Transmission of intelligence, working memory, and processing speed from parents to their seven-year-old offspring is function specific in families with schizophrenia or bipolar disorder

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ABSTRACT

Background: Prior studies have shown high heritability estimates regarding within-function transmission of neurocognition, both in healthy families and in families with schizophrenia but it remains an open question whether transmission from parents to offspring is function specific and whether the pattern is the same in healthy families and families with schizophrenia or bipolar disorder. We aimed to characterize the transmission of intelligence, processing speed, and verbal working memory functions from both biological parents to their 7-year-old offspring in families with parental schizophrenia, bipolar disorder, and population-based control parents.
Methods: The population-based cohort consists of 7-year-old children with one parent diagnosed with schizophrenia ($n = 186$), bipolar disorder ($n = 114$), and of parents without schizophrenia or bipolar disorder ($n = 192$). Children and both parents were assessed using identical, age-relevant neurocognitive tests of intelligence, verbal working memory, and processing speed.
Results: In multiple regression analyses children's intelligence, verbal working memory, and processing speed scores were significantly associated with the corresponding parental cognitive function score. All associations from parents to offspring across functions were non-significant. No significant parental cognitive function by group interaction was observed.
Conclusion: Transmissions of intelligence, processing speed, and verbal working memory from parents to offspring are function specific. The structure of transmission is comparable between families with schizophrenia, families with bipolar disorder and families without these disorders.

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1. Introduction

Neurocognitive functions are associated in healthy individuals (Carroll, 1993; Fry and Hale, 1996, 2000; Conway et al., 2002). Prior cross-sectional studies have yielded associations between intelligence, processing speed and working memory, and findings suggest that the relationship is the same in children and adults (Fry and Hale, 1996, 2000; Conway et al., 2002). The inter-correlations among cognitive functions are the basis for theories of general intelligence such as Spearman's g factor, which is considered a general factor of intelligence that contributes to all cognitive functions and is reflected in an individual's overall performance on cognitive tasks (Spearman, 1961; Lezak et al., 2004).

Extensive evidence confirms a generalized pattern of cognitive impairments in individuals with schizophrenia including functions such as intelligence, working memory, and processing speed (Heinrichs and Zakzanis, 1998a, 1998b; Fioravanti et al., 2012a, 2012b). These cognitive deficits seem to be stable and present premorbid as well as after symptoms have remitted (Reichenberg and Harvey, 2007; Szöke et al., 2008a, 2008b). In individuals with bipolar disorder, impairments of intelligence, working memory, and processing speed are also evident, although to a lesser degree than in schizophrenia (Bora et al., 2009a, 2009b; Bora, 2016).

The most robust risk factor predicting schizophrenia or bipolar disorder is a positive family history, and children of parents with severe mental illness have increased risk of developing, not only the disorder of the parent, but also other severe mental disorders (Rasic et al., 2013). Familial high-risk studies have demonstrated widespread neurocognitive abnormalities already in childhood of offspring of parents with schizophrenia (Agnew-Blais and Seidman, 2012; Hameed and Lewis, 2016; Burton et al., 2018; Hemager et al., 2018, 2019). The evidence regarding neurocognitive impairments in children at familial risk of bipolar disorder on the other hand is inconsistent with some studies demonstrating deficits in functions such as intelligence, processing speed and aspects of executive functioning while other studies found no impairments (de la Serna et al., 2016; Bora and Özerdem, 2017; Sharma et al., 2017; Hemager et al., 2018, 2019). The cognitive impairments of the offspring reflect an increased genetic risk for development of schizophrenia and bipolar disorder (Duffy et al., 2010; Reichenberg et al., 2010; Blokland et al., 2016). A substantial proportion of the variance in cognition and the liability to develop schizophrenia is due to genetic factors (Owens et al., 2012; Toulopoulou et al., 2015), partly shared with bipolar disorder (Lichtenstein et al., 2009).

