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Neurocognitive heterogeneity in 7-year-old children at familial high risk of schizophrenia or bipolar disorder: The Danish high risk and resilience study - VIA 7

Nicoline Hemager [a,b,c,*], Camilla Jerlang Christiani [a,c], Anne Amalie Elgaard Thorup [a,b,c,d], Katrine Søborg Spang [b,c], Ditte Ellersgaard [a,c], Birgitte Klee Burton [b,c], Maja Gregersen [a,c,d], Aja Neergaard Greve [c,e], Yunpeng Wang [f], Ron Nudel [c,g], Ole Mors [c,e], Kerstin Jessica Plessen [b,c,h], Merete Nordentoft [a,c,d], Jens Richardt Møllegaard Jepsen [a,b,c,i]

[a] Mental Health Center Copenhagen, Mental Health Services, Capital Region of Denmark, Gentoftevej 15, 4th floor, Copenhagen, Hellerup 2900, Denmark
[b] Child and Adolescent Mental Health Center, Mental Health Services, Capital Region of Denmark, Copenhagen, Denmark
[c] The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Aarhus, Denmark
[d] Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
[e] Psychosis Research Unit, Aarhus University Hospital, Aarhus, Denmark
[f] Center for Lifespan Changes in Brain and Cognition, Department of Psychology, University of Oslo, Oslo, Norway
[g] Mental Health Center Sct. Hans, Mental Health Services, Institute of Biological Psychiatry, Capital Region of Denmark, Roskilde, Denmark
[h] Division of Child and Adolescent Psychiatry, Department of Psychiatry, University Hospital Lausanne, Lausanne, Switzerland
[i] Center for Neuropsychiatric Schizophrenia Research and Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research, Mental Health Services, Capital Region of Denmark, Copenhagen, Denmark

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ABSTRACT

Background: Studies of neurocognitive heterogeneity in young children at familial high-risk of bipolar disorder (FHR-BP) or schizophrenia (FHR-SZ) are important to investigate inter-individual neurocognitive differences. We aimed to identify neurocognitive subgroups, describe prevalence of FHR-BP or FHR-SZ children herein, and examine risk ratios (RR) compared with controls.

Methods: In a population-based cohort of 514 7-year-old children (197 FHR-SZ, 118 FHR-BP, and 199 matched controls) we used hierarchical cluster analyses to identify subgroups across 14 neurocognitive indices.

Results: Three neurocognitive subgroups were derived: A Mildly Impaired (30%), Typical (51%), and Above Average subgroup (19%). The Mildly Impaired subgroup significantly underperformed controls (Cohen d = 0.11–1.45; $Ps < 0.001$) except in set-shifting ($P = .84$). FHR-SZ children were significantly more prevalent in the Mildly Impaired subgroup; FHR-BP children were more so in the Above Average subgroup (X^2 (2, N = 315) = 9.64, $P < .01$). 79.7% FHR-BP and 64.6% FHR-SZ children demonstrated typical or above average neurocognitive functions. Neurocognitive heterogeneity related significantly to concurrent functioning, psychopathology severity, home environment adequacy, and polygenic scores for schizophrenia ($Ps <$. 01). Compared with controls, FHR-SZ and FHR-BP children had a 93% (RR, 1.93; 95% CI, 1.40–2.64) and 8% (RR, 1.08; 95% CI, 0.71–1.66) increased risk of Mildly Impaired subgroup membership.

Limitations: Limitations include the cross-sectional design and smaller FHR-BP sample size.

Conclusions: Identification of neurocognitive heterogeneity in preadolescent children at FHR-BP or FHR-SZ may ease stigma and enable pre-emptive interventions to enhance neurocognitive functioning and resilience to mental illness in the impaired sub-population.

* Corresponding author at: Mental Health Center Copenhagen, Mental Health Services, Capital Region of Denmark, Gentoftevej 15, 4th floor, Copenhagen, Hellerup 2900, Denmark.
E-mail address: nicoline.hemager@regionh.dk (N. Hemager).

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1. Introduction

Neurocognitive impairments are core features of bipolar disorder and schizophrenia with more pronounced deficits in schizophrenia (Bora et al., 2010). Similar patterns of neurocognitive impairments exist in adult relatives and youth with familial high-risk (FHR) of schizophrenia or bipolar disorder (Agnew-Blais and Seidman, 2013; Bora, 2017; Bora and Ozerdem, 2017), in the premorbid phase of these disorders (Trotta et al., 2015; Liu et al., 2015; Bora et al., 2014), and in individuals with first-episode bipolar disorder or schizophrenia (Bora and Pantelis, 2015). Young preadolescent children with FHR of schizophrenia display widespread neurocognitive deficits (Hemager et al., 2018), whereas preadolescent children with FHR of bipolar disorder display selective impairments in interference control (Burton et al., 2018) and visual attention (Hemager et al., 2019). Moreover, deficits in verbal memory and attention are predictors of later psychosis in children of parents with schizophrenia (Erlenmeyer-Kimling et al., 2000). These findings confirm neurocognitive impairments as endophenotypic markers of both disorders with the strongest neurodevelopmental component in schizophrenia (Craddock and Owen, 2010). Neurocognitive diversity exists, however, on a continuum from near normal to severely and globally impaired neurocognitive functions (Kremen et al., 2004). Hence, inter-individual neurocognitive differences may be obscured by group mean differences. Neurocognitive heterogeneity is well documented in cross-disorder studies of individuals with bipolar disorder or schizophrenia (Bora, 2016; Bora et al., 2016; Van Rheenen et al., 2017; Lewandowski et al., 2014; Carruthers et al., 2019; Crouse et al., 2020). Studies characterizing neurocognitive heterogeneity in unaffected adult first-degree relatives of individuals with bipolar disorder (Russo et al., 2017) or schizophrenia (Islam et al., 2018) suggest that unaffected siblings have increased risk of cognitive deficits, if their affected sibling belongs to a neurocognitively impaired subgroup. A recent study of neurocognitive heterogeneity in individuals at clinical high-risk (CHR) for psychosis identified four distinct neurocognitive profiles with the most impaired profile predicting later transition to psychosis as well as lower social and role functioning (Velthorst et al., 2019). These findings underline the clinical relevance of neurocognitive profiling in individuals at CHR for psychosis, which may also be relevant for offspring at FHR for bipolar disorder and schizophrenia. Youth with FHR of bipolar disorder (age range 15–30 years) as well as younger bipolar and schizophrenia offspring with a wide age range (6–17 years) also present with neurocognitive heterogeneity; (Bora et al., 2019; Valli et al., 2021) however, no previous studies have used data-driven methods to investigate neurocognitive heterogeneity in young preadolescent children at familial high-risk of bipolar disorder or schizophrenia.

