-Revised Response Latency; PM, Pattern Meanings, TROG-2, Test for Reception of Grammar; CCC-2, Children's Communication Checklist-2, SRS, Social Responsiveness Scale; Vineland-II Soc, Socialization subdomain. *Significant at 0.008% level.

social functioning but not in the social cognitive functions. Thus, our first hypothesis was only partly supported. Our second hypothesis that FHR-BP children present intermediate impairments between FHR-SZ and controls in the same domains was not supported because no significant impairments in any domain were observed after Bonferroni correction (figure 1).

Demographic and Clinical Factors

FHR-SZ and FHR-BP children present with significantly more dimensional psychopathology similar to earlier findings.[58] The primary caregivers of children at FHR-SZ and FHR-BP had a lower psychosocial functioning. Furthermore, a higher percentage of the parents with BP than parents with SZ completed formal education. This could reflect differences between the two mental diseases, with more severe cognitive impairments characterizing schizophrenia than bipolar disorder, which could influence the ability to complete an education. Other studies have found more severe cognitive impairments in first-episode schizophrenia than in first-episode bipolar disorder.[59]

Social Cognition—Theory of Mind and Emotion Recognition

FHR-SZ children displayed nonsignificant and small differences of Theory of Mind (Strange Stories-Revised mentalizing stories) compared to the FHR-BP children and the PBCs after Bonferroni correction. Similarly, compared to PBCs FHR-SZ children did

not show any Theory of Mind deficits assessed with the Animated Triangles Test. These tests may represent different aspects of Theory of Mind, because the Strange Stories-Revised mentalizing stories seemingly measure explicit mentalizing, whereas the free description of the Animated Triangles Test elicits the implicit mentalizing.[60] Our results are comparable with a study of adolescents at genetic risk of schizophrenia that did not find significant Theory of Mind impairments, using the Eyes Test. The Eyes Test may be an assessment of a more implicit Theory of Mind that demands more decoding than reasoning about others' mental states.[22] Also, neurocognitive functions, eg, verbal fluency or verbal working memory may have influenced the Strange Stories-Revised task performance.[61,62] The explicit Theory of Mind deficit remained significant when we corrected for the nonmentalizing stories in Strange Stories-Revised but not after correction for multiple testing. Compared to FHR-SZ, FHR-BP children showed nonsignificantly better ideational generativity and Theory of Mind (Strange Stories-Revised, Animated Triangles Accuracy) after Bonferroni correction. Our results may suggest unaffected metalizing in both FHR-SZ and FHR-BP children at this developmental phase.

In terms of emotion recognition and emotion recognition response latency, we did not find deficits for FHR-SZ or FHR-BP children. Impairments in these functions have earlier been associated to polygenic risk for schizophrenia,[63] but most studies on offspring at genetic risk of schizophrenia have reported nonsignificant deficits for emotion recognition.[64,65] Our results support the findings derived from several studies in offspring at risk for BP (<30 years of age),[32–34]albeit other studies have reported significant emotion labeling impairments in offspring at-risk BP with the offspring BP demanding a higher intensity of the emotions displayed.[66,67] Wide age ranges in samples, different assessment methodology, and small sample sizes may explain the conflicting findings. Also, social cognitive functions are not fully matured until early adulthood,[24] thus collapsing different ages into one group can potentially mask significant differences across groups. If cognitive functions develop at a slower pace, ie, developmental lag, compared to the typical cognitive development, it may be difficult to detect potential impairments in the early developmental years.[68] Furthermore, social cognition is a multidimensional construct; thus, it could be beneficial to explore all aspects, ie, emotional processing, Theory of Mind, and social perception and knowledge in the same population during the early maturational years as to understand their potential different developmental trajectories. Our results may suggest that the aspects of social cognition currently included are not vulnerability markers at this early developmental phase. Thus, follow-up studies are warranted.

Language—Receptive and Pragmatic Skills

FHR-SZ children present with significant receptive as well as pragmatic language impairments of small-to-moderate effect-sizes compared to PBCs but not compared to FHR-BP after Bonferroni correction. Our results allude to earlier prospective, birth cohort studies, where language impairments were found in children who later transitioned into schizophrenia.[17,27] Several studies have shown that language deficits relate to formal thought disorder in schizophrenia,[69,70] and brain imaging studies found that individuals at clinical high-risk of psychosis presented with language network dysfunctions.[71] Further, many studies have reported verbal ability impairments of medium effect-sizes in offspring at-risk of schizophrenia,[15,72] which are comparable with the effect-sizes for receptive and pragmatic language deficits currently found in FHR-SZ children. The associations found in the Avon Longitudional Study of Parents and Children birth cohort in young children between language intelligibility deficits and schizophrenia polygenic risk scores,[73] further support the assumption that language impairments could be a marker of vulnerability or even a premorbid antecedent for transition into psychosis. A potential weakness of many studies of language impairments or verbal ability deficits in offspring at-risk for schizophrenia is that studies frequently apply tests that assess other cognitive functions than language proper, including intelligence, verbal memory, and executive functions.[15,72] Considering the robust finding of lower IQ in offspring at-risk of schizophrenia, the effect of (verbal) intelligence on language performance should be considered, also in the choice of assessment battery.