In a systematic review of heritability estimates of neurocognitive functions in schizophrenia and healthy populations Blokland et al. (2016) were the first to show that the heritability estimates in individuals with schizophrenia did not differ significantly from those observed in healthy populations. The authors demonstrated high heritability estimates for general cognitive ability, both in families with schizophrenia and in healthy populations ($h^2 = 0.63$ versus $h^2 = 0.53$) (Blokland et al., 2016). The heritability of working memory was also high in studies of families with schizophrenia and in healthy populations ($h^2 = 0.43$ versus $h^2 = 0.41$) (Blokland et al., 2016) and heritability estimates of the function attention/processing was $h^2 = 0.26$ versus $h^2 = 0.45$ in families with schizophrenia and healthy populations (Blokland et al., 2016).

To the best of our knowledge, no study has investigated if the transmissions of different neurocognitive functions from both parents to offspring in families with schizophrenia or bipolar disorder are associated across functions, are partly associated, or are function specific. The objective of this study was to investigate the structure of transmission of intelligence, processing speed, and verbal working memory from both biological parents to their 7-year-old offspring in three groups of families where one parent was diagnosed with schizophrenia, bipolar disorder, or none of these disorders.

2. Methods

This study is part of The Danish High Risk and Resilience Study – VIA 7, a nationwide cohort established in Denmark between January 2013 and January 2016. The VIA 7 cohort consists of 522 children aged 7 with no, one, or two parents diagnosed with schizophrenia or bipolar disorder. The design of the VIA 7 study is described in detail elsewhere (Thorup et al., 2015).

2.1. Participants

Participants were identified through the Danish Civil Registration System (Pedersen et al., 2006) and the Danish Psychiatric Central Research Register (Mors et al., 2011). Schizophrenia was defined as schizophrenia, delusional disorder, or schizoaffective disorder (ICD-10-codes: F20, F22, and F25 or ICD-8-codes: 295, 297, 298.29, 298.39, 298.89, 298.99) and bipolar disorder as ICD 10-code: F30 and F31 and ICD 8-codes: 296.19, 296.39. The VIA 7 sample was drawn from the total population of 7-year-old children in the study period who had parents diagnosed with schizophrenia or bipolar disorder together with population-based control (PBC) children of the same age and sex (eFigure in the Supplement). We chose to assess the children at age 7 because in Denmark most children have started school at age 7. Beginning school denotes an important developmental step for the child with increased cognitive, academic and social demands.

Index parents were defined as the affected parent or the PBC parent, and co-parents were defined as the other biological parent without a diagnosis of schizophrenia and bipolar disorder in the registers. Children from the PBC group were matched with children from the familial high risk schizophrenia group on age, sex, and municipality. Children at familial high risk of bipolar disorder were included as an unmatched comparison group. The gender of the index parent in the schizophrenia group defined the gender of the index parent in the matched PBC family. Demographic characteristics of the cohort are presented in Table 1. The main analyses in this study were based on 492 children, 492 index parents and 492 co-parents from 186 families with one parent diagnosed with schizophrenia, 114 families with one parent diagnosed with bipolar disorder, and 192 PBC families.

2.2. Procedures

All adult participants provided written informed consent after receiving both a verbal and written description of the study. The Danish Data Protection Agency approved the study. The Danish Ministry of Health granted permission to retrieve data from the Danish registers. The study protocol was evaluated by the Danish Committee on Health Research Ethics, but according to Danish law observational studies do not require ethical approval. All assessors (psychologists, medical doctors, and nurses) were trained, certified and supervised by a specialist in child neuropsychology (JRMJ). All assessors of children were blinded to the illness status of the family. The majority of assessments were conducted at the Psychosis Research Unit, Aarhus University Hospital, Risskov, Denmark, and at the Research Unit, Mental Health Centre Copenhagen, Copenhagen, Denmark, and a minority of assessments in the homes of the participating families.

2.3. Clinical measures

We used the Children's Global Assessment Scale (CGAS) (Shaffer et al., 1983) to assess the current level of functioning of the children. Levels of social functioning for the index parent and the biological co-parent were rated using the Personal and Social Performance scale (PSP) (Morosini et al., 2000). Both CGAS and PSP were rated based on the previous month, and consensus meetings were held regularly to secure agreement among raters.

Table 1
Demographics and clinical characteristics of children and biological parents from the full VIA 7 cohort.