The objective was to investigate neurocognitive heterogeneity in 7-year-old children at FHR of schizophrenia (FHR-SZ) or bipolar disorder (FHR-BP) by (1) identifying relatively homogenous and distinct neurocognitive subgroups across FHR status. The rationale for using a cross-diagnostic approach was that both children at FHR-SZ and children at FHR-BP are at risk for developing other severe mental disorders than that of the parent (Rasic et al., 2014). We further aimed to (2) assess the prevalence of children with FHR-BP or FHR-SZ in the identified neurocognitive subgroups as well as (3) the risk rates for subgroup membership compared with controls that were used as a reference group. Exploratively, we aimed to (4) compare the neurocognitive subgroups regarding concurrent functioning and level of psychopathology, which are negatively affected in children at FHR-SZ and FHR-BP (Ellersgaard et al., 2018). Further, although heritability of neurocognition is generally high in both disorders (bipolar disorder: h^2 19–64% (Glahn et al., 2010); schizophrenia: h^2 15–74% (Blokland et al., 2016)) as is the heritability of the disorders themselves (bipolar disorder: h^2 59–85%; (Lichtenstein et al., 2009; Barnett and Smoller, 2009) schizophrenia: h^2 64–79% (Lichtenstein et al., 2009; Hilker et al., 2018)) it is not absolute and therefore, we aimed to (5) compare the neurocognitive subgroups regarding polygenic scores (PGS) for SZ and BP. Finally, although cognitive abilities show substantial heritability estimates, we aimed to (6) investigate potential differences in the adequacy of the home environment between the neurocognitive subgroups. Potential associations between the neurocognitive subgroups and the home environment may reflect both parental and child neurocognitive functions (Gantriis et al., 2019). Based on previous evidence from cluster or latent class analyses of cognition in FHR offspring (Bora et al., 2019; Valli et al., 2021), we hypothesized three distinct neurocognitive subgroups. We expected both FHR groups to be represented in all neurocognitive subgroups with children at FHR-SZ being more prevalent than children at FHR-BP in the neurocognitively most impaired subgroup. Due to evidence of increased risk of bipolar disorder in individuals with excellent school performance (MacCabe et al., 2010), we expected children at FHR-BP to be more prevalent in the highest functioning subgroup. Finally, we expected the most impaired neurocognitive subgroup to display lower concurrent functioning, higher levels of psychopathology, and higher PGS for SZ and BP. Due to poorer parental cognitive and social functioning and a tendency to non-random mating in the high-risk families (Greve et al., 2021), we also expected a less adequate home environment in this subgroup. The best neurocognitive subgroup was expected to display the opposite pattern regarding concurrent functioning, levels of psychopathology, and adequacy of the home environment, whereas the load on PGS for SZ and BP was expected to be at an intermediate level since both high and low neurocognitive functioning confers risk to bipolar disorder.

2. Methods

2.1. Participants

The Danish High Risk and Resilience Study - VIA 7 (hereafter the VIA 7 study) is a population-based, multi-site cohort study of 522 7-year-old children with at least one parent with either schizophrenia spectrum psychosis (ICD 10-codes F20, F22, F25 or ICD 8-codes 295, 297, 298.29, 298.39, 298.89, 298.99) ($N = 202$), bipolar disorder (ICD 10 codes F30, F31 or ICD 8-codes 296.19, 296.39) ($N = 120$) or neither disorder ($N = 200$). The Danish Civil Registration System (Pedersen et al., 2006) and The Danish Psychiatric Central Research Register (Mors et al., 2011) were used to recruit the participating families and data collection took place from January 2013 to January 2016. Contact by mail and thereafter by telephone and text messages was attempted with 410 of 1073 eligible children with FHR-SZ (38.2%) and 214 of 774 eligible children with FHR-BP (27.6%) (Supplementary Figure in the online Supporting information). The reasons for the relatively low proportion of families approached were that (1) during part of the data collection period, approximately 20% of the families were registered as protected from being contacted for research purposes due to legislation enacted in May 2011; and (2) for the entire period, some of the eligible children turned eight years of age before the assessment resources allowed for them to be included. The Danish Data Protection Agency approved the study and all procedures were in accordance with the guidelines of the National Committee for Health Research Ethics. Due to the non-interventional study design a formal approval was not deemed necessary by this authority. The genetic part of the study was incorporated as an appendix to the protocol "Arv og Miljø", which has obtained ethical approval by the National Committee for Health Research Ethics (H-B-2009-026). Prior to enrollment, all participants received oral and written information about the study, and the legal guardians gave written consent to child participation. Less than 2% dropped out. The population-based control group (hereafter controls) was matched with the FHR-SZ group by age, sex, and municipality. The non-matched FHR-BP group did not differ significantly from the other groups on the matching variables. Data extraction and recruitment procedures are described in the Supplementary Figure in the online Supporting information. All participating children had Danish as their first language. The VIA 7 study design is

described in further detail elsewhere (Thorup et al., 2015). Five-hundred-and-fourteen children (FHR-SZ: $N = 197$; FHR-BP: $N = 118$; controls: $N = 199$) with neurocognitive data were included in the present study.

2.2. Procedures

The assessors were trained psychologists, physicians, or nurses, instructed and supervised by a specialist in child neuropsychology (JRMJ). Assessments were conducted at the research sites in Copenhagen and Aarhus, Denmark and in the homes of the participants. The assessors were blinded to risk status.

2.3. Measures

2.3.1. Neurocognitive measures

To assess neurocognitive functioning, we used a comprehensive neuropsychological assessment battery covering general intelligence, processing speed, verbal and visuospatial memory, working memory, attention, planning, set-shifting, and verbal fluency. A key measure from each test was chosen a priori. Table S1 in the online Supporting information depicts an overview of the neurocognitive test battery.

2.3.2. Clinical measures and adequacy of the home environment

We used the Children's Global Assessment Scale (Shaffer et al., 1983) to assess concurrent level of functioning and the Child behavior Checklist (CBCL) School-Age Version (Achenbach and Rescorla, 2001) to assess level of psychopathology. The CBCL was completed by the primary caregiver defined as the parent/legal guardian spending most time with the child. The semi-structured interview the Middle Childhood-HOME Inventory for children aged 6–10 (Bradley et al., 1988) was carried out with the child and the primary caregiver to assess adequacy of the home environment; i.e. level of stimulation and support.

2.3.3. Polygenic scores

PGS for SZ and BP were generated for a subset of the sample from whom DNA samples were obtained (procedure described in Supplementary Methods in the online Supporting information).