Our results concerning receptive and pragmatic language impairments underline the importance to follow their development closely, to discern whether language functions develop at a slower pace than in typically developing children, or whether the impairments will remain stable, or worsen over time. Also, language functions may catch up during development,[68] although there is growing evidence for language impairments at the phenotypic level. From a clinical intervention perspective, it is important to shed attention on those FHR-SZ children who present with language impairments at an early age because these impairments could affect the child's academic performance and social functioning.[70]

Social Behavior—Social Responsiveness and Adaptive Social Functioning

Small-to-moderate social responsiveness and adaptive social functioning deficits were present in FHR-SZ compared to controls. These results are comparable with other studies in characterizing FHR-SZ children as profoundly more vulnerable in their social development. In several population-based cohort studies, children and adolescents who later developed schizophrenia showed premorbid social impairments.[19] Interestingly, the severity of

social impairments in FHR-SZ children was indicative of those children who later transitioned into psychosis. For FHR-BP children and adolescents, results are divergent with some studies reporting no adaptive social functioning deficits,[35] whereas others described deficits of social reciprocity.[33] The latter is not comparable with the non-significant social responsiveness differences (small effect-sizes) for FHR-BP children after Bonferroni correction. Our study results may suggest that significantly lower social responsiveness is not shared between FHR-SZ and FHR-BP children, although the difference between the FHR-groups was very small. In terms of adaptive social functioning, only FHR-SZ children showed significant impairments of small-to-moderate effect-sizes, which stresses the importance of the potential developmental vulnerability of these children. FHR-BP children showed significantly better overall adaptive social functioning than FHR-SZ children, which might be explained by significantly better coping skills, although the effect-size was small. Thus, adaptive social functioning impairments appear non-shared between FHR-SZ and FHR-BP children and cannot be explained by shared risk factors between schizophrenia and bipolar disorder.

Strengths and Limitations

The familial high-risk study design provides a valuable window into pathways of alternations of neurodevelopment. The VIA 7 study includes a large FHR sample with a very narrow age span, which is a strength because the neurodevelopment in the childhood years is characterized by an immense maturation in all cognitive domains. Thus, to focus on a narrow age span in the maturational process provides a unique knowledge of the phenotypic expression of the typically and potentially pathological neurodevelopment. Further, the cohort is representative due to recruitment through the Danish registers. Other strengths include the choice of well-validated tests for our age group that likewise allow for follow-up studies. A limitation of the study is the lack of assessment of the potential effects of neurocognitive functions on social cognition, language, and social behavior. Thus, we cannot rule out the possibility that the deficits observed in FHR-SZ children are explained by general cognitive impairment rather than reflective of impairments of specific functions. Furthermore, the smaller sample size of FHR-BP children may explain the lack of significant findings in some of the domains. Also, in few cases the child assessors' blindness was broken.

Our findings indicate that FHR-SZ children, already at the age of seven, present with impairments of their receptive and pragmatic language, social responsiveness, and adaptive social functioning. FHR-BP children resemble typically developing control children in all domains assessed. Our results stress the importance of language, and social behavior as vulnerability indicators for FHR-SZ children. However, the observed medium-to-small effect-sizes may render it difficult to reliably identify high-risk children in this early developmental phase. Moreover, these mean effect-sizes may reflect functional heterogeneity and the familial high-risk children with the most severely affected functions may be reliably detectable at this young age. Future studies are warranted to characterize the maturational development of the multidimensional aspects of social cognitive functioning in offspring at FHR-SH and FHR-BP.

It seems important that clinicians as well as professionals at schools pay special attention to those children at FHR-SZ that present with deviations in their early neurodevelopment of language and social responsiveness or with adaptive social functioning impairments because these deviations could potentially disturb their quality of life and academic performance. Further characterization of the neurodevelopmental trajectories of social cognition, language, and social behavior in children at FHR-SZ and FHR-BP is important for the goal of designing preventive interventions.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin* online.

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