	FHR-SZ	FHR-BP	PBC	P-value Pairwise comparisons		
				FHR-SZ vs. PBC	FHR-BP vs. PBC	FHR-BP vs. FHR-SZ
Children, N	202	120	200	–	–	–
Female, N (%)	93 (46.0)	56 (46.7)	93 (46.5)	0.926[c]	0.977[c]	0.913[c]
Age at inclusion, mean (SD)	7.84 (0.22)	7.86 (0.20)	7.81 (0.20)	0.532[d]	0.106[d]	1.000[d]
Two biological parents with SZ and/or BP, N (%)	8 (4.0)	1 (0.8)	–	–	–	–
CGAS[a], N, mean (SD), (N = 514)	N = 199	N = 118	N = 197	**<0.001[d]**	**0.044[d]**	**0.004[d]**
	68.1 (15.4)	73.6 (14.9)	77.7 (13.5)			
Child's home environment						
Living with both biological parents, N (%)	82 (40.6)	63 (52.5)	169 (84.5)	**<0.001[c]**	**<0.001[c]**	**0.038[c]**
Living out of home, N (%)	11 (5.4)	0 (0.0)	1 (0.5)	**0.004[c]**	0.438[c]	**0.009[c]**
Living with index parent, N (%)	124 (61.4)	84 (70.0)	189 (94.5)	**<0.001[c]**	**<0.001[c]**	0.118[c]
Living with a single parent, N (%) (N = 521)	75 (37.1)	39 (32.5)	21 (10.6)	**<0.001[c]**	**<0.001[c]**	0.401[c]
Index parents, N	200	116	204	–	–	–
Female, N (%)	111 (55.5)	64 (55.2)	115 (56.4)	0.860[c]	0.835[c]	0.955[c]
Age at inclusion, mean (SD)	38.10 (6.07)	41.00 (6.99)	40.62 (4.84)	**<0.001[d]**	1.000[d]	**<0.001[d]**
PSP[b], mean (SD) (N = 454)	N = 158	N = 102	N = 194	**<0.001[d]**	**<0.001[d]**	0.286[d]
	66.1 (15.7)	68.9 (14.1)	84.3 (9.9)			
Employed or studying, N (%) (N = 497)	93 (49.7)	61 (56.0)	185 (92.0)	**<0.001[c]**	**<0.001[c]**	0.301[c]
Education, N (N = 481)	178	109	197			
Primary/lower secondary, N (%)	54 (30.3)	10 (9.2)	8 (4.1)	**<0.001[c]**	0.985[c]	**<0.001[c]**
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 co-parents, N	186	114	192			
Female, N (%)	82 (44.1)	51 (44.7)	83 (43.2)	0.867[c]	0.797[c]	0.912[c]
Age at inclusion, mean (SD)	38.77 (6.35)	40.95 (5.37)	40.77 (4.26)	**0.001[d]**	1.000[d]	**0.002[d]**
PSP[b], mean (SD) (N = 437)	N = 163	N = 94	N = 180	**<0.001[d]**	**0.040[d]**	**0.002[d]**
	76.4 (14.3)	81.8 (13.1)	85.5 (8.4)			
Employed or studying, N (%) (N = 474)	133 (75.1)	93 (85.3)	179 (95.2)	**<0.001[c]**	**0.003[c]**	**0.040[c]**
Education, N (N = 469)	176	106	187			
Primary/lower secondary, N (%)	31 (17.6)	5 (4.7)	10 (5.3)	**0.002[c]**	0.276[c]	**<0.001[c]**
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)			

In the case of siblings, parent information is only included from the first included sibling in order not to count the same parent twice. P-values < 0.05 are shown in bold.

FHR-SZ = familial high risk for schizophrenia, FHR-BP = familial high risk for bipolar disorder, PBC = Population based controls, Index parent = the affected parent or the matched control, Co-parents = other biological parent.

[a] Children's Global Assessment Scale.
[b] The Personal and Social Performance Scale.
[c] Chi squared test of independency in contingency table.
[d] One-way ANOVA.