2.4. Statistical analysis

Demographic and clinical data were compared using univariate analysis of variance (ANOVA) and chi-square test. Log-transformation was applied to approximate a normal distribution (CBCL Total Score).

2.4.1. Neurocognitive data

Methods for missing value analysis, imputation, and transformation are described elsewhere (Hemager et al., 2018). The 23 test scores were standardized into z-scores using the means and standard deviations of the controls as reference. Negative values denoted poorer performance than the control group mean. To increase reliability, we generated composite scores of theoretically related test scores on the condition of Cronbach's $\alpha \geq 0.70$. This procedure (described in Supplementary Methods in the online Supporting information) rendered three composite z-scores and 11 separate z-scores (Table S2).

2.4.2. Cluster analysis

Hierarchical cluster analysis (HCA) was applied on the neurocognitive measures of the children with FHR-BP and FHR-SZ (total $N = 315$; FHR-SZ: $N = 197$; FHR-BP: $N = 118$) using Ward's method to minimize the total within-cluster variance. Squared Euclidean distance was used as the dissimilarity measure to evaluate the appropriateness of a three-cluster solution and explore whether a different number of clusters offered a better fit to the data. The optimal number of clusters was determined by visual inspection of the dendrogram and the elbow method (Kassambara, 2017). The elbow method uses the total within-cluster sum of square (WSS) as a function of the number of clusters. When plotting the WSS against the number of clusters, the bend of the curve indicates a parsimonious number of clusters, where additional clusters would add little value. To confirm the cluster fit generated by the HCA, K means clustering was applied. To investigate the relative risk of cluster participation compared with controls, we repeated the HCA including the controls ($N = 199$).

2.4.3. Pairwise comparisons of neurocognitive clusters

To reduce the risk of type I errors we conducted a multivariate analysis of variance (MANOVA) with Scheffé post hoc correction in the pairwise comparisons of the neurocognitive cluster and control group performances on the neurocognitive measures. The identified neurocognitive cluster profiles were characterized as jagged if some but not all of the neurocognitive indices differed significantly from the control group, whereas they were characterized as flat, if all or none of the neurocognitive indices differed significantly from the control group. To confirm the flatness or jaggedness of the cluster profiles, we exploratively conducted a series of *t*-test within each cluster.

2.4.4. Prevalence of subgroup membership

Differences in the prevalence of subgroup membership across FHR status were examined using Pearson's chi squared test followed by a column proportions test.

2.4.5. Exploratory analyses

In exploratory analyses we assessed the clinical relevance of the neurocognitive clusters in terms of concurrent level of functioning, dimensional psychopathology, adequacy of the home environment, and PGS using one-way ANOVA with Fisher's Least Significant Difference post hoc test. Data were analyzed using SPSS Statistics software version 25 (Corp. I 2017) and R version 3.5.3 (Team RDC, 2011).

3. Results

3.1. Demographic and clinical characteristics

See Table 1 for demographic, clinical, environmental, and polygenic characteristics and Table S2 for neurocognitive characteristics of the total cohort.

3.2. Hierarchical cluster analysis of neurocognitive functions

Visual inspection of the dendrogram followed by the elbow test supported a three-cluster solution (i.e. the optimal number of clusters indicating a good model fit) to best distinguish the participants based on their neurocognitive performance, while creating distinct subgroups of a reasonable size. This was confirmed in a K-means cluster analysis specifying a three-cluster solution. Based on their neurocognitive performance, the subgroups were labeled (1) Mildly Impaired, $N = 94$ (30%), (2) Typical, $N = 162$ (51%), and (3) Above Average, $N = 59$ (19%) (Table 2 and Fig. 1).

3.3. Pairwise comparisons of neurocognitive functions across neurocognitive subgroups and controls

The MANOVA showed a statistically significant effect of subgroup ($F = 13.48$; $P < .001$; Wilks $\lambda = 0.38$).

The Mildly Impaired subgroup performed significantly below controls (Cohen $d = 0.50$–1.45; $Ps < .001$) on all measures but set-shifting (IED EDS Errors, Cohen $d = 0.11$; $P = .84$) (Table 2). The Typical subgroup performed comparable to controls on all measures (Cohen $d = 0.00$–0.26; $Ps > 0.05$) but set-shifting (Trail Making Test Switching, Cohen $d = 0.35$; $P = .01$). The Above Average subgroup performed significantly above the controls on nine of 14 neurocognitive functions (Cohen $d = 0.44$–1.21; $Ps < 0.05$) and comparable to controls on five

Table 1
Demographic, clinical, environmental, and polygenic characteristics of 514 7-year-old children with familial high-risk of schizophrenia or bipolar disorder, and population-based controls.

Variables	Controls (*N* = 199)	FHR-SZ (*N* = 197)	FHR-BP (*N* = 118)	*P* Value	*P* Values Pairwise Comparisons		
					Controls vs FHR-SZ	Controls vs FHR-BP	FHR-SZ vs FHR-BP
Demographic characteristics							
Female, No. (%)	92 (46.2)	91 (46.2)	55 (46.6)	>0.99[a]	NA	NA	NA
Age at inclusion, mean (SD)	7.8 (0.2)	7.8 (0.2)	7.9 (0.2)	.09[b]	NA	NA	NA
Functioning and Dimensional Psychopathology	Mean (SD) Raw Score	Mean (SD) Raw Score	Mean (SD) Raw Score				
Children's Global Assessment Scale[c] (Total *N* = 512; Controls *N* = 197; FHR-SZ *N* = 197; FHR-BD *N* = 118)	77.7 (13.5)	68.1 (15.5)	73.6 (14.9)	<0.001[b]	<0.001	.02	.001
Child behavior Checklist, Total Score[d] (Total *N* = 492; Controls *N* = 191; FHR-SZ *N* = 190; FHR-BD *N* = 111)	17.0 (14.7)	27.2 (21.1)	23.4 (19.7)	<0.001[b]	<0.001	.009	.06
Home Environment	Mean (SD) Raw Score[e]	Mean (SD) Raw Score[f]	Mean (SD) Raw Score				
Middle Childhood-HOME Inventory, Total Score[g] (Total *N* = 505; Controls *N* = 196; FHR-SZ *N* = 193; FHR-BD *N* = 116)	49.03 (4.35)	45.09 (6.13)	46.70 (4.68)	<0.001[b]	<0.001	<0.001	.009
Polygenic Scores	Mean (SD) *z* Score[h]	Mean (SD) *z* Score[h]	Mean (SD) *z* Score[h]				
Polygenic Score for Schizophrenia from SNPs at *p*-value 1.0 threshold (Total *N* = 402; Controls *N* = 158; FHR-SZ *N* = 147; FHR-BD *N* = 97)	0.00 (1.00)	-0.21 (0.98)	-0.31 (1.03)	.04[b]	.07	.02	.43
Polygenic Score for Bipolar Disorder from SNPs at *p*-value 1.0 threshold (Total *N* = 402; Controls *N* = 158; FHR-SZ *N* = 147; FHR-BD *N* = 97)	0.00 (1.00)	-0.20 (0.87)	-0.19 (1.01)	.13[b]	NA	NA	NA

Abbreviations: NA = Not applicable; FHR-SZ, familial high risk of schizophrenia; FHR-BP, familial high risk of bipolar disorder.
[a] Pearson X^2 test.
[b] One-Way ANOVA with Fisher's Least Significant Difference (LSD) post hoc test.
[c] Minimum and maximum scores for this scale range from 1 to 100, with higher scores indicating higher level of functioning; scores in this cohort range from 35 to 100.
[d] Minimum and maximum scores for this scale range from 0 to 226, with higher scores indicating more problems; scores in this cohort range from 0 to 103.
[e] Minimum and maximum scores for this scale range from 0 to 27, with higher scores indicating more inattention; scores in this cohort range from 0 to 26.
[f] Minimum and maximum scores for this scale range from 0 to 195, with higher scores indicating more social reciprocity deficits in social settings; scores in this cohort range from 0 to 170.
[g] Minimum and maximum scores for this scale range from 0 to 59, with higher scores indicating a more adequate home environment; scores in this cohort range from 27 to 58.
[h] All scores are standardized into *z* scores with the control group mean as reference. Negative values denote poorer outcome.

(Cohen d = 0.20–0.46; *Ps* > 0.05). Thus, the within-subgroup profiles were significantly jagged in all three subgroups. Within-subgroup explorative paired t-tests across all indices confirmed that the three neurocognitive profiles were all jagged. Numerous but not all comparisons within each subgroup were significantly different with *P* values ranging from <0.001 to 0.896 in the Mildly Impaired subgroup, <0.001 to 0.980 in the Typical subgroup, and <0.001 to 0.990 in the Above Average subgroup (data not shown).

3.4. Pairwise comparisons of neurocognitive functions across neurocognitive subgroups excluding controls

For information only, the pairwise comparisons across neurocognitive subgroups excluding controls are depicted in Table S3 and described in the Supplementary Results in the online Supporting information.

3.5. Prevalence of subgroup membership

The distribution of children at FHR-SZ was 35.53% in the Mildly Impaired subgroup, 49.24% in the Typical, and 15.23% in the Above Average subgroup (Fig. 2). For children at FHR-BP it was 20.3% in the Mildly Impaired subgroup, 55.1% in the Typical, and 24.6% in the Above Average subgroup. The prevalence of subgroup membership was overall significantly different between children at FHR-SZ and FHR-BP (x^2 (2, N = 315) = 9.64; P < .01). A significantly larger proportion of children at FHR-SZ was in the Mildly Impaired subgroup, and a significantly larger proportion of children at FHR-BP was in the Above Average subgroup, while the difference in the Typical subgroup was non-significant (data not shown).

3.6. Risk ratios of subgroup membership between children at FHR-SZ or FHR-BP versus controls

Compared with controls, children at FHR-SZ had a 93% increased risk of being in the Mildly Impaired subgroup (risk ratio [RR], 1.93; 95% CI, 1.40–2.64); they were 17% less likely to be in the Typical (RR, 0.83; 95% CI, 0.67–1.03) and 39% less likely to be in the Above Average subgroup (RR, 0.61; 95% CI, 0.42–0.90). Compared with controls children at FHR-BP had an 8% increased risk of being in the Mildly Impaired subgroup (RR, 1.08; 95% CI, 0.71–1.66); they were 1% less likely to be in the Typical (RR, 0.99; 95% CI, 0.79–1.24) and 4% less likely to be in the Above Average subgroup (RR, 0.96; 95% CI, 0.67–1.40) (Table S4).

3.7. Pairwise comparisons of concurrent functioning, level of psychopathology, adequacy of the home environment, and polygenic scores across neurocognitive subgroups

The Mildly Impaired subgroup had a significantly lower level of concurrent functioning than the Typical (Cohen d = 0.90; P < .001) and the Above Average subgroup (Cohen d = 1.25; P < .001), whereas the latter subgroup functioned significantly better than the Typical subgroup (Cohen d = 0.35; P = .03) (Table 3). The Above Average subgroup had a significantly lower level of psychopathology than the Typical (Cohen d = 0.34; P = .04) and the Mildly Impaired Subgroup (Cohen d = 0.56; P < .001), whereas the latter two were non-significantly different (Cohen d = 0.23; P = .08). The Mildly Impaired subgroup lived in significantly less adequate home environments than the Typical (Cohen d = 0.33; P = .008) and the Above Average subgroup (Cohen d = 0.61; P < .001), whereas the latter two were non-significantly different (Cohen d = 0.29; P = .09). The Typical subgroup's PGS for SZ were significantly

Table 2
Pairwise comparisons of neurocognitive performance by neurocognitive subgroups in children at familial high-risk of schizophrenia or bipolar disorder versus population-based controls (Total $N = 514$).