2.4. Neurocognition

Intelligence was estimated using The Reynolds Intellectual Screening Test (RIST) (Reynolds and Kamphaus, 2003, 2009), an individually administered screening of intelligence that consists of a verbal subtest (Guess What) and a nonverbal subtest (Odd-Item Out). The RIST index is based on norms stratified on the basis of age (Danish norms are provided by the publisher, 2011) and cover a broad age range (3–90 years). Reliability of the RIST index is 0.98 (Cronbachs alfa, calculated from the subtests) (Reynolds and Kamphaus, 2003). Verbal working memory in children was assessed with Letter-Number Sequencing (LNS) from the Wechsler Intelligence Scale for Children–fourth edition (WISC-IV) (Wechsler, 2003) and in parents with LNS from Wechsler Adult Intelligence Scale–fourth edition (WAIS-IV) (Wechsler, 2008). Processing speed in children was measured with Coding from WISC-IV and in parents with Coding from the WAIS-IV (Wechsler, 2004, 2008) using published Danish, age stratified norms for adults (co-parents and index parents) and raw scores for children. Trained research assistants who were blinded to the illness status of the parents and the risk status of the children carried out the scoring of the neurocognitive tests under supervision of the first author (ANG) and a specialist in clinical child psychology (NH).

2.5. Data analysis

All analyses were performed with Stata 13 statistical software, and a significance level of 5 % was applied. Demographic and clinical characteristics of the three study groups (schizophrenia, bipolar disorder, and PBC) were compared using one-way ANOVA or chi-squared test of independence as appropriate. The assumption of normality was met for the three neurocognitive variables for index parents, co-parents, and children. Because of missing observations on the three neurocognitive variables (1.0 % to 1.5 % for children, 12.2 % to 14.0 % for index parents, and 10.6 % to 10.8 % for co-parents), we applied multiple imputation with 50 imputations using a multivariate normal distribution separately for index parents, co-parents and children and with high risk status, age, and gender entered into the models as predictors. We assumed missingness at random (MAR) and due to arbitrary missing data pattern, we used Markov Chain Monte Carlo (MCMC) imputation methods to simulate imputed values from the posterior predictive distribution of the missing data given the observed data. Results based on multiple imputation were essentially the same as results based on a reduced sample with complete data. We compared the three study groups on their performance on the three neurocognitive test scores using multivariate analysis of variance (MANOVA) calculated separately for index parents, co-parents and children. Comparisons between the three study groups on measures of intelligence, verbal working memory, and processing speed were performed using a general linear regression model. The three neurocognitive test scores were standardized into z-scores using the means and SDs of the control group as reference for children, index parents, and co-parents, respectively. The z-scores were constructed so a lower score reflects a poorer performance. Multiple regression analyses were applied with the child neurocognitive scores as dependent variable and index parents' and co-parents' neurocognitive scores, group, gender of the index parents, and gender of the children as predictors. The control group was used as reference category. Female gender was used as reference category. Interaction term were applied between index parents' neurocognitive function score and group to test potential differential association across risk groups. A likelihood ratio test was used to test the multiple regression analysis with and without interaction effect. Due to the risk of overcorrecting, we did not co-vary for socioeconomic status, which is intrinsically associated with group status.

3. Results

The children from the three study groups did not differ significantly by age or gender. Compared with the control group, children of parents diagnosed with schizophrenia or bipolar disorder displayed a significantly lower mean CGAS score. Index parents and co-parents from the three study groups did not differ significantly in gender but index parents with schizophrenia were significantly younger compared to index parents from the control group and index parents with bipolar disorder. Compared with parents from the control group, both index parents and co-parents from families with schizophrenia or bipolar disorder displayed a significantly lower mean PSP score (Table 1).

MANOVA showed a statistically significant effect of group on RIST index score, LNS score, and Coding score for index parents ($F = 439.24$; $P < 0.001$; Wilks = 0.90), for co-parents ($F = 201.30$; $P < 0.001$; Wilks = 0.95), and for children ($F = 189.93$; $P < 0.001$; Wilks = 0.96). Index parents with schizophrenia scored significantly lower than population-based control (PBC) index parents on the RIST index score, the LNS

Table 2
RIST index, Coding score, and Letter-number sequencing score in index parents ($n = 492$), co-parents (n = 492) and children (n = 492).