Variables	Controls ($N = 199$)	Mildly Impaired ($N = 94$)	Typical ($N = 162$)	Above Average ($N = 59$)	P value	Pairwise Comparisons *P* Values & Effect Sizes (Cohen *d*)					
						Mildly Impaired vs Controls		Typical vs Controls		Above Average vs Controls	
						P	*d*	*P*	*d*	*P*	*d*
Female, No. (%)	92 (46)	33 (35)	87 (54)	26 (44)	**.04**[a]	0.08	NA	0.16	NA	.77	NA
Age, Mean (SD)	7.8 (0.20)	7.8 (0.25)	7.9 (0.21)	7.9 (0.17)	**.04**[b]	0.94	0.00	**.04**	0.49	**.02**	0.54
Neurocognition	Mean (SD) *z* score[c]	Mean (SD) *z* score[c]	Mean (SD) *z* score[c]	Mean (SD) *z* score[c]							
1. Verbal Memory (Composite Score)	0.00 (1.00)	-0.87 (0.92)	0.25 (0.91)	0.72 (0.98)	**<0.001**[d]	**<0.001**	0.91	.10	0.26	**<0.001**	0.73
2. Processing Speed (Composite Score)	0.00 (1.00)	-1.30 (0.92)	-0.07 (0.80)	0.48 (0.78)	**<0.001**[d]	**<0.001**	1.35	.92	0.08	**.005**	0.54
3. Working Memory (Composite Score)	0.00 (1.00)	-1.36 (0.87)	-0.06 (0.89)	0.89 (0.90)	**<0.001**[d]	**<0.001**	1.45	0.96	0.06	**<0.001**	0.94
4. Verbal Intelligence (Guess What)	0.00 (1.00)	-0.92 (1.28)	-0.13 (1.05)	0.41 (0.77)	**<0.001**[d]	**<0.001**	0.80	0.69	0.13	.08	0.46
5. Nonverbal Intelligence (Odd-Item Out)	0.00 (1.00)	-0.77 (0.76)	0.10 (1.03)	0.71 (1.05)	**<0.001**[d]	**<0.001**	0.87	0.80	0.10	**<0.001**	0.69
6. Sustained Attention (RVP A')	0.00 (1.00)	-1.17 (1.41)	-0.05 (0.90)	0.33 (0.77)	**<0.001**[d]	**<0.001**	0.96	0.98	0.05	.20	0.37
7. Visuospatial Memory I (SRM percent correct)	0.00 (1.00)	-1.01 (1.06)	-0.15 (0.89)	0.44 (0.84)	**<0.001**[d]	**<0.001**	0.98	0.56	0.16	**.03**	0.48
8. Visuospatial Memory II (RCFT Immediate Recall)	0.00 (1.00)	-0.80 (0.70)	-0.09 (0.91)	0.19 (0.92)	**<0.001**[d]	**<0.001**	0.93	0.83	0.09	.59	0.20
9. Planning (SOC PSIMM)	0.00 (1.00)	-0.52 (1.09)	0.00 (1.00)	0.43 (0.96)	**<0.001**[d]	**<0.001**	0.50	1.00	0.00	**.04**	0.44
10. Set shift I (IED EDS Errors)	0.00 (1.00)	0.11 (1.07)	-0.21 (0.85)	1.04 (0.69)	**<0.001**[d]	.84	0.11	.20	0.23	**<0.001**	1.21
11. Set shift II (TMT Switching)	0.00 (1.00)	-0.90 (0.63)	-0.33 (0.86)	0.72 (0.78)	**<0.001**[d]	**<0.001**	1.08	**0.01**	0.35	**<0.001**	0.80
12. Set Shift III (Verbal Fluency Switching)	0.00 (1.00)	-0.59 (0.91)	0.11 (0.93)	0.30 (0.86)	**<0.001**[d]	**<0.001**	0.62	0.75	0.11	.20	0.32
13. Verbal Fluency I (Phonemic)	0.00 (1.00)	-0.97 (0.79)	0.11 (0.95)	0.56 (0.93)	**<0.001**[d]	**<0.001**	1.08	0.72	0.11	**.001**	0.58
14. Verbal Fluency II (Semantic)	0.00 (1.00)	-0.83 (0.84)	-0.07 (0.89)	0.27 (0.97)	**<0.001**[d]	**<0.001**	0.90	0.93	0.07	.29	0.27

Abbreviations: FHR-BP, familial high risk of bipolar disorder, FHR-SZ, familial high risk of schizophrenia; EDS = Extra-Dimensional Stage; IED = Intra-Extra Dimensional Set Shift; NA, not applicable; PSIMM = Problems Solved in Minimum Moves; RCFT = Rey Complex Figure Test and Recognition Trial; RVP = Rapid Visual Information Processing; SOC = Stockings of Cambridge; SRM = Spatial Recognition Memory; TMT = Trail Making Test.
Bold indicates significance at the 0.05 level.
[a] Pearson Chi-square.
[b] One-Way ANOVA with Fisher's Least Significant Difference (LSD) post hoc test.
[c] All scores are standardized into *z* scores with the control group mean as reference. Negative values denote poorer outcome.
[d] To reduce the risk of Type I errors, a MANOVA was conducted on all the neurocognitive functions and followed by a series of ANOVAs and Scheffé post hoc tests for between-subgroup comparisons.

poorer than those of the Mildly Impaired subgroup (Cohen $d = 0.47$; $P = .002$), but non-significantly different from the Above Average subgroup (Cohen $d = 0.29$; $P = .09$). Given the counterintuitive results on PGS for SZ, we conducted non-parametric analyses with Spearman's Rho to investigate the correlations between PGS for SZ and the neurocognitive functions in the two high risk groups separately and then in the total sample of children at FHR-SZ and FHR-BP. The majority of correlations were rendered non-significant (data not shown). In children at FHR-SZ the PGS for SZ was significantly, but weakly correlated to five functions (r_s range = 0.16–0.22; $p < .05$). In children at FHR-BP the PGS for SZ was significantly, but weakly correlated to two functions (r_s range = 0.20–0.30; $p < .05$). In the total sample of children at FHR-SZ and FHR-BP, the PGS for SZ was significantly, but weakly correlated to five functions (r_s range = 0.15–0.18; $p < .05$). The PGS for BP were non-significantly different across subgroups (Cohen $d = 0.02$–0.09; $P = .87$).

4. Discussion

This study investigated neurocognitive heterogeneity in preadolescent, same-aged children at FHR-BP and FHR-SZ using a data-driven method. In this large, population-based cohort study with comprehensive neurocognitive phenotyping, we identified three distinct neurocognitive subgroups with a (1) Mildly Impaired, (2) Typical, and (3) Above Average neurocognitive profile. The Mildly Impaired subgroup underperformed the controls on all indices but one aspect of set-shifting, whereas the Typical subgroup performed comparable to controls on all but another aspect of set-shifting, where they underperformed the controls. The Above Average subgroup performed better on 9 of the 14 neurocognitive indices. Thus, neurocognitive heterogeneity exits in young children at FHR of schizophrenia and bipolar disorder. This is in line with previous findings in unaffected adult relatives (Russo et al., 2017; Islam et al., 2018), individuals at CHR of psychosis (Velthorst et al., 2019), youth at FHR of BP and young offspring at FHR of bipolar disorder and schizophrenia with a wide age range (Bora et al., 2019; Valli et al., 2021). The considerable percentage of children in both FHR groups with a Mildly Impaired neurocognitive profile may reflect the effect of shared risk factors such as genetic risk factors contributing to neurocognitive impairment. Importantly, 64.4% of the children at FHR-SZ and 79.7% of the children at FHR-BP had typical or above average neurocognitive functioning across neurocognitive indices. This

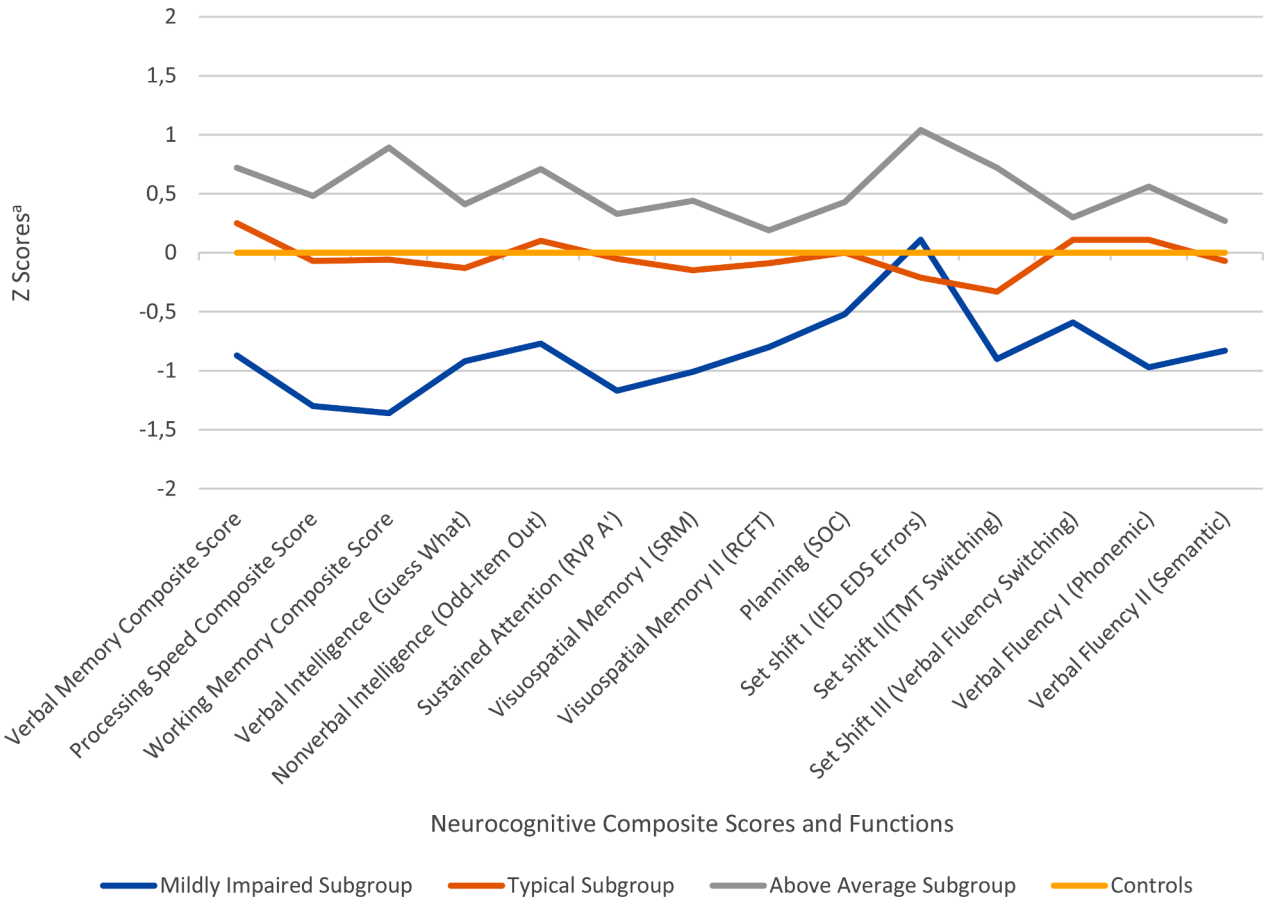

Fig. 1. Neurocognitive profiles by subgroup
Includes 315 children at familial high risk of schizophrenia or bipolar disorder (94 children in the Mildly Impaired subgroup, 162 children in the Typical subgroup, 59 children in the Above Average subgroup) and 199 controls. EDS indicates extradimensional stage; IED, Intra-Extra Dimensional Set Shift; RCFT, Rey Complex Figure Test and Recognition Trial; RVP, Rapid Visual Information Processing; SOC, Stockings of Cambridge; SRM, Spatial Recognition Memory; TMT, Trail-Making Test
[a] Standard deviations and effect sizes are included in Table 2.

finding may help destigmatize young children at FHR-BP and FHR-SZ. This prevalence however, is considerably higher than in previous studies of offspring of parents with bipolar disorder or schizophrenia (ranging between 25.4% and 46.9%) (Bora et al., 2019; Valli et al., 2021) with considerably wider age ranges (15–30 years and 6–17 years, respectively) as well as higher mean ages (23.3 and 11.7 years, respectively). This may be explained by the effect of a potential cognitive developmental lag (i.e., slower neurocognitive maturation compared with controls, which leads to increasingly larger deficits with age) (Reichenberg et al., 2010). Of note are also the 15.2% of children at FHR-SZ and 24.6% children at FHR-BP who were in the Above Average subgroup. On one hand, evidence from individuals at clinical high-risk for psychosis indicates that these children may be at less risk of later transition to psychosis (Velthorst et al., 2019). On the other hand, evidence from studies on premorbid functioning in individuals with nonpsychotic bipolar disorder (Reichenberg et al., 2002) and school performance in children of parents with bipolar disorder (Ranning et al., 2018) suggests that intellectual well-functioning children at FHR-BP may be at increased risk of later transition to bipolar disorder. The neurocognitive profiles were jagged in all three subgroups. Moreover, the profile pattern of the Above Average subgroup was more heterogeneous (nine out of 14 indices were significantly higher the those of the controls) than those of the two other subgroups (one out of 14 indices did not differ from the those of the controls in the Mildly Impaired subgroup and one out of 14 indices differed from those of the controls in the Typical subgroup). This pattern of subgroups is in line with previous studies of neurocognitive heterogeneity in offspring of parents with bipolar disorder or schizophrenia (Bora et al., 2019; Valli et al., 2021). Given a neurocognitive development that is stable or even lagging, all the neurocognitive indices in the Mildly Impaired subgroup but set-shifting (as observed in the extra-dimensional stage of the Intra-Extra Dimensional Set-Shift task) may be potential risk markers for later transition to illness. All neurocognitive indices but verbal intelligence, sustained attention, visuospatial memory, and verbal fluency (switching and semantic) in the Above Average subgroup are potential markers for risk in the children at FHR-BP (MacCabe et al., 2010) and resilience in the children at FHR-SZ (Velthorst et al., 2019). In the Typical subgroup, set-shifting as measured with verbal fluency may be a risk marker for later transition to illness. Taken together, these risk markers may be of clinical relevance in future treatment trials targeting specific neurocognitive deficits. Moreover, working memory demonstrates protracted maturational courses in population-based (Gur et al., 2012) and psychosis spectrum youth (ages 8–21) (Gur et al., 2014) and young adults (18 months to 20 years) together with processing speed and attention (Mollon et al., 2018). Thus, one may speculate that the working memory, processing speed, and attention indices in the Mildly Impaired subgroup will lag further behind with increasing age. Importantly, impairment in these functions are known indicators of conversion to psychosis in clinical high-risk populations (Seidman et al., 2016). Finally, the risk ratios of neurocognitive subgroup membership showed that, compared with controls, children at FHR-SZ had an almost 2-fold higher risk of being in the Mildly Impaired subgroup, while the risk of