Test/variable	FHR-SZ	FHR-BP	PBC	Pairwise comparisons		
				FHR-SZ vs. PBC	FHR-BP vs. PBC	FHR-BP vs. FHR-SZ
	Mean (SD)	Mean (SD)	Mean (SD)	P[d]	P[d]	P[d]
RIST index[a]						
- Index parent	101.4 (9.9)	104.4 (8.1)	103.8 (8.2)	**0.015**	0.561	**0.011**
- Co-parent	102.1 (8.6)	105.9 (8.2)	104.2 (8.2)	**0.021**	0.099	**<0.001**
- Child	102.4 (10.9)	104.4 (8.8)	105.0 (9.9)	**0.021**	0.616	0.113
LNS score[b]						
- Index parent	18.4 (3.2)	19.8 (3.1)	19.6 (3.1)	**0.001**	0.644	**0.001**
- Co-parent	18.8 (2.7)	19.3 (2.5)	19.3 (2.9)	0.144	0.853	0.135
- Child	12.5 (4.0)	13.9 (3.8)	13.7 (3.6)	**0.002**	0.644	**0.003**
Coding score[c]						
- Index parent	63.1 (15.9)	66.0 (12.9)	72.6 (14.4)	**<0.001**	**<0.001**	0.139
- Co-parent	67.0 (14.8)	69.7 (13.8)	71.9 (12.9)	**0.001**	0.189	0.144
- Child	26.6 (7.7)	28.9 (7.7)	29.3 (7.3)	**0.001**	0.591	**0.012**

P-values < 0.05 are shown in bold.
FHR-SZ = familial high risk for schizophrenia, FHR-BP = familial high risk for bipolar disorder, PBC = Population based controls, Index parent = the affected parent or the population based control, Co-parents = other biological parent, LNS = Letter-Number Sequencing.
[a] RIST index, Reynolds Intellectual Screening Test.
[b] Letter-Number Sequencing, Wechsler Adult Intelligence Scale–fourth edition (WAIS-IV)/Wechsler Intelligence Scale for Children-fourth edition (WISC-IV).
[c] Coding, WAIS-IV/WISC-IV.
[d] General linear regression model.

Table 3

Multivariate associations of RIST index, Coding score, and Letter-number sequencing score between children, index parents and co-parents, group, gender of child and gender of index parent.

Factor	β	SE	95 % CI	P
Child RIST index[a]				
Intercept	0.22	0.09	0.04; 0.41	**0.018**
Index parent RIST index	0.18	0.05	0.09; 0.28	**<0.001**
Co-parent RIST index	0.14	0.05	0.05; 0.24	**0.004**
Index parent Coding score	0.04	0.05	−0.07; 0.14	0.497
Co-parent Coding score	0.03	0.05	−0.06; 0.13	0.489
Index parent LNS score	0.06	0.05	−0.04; 0.17	0.243
Co-parent LNS score	0.07	0.06	−0.04; 0.18	0.202
Bipolar disorder group	−0.08	0.12	−0.31; 0.16	0.515
Schizophrenia group	−0.10	0.11	−0.30; 0.11	0.368
Gender of child (male)	−0.18	0.09	−0.36; −0.01	**0.039**
Gender of index parent (male)	−0.04	0.10	−0.23; 0.15	0.694
Child Coding score[b]				
Intercept	0.31	0.09	0.13; 0.49	**0.001**
Index parent Coding score	0.07	0.05	−0.03; 0.17	0.187
Co-parent Coding score	0.14	0.05	0.05; 0.24	**0.003**
Index parent RIST index score	0.07	0.05	−0.02; 0.16	0.131
Co-parent RIST index score	−0.00	0.05	−0.10; 0.10	0.943
Index parent LNS score	0.02	0.05	−0.08; 0.12	0.683
Co-parent LNS score	0.03	0.06	−0.08; 0.14	0.601
Bipolar disorder group	−0.01	0.12	−0.24; 0.22	0.940
Schizophrenia group	−0.25	0.10	−0.45; −0.04	**0.019**
Gender of child (male)	−0.55	0.09	−0.72; −0.38	**<0.001**
Gender of index parent (male)	−0.05	0.10	−0.24; 0.14	0.603
Child LNS score[c]				
Intercept	0.08	0.10	−0.11; 0.28	0.413
Index parent LNS score	0.16	0.06	0.05; 0.27	**0.004**
Co-parent LNS score	0.11	0.06	−0.01; 0.23	0.081
Index parent RIST index score	0.06	0.05	−0.03; 0.16	0.202
Co-parent RIST index score	0.07	0.05	−0.03; 0.18	0.173
Index parent Coding score	0.05	0.06	−0.06; 0.16	0.417
Co-parent Coding score	0.02	0.05	−0.08; 0.13	0.662
Bipolar disorder group	0.06	0.13	−0.19; 0.31	0.634
Schizophrenia group	−0.19	0.11	−0.42; 0.03	0.086
Gender of child (male)	−0.20	0.09	−0.38; −0.01	**0.037**
Gender of index parent (male)	0.05	0.10	−0.15; 0.26	0.614