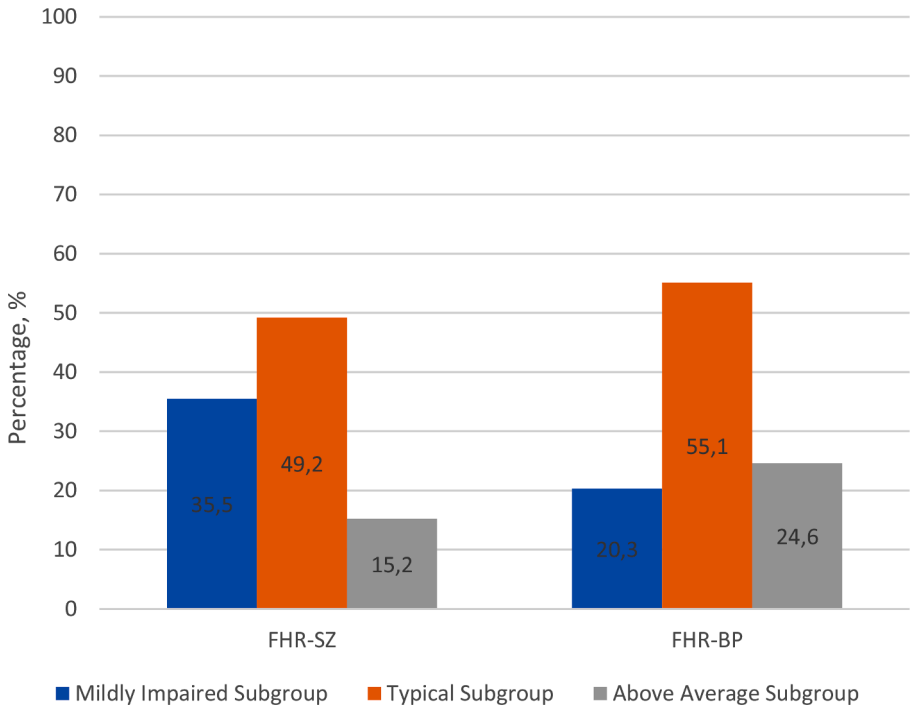

Fig. 2. Familial high-risk status by neurocognitive subgroup
FHR-SZ indicates familial high risk of schizophrenia; FHR-BP, familial high risk of bipolar disorder.

children at FHR-BP was only 8% increased. To our knowledge, this is the first study to investigate the relative risk of neurocognitive subgroup membership in bipolar and schizophrenia offspring compared with controls (Bora et al., 2019; Valli et al., 2021), which allows for the comparison of the neurocognitive heterogeneity of the combined FHR groups with that of a low-risk reference group. Using a cross-diagnostic approach enables identification of subgroups of children at familial high-risk of schizophrenia or bipolar disorders who may be at increased risk of developing severe mental illness irrespective of parental diagnosis.

The clinical relevance of the identified neurocognitive subgroups was demonstrated in associations to concurrent level of functioning, level of psychopathology, and adequacy of the home environment, which is in line with previous findings in familial high-risk offspring (Bora et al., 2019; Valli et al., 2021) except from the home environment, which has not previously been investigated in neurocognitive subgroups. Given the aforementioned high heritability of neurocognitive functions, we speculate that poorer parental cognitive and social functioning in the high-risk families (Greve et al., 2021) in concert with the children's own neurocognitive impairments in the Mildly Impaired subgroup may affect and thus explain the less adequate home environment in this subgroup.

Although the predictive value of neurocognitive profiles in these preadolescent high-risk offspring with regard to later transition to severe mental illness and long-term functional outcome has yet to be investigated, evidence from studies of individuals at CHR of psychosis (Velthorst et al., 2019) and young adults with emerging mental disorders (Crouse et al., 2020) suggests increased risk of transitioning as well as poorer functional outcome in the most impaired cognitive subgroup. PGS for schizophrenia reflected a seemingly counterintuitive pattern with the Typical neurocognitive subgroup displaying a higher genetic risk for schizophrenia than the Mildly Impaired neurocognitive subgroup. The fact that only few and very weak correlations between PGS for SZ and the neurocognitive functions were identified, may to some degree elucidate, why the results on PGS for SZ in the neurocognitive subgroups seem counterintuitive. Additionally, evidence suggests that PGS for schizophrenia is a genetically heterogeneous trait aggregating over several sub-phenotypes with different genetic make-up and therefore may not follow a consistent pattern of either positive or negative association to neurocognitive impairment (Bansal et al., 2018). Moreover, PGS for schizophrenia seemed independent of cognition in patients with schizophrenia or psychosis in previous studies (Richards et al., 2020; Shafee et al., 2018). This cross-sectional evidence of lower concurrent functioning, less adequacy of the home environment, and a higher level of psychopathology in the Mildly Impaired neurocognitive subgroup is of potential clinical utility in the guidance and tailoring of future interventions in e.g. school settings for the neurocognitively affected FHR children. Neuropsychological testing represents a relatively low-cost and low-risk method to identify children who are at potential higher risk of poorer concurrent and long-term functioning as well as later transition to bipolar disorder or schizophrenia. Neurocognitive impairments are endophenotypes for both schizophrenia and bipolar disorder (Bora, 2017; Gottesman and Gould, 2003). Targeting these neurocognitive deficits with e.g. cognitive remediation may prove a viable method (Hooker et al., 2014; Keshavan et al., 2014; Piskulic et al., 2015; Wykes et al., 2011) for pre-emptive interventions to improve neurocognitive and concurrent functioning, academic achievement, and potentially resilience to mental illness in children at FHR-SZ or FHR-BP. Owing to the cross-sectional study design we have identified bidirectional associations where cause and effect cannot be inferred except that of genetic disposition. In terms of neurocognitive maturation during late childhood and onwards, future planned follow-up studies will show how stable these clusters are and how they potentially relate to the risk of schizophrenia or bipolar disorder. Moreover, as the heritability of intelligence increases with age, one may speculate that the association between PGS and the identified subgroups may also grow stronger with increasing age (Plomin et al., 2016).