P-values < 0.05 are shown in bold.

Index parent = the affected parent or the matched control, Co-parents = other biological parent, LNS = Letter-Number Sequencing.

[a] RIST index, Reynolds Intellectual Screening Test.

[b] Coding, Wechsler Adult Intelligence Scale–fourth edition (WAIS-IV)/ Wechsler Intelligence Scale for Children-fourth edition (WISC-IV).

[c] Letter-Number Sequencing, WAIS-IV/WISC-IV.

score and the Coding score. Co-parents to index parents with schizophrenia scored significantly lower than co-parents from the PBC group on the RIST index score and the Coding score (results already presented (Greve et al., 2021)). Index parents with bipolar disorder performed significantly poorer on the Coding score compared to PBC index parents. Co-parents to index parents with bipolar disorder did not differ significantly from PBC co-parents on any of the measured functions. Children of parents with schizophrenia scored significantly lower than PBC children on the RIST index score, the LNS score, and the Coding score, while the children of parents with bipolar disorder did not differ significantly from PBC children (see Table 2). The results about neurocognitive functions of the children from this cohort are already presented elsewhere (Hemager et al., 2018).

The children's RIST index score was significantly predicted by index parents' RIST index score (β = 0.18, 95 % CI: 0.09; 0.28, *p* < 0.001), co-parents' RIST index score (β = 0.14, 95 % CI: 0.05; 0.24, *p* = 0.004) as well as by gender of the child (male: β = −0.18, 95 % CI: −0.36; −0.01, *p* < 0.039). There was no significant effect of index parents' Coding score or LNS score, co-parents Coding score or LNS score, or group. The children's Coding score was significantly predicted by co-parents'

Coding score (β = 0.14, 95 % CI: 0.05; 0.24, *p* = 0.003) as well as by schizophrenia (β = −0.25, 95 % CI: −0.45; −0.04, *p* = 0.019), and the gender of the children (male: β = −0.55, 95 % CI: −0.72; −0.38, *p* < 0.001). There was no significant effect of index parents' Coding score, RIST index score, or LNS score; neither was there a significant effect of the co-parents RIST index score or LNS score, nor of bipolar disorder. Further, the children's LNS score was significantly predicted by index parents' LNS score (β = 0.16, 95 % CI: 0.05; 0.27, *p* = 0.004), and the gender of the children (male: β = −0.20, 95 % CI: −0.38; −0.01, *p* = 0.037). There was no significant effect of index parents' RIST index score or Coding score nor of the co-parents' LNS score, RIST index score, and Coding score nor of group (see Table 3). Interaction between index parents' RIST index score, Coding score and LNS score and group were all non-significant and for none of the three outcomes the fit of the models improved significantly when interaction terms were added.