This study has several strengths including a large population-based cohort of young preadolescent children at FHR-SZ or FHR-BP and controls assessed with a detailed neurocognitive test battery. To the best of our knowledge, this is the first study to investigate neurocognitive heterogeneity in same-aged preadolescent children at FHR-BP or FHR-SZ, which allows for the identification of potentially shared risk factors that contribute to cognitive impairment in distinct subgroups. We are

Table 3
Pairwise comparisons of concurrent functioning, psychopathology, polygenic scores, and the home environment across neurocognitive subgroups of children at familial high-risk of schizophrenia or bipolar disorder ($N = 315$).

Variables	Mildly Impaired	Typical	Above Average	*P* Value	Pairwise Comparisons *P* Values & Effect Sizes (Cohen *d*)					
					Mildly Impaired vs Typical		Mildly Impaired vs Above Average		Typical vs Above Average	
					P	*d*	*P*	*d*	*P*	*d*
No. (%)	94 (30)	162 (51)	59 (19)	NA	NA	NA	NA	NA	NA	NA
Female, No. (%)	33 (35)	87 (54)	26 (44)	**.02**[a]	**.004**	NA	.27	NA	.21	NA
Age at inclusion, Mean (SD)	7.8 (0.25)	7.9 (0.21)	7.9 (0.17)	.10[b]	NA	NA	NA	NA	NA	NA
Clinical Symptomatology and Functioning	Mean (SD) *z* score[c]	Mean (SD) *z* score[c]	Mean (SD) *z* score[c]							
Children's Global Assessment Scale (Total $N = 315$; Mildly Impaired $N = 94$; Typical $N = 162$; Above Average $N = 59$)	-1.31 (1.17)	-0.33 (0.99)	0.00 (0.91)	**<0.001**[b]	**<0.001**	0.90	**<0.001**	1.25	**.03**	0.35
Child behavior Checklist, Total Score (Total $N = 301$; Mildly Impaired $N = 94$; Typical $N = 151$; Above Average $N = 56$)	-3.15 (0.92)	-2.94 (0.89)	-2.64 (0.89)	**.004**[b]	.08	0.23	**<0.001**	0.56	**.04**	0.34
Home Environment										
Middle Childhood-HOME Inventory, Total score (Total $N = 309$; Mildly Impaired $N = 92$; Typical $N = 159$; Above Average $N = 58$)	-1.14 (1.47)	-0.70 (1.23)	-0.36 (1.08)	**.001**[b]	**.008**	0.33	**<0.001**	0.61	.09	0.29
Polygenic Scores[d]										
Polygenic Score for Schizophrenia from SNPs at *p*-value 1.0 threshold (Total $N = 244$; Mildly Impaired $N = 66$; Typical $N = 128$; Above Average $N = 50$)	0.04 (0.95)	-0.43 (1.04)	-0.15 (0.86)	**.006**[b]	**.002**	0.47	.32	0.21	.09	0.29
Polygenic Score for Bipolar Disorder from SNPs at *p*-value 1.0 threshold (Total $N = 244$; Mildly Impaired $N = 66$; Typical $N = 128$; Above Average $N = 50$)	-0.17 (1.16)	-0.19 (0.82)	-0.26 (0.86)	.87[b]	NA	0.02	NA	0.09	NA	0.08

Bold indicates significance at the 0.05 level.
Abbreviations: NA, Not applicable.
[a] Pearson X^2 test.
[b] One-Way ANOVA with Fisher's Least Significant Difference (LSD) post hoc test.
[c] All scores are standardized into *z* scores with the control group mean as reference. Negative values denote poorer outcome.
[d] All analyses were run with both children in sibling pairs ($N = 16$) and then with only the one sibling who was first included. Excluding the second sibling from analyses did not change the significant results and therefore all siblings are included in the results reported.

also the first to examine the relative risk of neurocognitive subgroup membership in children at FHR-BP or FHR-SZ compared to controls. Limitations include the cross-sectional study design and smaller sample size of the FHR-BP group. Further, the relatively high dispersion of within-subgroup neurocognitive scores reflects less homogeneity. Finally, regarding environmental factors we examined psycho-social environmental aspects of the neurocognitive subgroups, whereas biological environmental factors such as obstetric complications known to be associated with schizophrenia (Demjaha et al., 2012) were not investigated.

5. Conclusions

Neurocognitive heterogeneity exists in young preadolescent children at familial high-risk of bipolar disorder or schizophrenia. Both children at FHR-BP and FHR-SZ were represented in all three neurocognitive subgroups with a significantly higher prevalence of children at FHR-SZ in the Mildly Impaired subgroup, and a significantly higher prevalence of children at FHR-BP in the Above Average subgroup. Noteworthy, 79.7% of the children at FHR-BP and 64.4% of the children at FHR-SZ had typical or above average neurocognitive functioning. The Mildly Impaired neurocognitive profile related to lower concurrent functioning, worse psychopathology, less adequate home environments, and less genetic risk for schizophrenia. Identification of neurocognitively impaired FHR offspring enables targeted pre-emptive interventions to enhance neurocognitive functioning and potentially also prevent transition to mental illness.

Author statement

Disclosure

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CRediT authorship contribution statement

Nicoline Hemager: Conceptualization, Formal analysis, Data curation, Writing – original draft, Writing – review & editing. **Camilla Jerlang Christiani:** Conceptualization, Data curation, Writing – review & editing. **Anne Amalie Elgaard Thorup:** Data curation, Writing – review & editing, Funding acquisition. **Katrine Søborg Spang:** Data curation, Writing – review & editing. **Ditte Ellersgaard:** Data curation, Writing –

review & editing. **Birgitte Klee Burton:** Data curation, Writing – review & editing. **Maja Gregersen:** Data curation, Writing – review & editing. **Aja Neergaard Greve:** Data curation, Writing – review & editing. **Yunpeng Wang:** Data curation, Writing – review & editing. **Ron Nudel:** Data curation, Writing – review & editing. **Ole Mors:** Writing – review & editing, Funding acquisition. **Kerstin Jessica Plessen:** Writing – review & editing, Funding acquisition. **Merete Nordentoft:** Writing – review & editing, Funding acquisition. **Jens Richardt Møllegaard Jepsen:** Conceptualization, Formal analysis, Data curation, Writing – original draft, Writing – review & editing.

Declarations of Competing Interest

None.

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Supplementary materials

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