4. Discussion

Findings from this nationwide familial high-risk cohort study show that parents diagnosed with schizophrenia have poorer functioning on the neurocognitive functions intelligence, processing speed, and verbal working memory compared to population-based control (PBC) index parents. Parents with bipolar disorder performed poorer than PBC index parents on processing speed. These results are in line with extensive research on neurocognition in relation to schizophrenia (Heinrichs and Zakzanis, 1998a, 1998b; Fioravanti et al., 2005, 2012a, 2012b) and also regarding the evidence of neurocognition in bipolar disorder (Torres et al., 2007; Bora et al., 2009a, 2009b). Co-parents to index parents with schizophrenia have lower intelligence and processing speed compared to PBC co-parents while co-parents from the bipolar group did not differ significantly from PBC co-parents (results on assortative mating for co-parents from the VIA 7 study are already presented and discussed elsewhere (Greve et al., 2021)). The results are consistent with evidence of assortative mating in relation to intelligence (Vinkhuyzen et al., 2012) and also among individuals with schizophrenia (Nordsletten et al., 2016). Children of parents with schizophrenia performed poorer than PBC children on all three neurocognitive functions, while the children of parents with bipolar disorder did not differ significantly from PBC children on any of the three neurocognitive functions assessed (results on neurocognition for the children from the VIA 7 study are already presented and discussed elsewhere (Hemager et al., 2018)).

Of particular interest, our results from multiple regression analyses support a function specific transmission of the neurocognitive functions intelligence, processing speed, and verbal working memory from parents to their offspring. We found that children's intelligence was uniquely predicted by one of the parent's intelligence and not by parent's processing speed or verbal working memory. Children's working memory was uniquely predicted by one of the parent's verbal working memory but not by parent's intelligence or processing speed and finally that children's processing speed was uniquely predicted by one of the parent's processing speed but not by parents' intelligence or verbal working memory. Our results suggest that the parent to child transmission of neurocognition is function specific and thus unaffected by other neurocognitive functions of the parents. Prior cross sectional studies have established that neurocognitive functions correlate positively and share considerable variance, both in healthy populations (Carroll, 1993) and in schizophrenia (Dickinson and Gold, 2007; Georgiades et al., 2017). Therefore, we were surprised not to find significant cross-function transmissions from parents to offspring, which supports the conceptualization of 'specific' neurocognitive functions. In particular, it was surprising that parental intelligence seemed independent of the working memory or processing speed functions in the offspring. This is in contrast to the idea of theories of intelligence as a general factor that contributes to all neurocognitive functions and reflects an individual's overall performance on neurocognitive tasks (Spearman, 1961; Lezak et al., 2004).

We also found that the transgenerational transmissions of the assessed neurocognitive functions are comparable in families with schizophrenia, families with bipolar, and control families. This finding is in line with the similar cognitive heritability estimates in schizophrenia and healthy populations (Blokland et al., 2016). It has been proposed that having schizophrenia can affect the current level of intelligence (Trotta et al., 2015). Thus, one may speculate, that if we had used a premorbid intelligence measure (Bright and van der Linde, 2018) instead of our measure of current intelligence (Reynolds and Kamphaus, 2003), it might have led to different associations (Jonas et al., 2022; Zanelli et al., 2022). Furthermore, the trans-generational transmission in our study appears independent of the gender of the affected parent. We found a significant effect of the child's gender, reflecting better neuro-cognitive performance in girls than boys, but the transgenerational transmission appears independent of the gender of the child.

Being a child in a family with severe mental disorder involves both genetic and environmental exposures (Rutter and Silberg, 2002; Gantriis et al., 2019). It has been established that most neurocognitive functions show moderate to high heritability estimates, although these estimates range widely across cognitive functions (Blokland et al., 2016). However, the associations between parents and offspring found in this study were small to moderate. This may be partly explained by the young age of the children (7 years), where environmental influences may play a larger role. Thus, a large twin study of heritability of general cognitive ability has shown that genetic influence on general cognitive ability increases significantly and linearly from childhood to adolescence to young adulthood (Haworth et al., 2010). Therefore, we may expect stronger associations later in development in these children, at least in the intelligence function. Moreover, the reliability of the neurocognitive measures is important to consider, as lower reliability could lead to weaker associations. The Reynolds intellectual Screening Test (RIST) is a very brief intelligence measure and may not be as valid and reliable as other intelligence measures based on more than two sub-scales but it has the advantage of covering a very broad age span (3–94 years). We only used one test for processing speed and one test for verbal working memory. Aggregated scores from two or more tests of the same cognitive functions might have improved the reliability of each cognitive function variable and potentially strengthened the observed associations.

To the best of our knowledge, our study is the first study to investigate associations between cognitive functions in both biological parents and their offspring using the same cognitive test methodology and relatively early in the offspring development. Our data comes from a representative and large nationwide cohort. The narrow age span of the children in the current study is an important characteristic of our sample because the associations on parental functions may be affected by increasing heritability with increasing maturation (Haworth et al., 2010). Finally, all assessors of the children were blinded to the risk status of the child. Our findings should, however, also be interpreted in the context of some limitations. First, the sample size of the bipolar disorder group is substantially smaller and was not matched with the control group. Second, the neuropsychological test battery was short and if reliability of the aggregated score from several neurocognitive measures had been higher, we might have observed stronger associations.

In conclusion, the present study shows that the transgenerational transmission of intelligence, verbal working memory, and processing speed from parents to their 7-year-old offspring is function specific. Moreover, the transgenerational transmission of the cognitive functions is not significantly different in families with one parent diagnosed with schizophrenia, in families with one parent diagnosed with bipolar and in control families. A greater understanding of the function structure of transmission of cognition and genetic overlap with schizophrenia and bipolar disorder is important to increase our understanding of the pathways from familial risk to neurocognitive phenotype and to psychopathology.

References

Agnew-Blais, J., Seidman, L.J., 2012. Neurocognition in youth and young adults under age 30 at familial risk for schizophrenia: a quantitative and qualitative review. Cogn. Neuropsychiatry 1–39 (ahead-of-print).

Blokland, G.A., et al., 2016. Heritability of neuropsychological measures in schizophrenia and nonpsychiatric populations: a systematic review and meta-analysis. Schizophr. Bull. 43 (4), 788–800.

Bora, E., 2016. Differences in cognitive impairment between schizophrenia and bipolar disorder: considering the role of heterogeneity. Psychiatry Clin. Neurosci. 70 (10), 424–433.

Bora, E., Özerdem, A., 2017. A meta-analysis of neurocognition in youth with familial high risk for schizophrenia. Eur.Psychiatry 44, 17–23.

Bora, E., et al., 2009. Cognitive endophenotypes of bipolar disorder: a meta-analysis of neuropsychological deficits in euthymic patients and their first-degree relatives. J. Affect. Disord. 113 (1–2), 1–20.

Bora, E., et al., 2009. In: Cognitive Endophenotypes of Bipolar Disorder: A Meta-analysis of Neuropsychological Deficits in Euthymic Patients and Their First-degree Relatives, 113(1-2), pp. 1–20.

Bright, P., van der Linde, I., 2018. Comparison of methods for estimating premorbid intelligence. Neuropsychol.Rehabil. 30 (1), 1–14.

Burton, B.K., et al., 2018. Sustained attention and interference control among 7-year-old children with a familial high risk of schizophrenia or bipolar disorder–a nationwide observational cohort study. Biol. Psychiatry Cogn. Neurosci. Neuroimaging 3 (8), 704–712.

Carroll, J.B., 1993. Human Cognitive Abilities: A Survey of Factor-analytic Studies. Cambridge University Press.

Conway, A.R., et al., 2002. A latent variable analysis of working memory capacity, short-term memory capacity, processing speed, and general fluid intelligence. Intelligence 30 (2), 163–183.

Dickinson, D., Gold, J.M.J.S.B., 2007. In: Less Unique Variance Than meets the Eye: Overlap Among Traditional Neuropsychological Dimensions in Schizophrenia, 34 (3), pp. 423–434.

Duffy, A., et al., 2010. Early stages in the development of bipolar disorder. J. Affect. Disord. 121 (1), 127–135.

Fioravanti, M., et al., 2005. In: A Meta-analysis of Cognitive Deficits in Adults With a Diagnosis of Schizophrenia, 15(2), pp. 73–95.

Fioravanti, M., et al., 2012. Cognitive deficits in schizophrenia: an updated metanalysis of the scientific evidence. BMC Psychiatry 12 (1), 64.

Fioravanti, M., et al., 2012. In: Cognitive Deficits in Schizophrenia: An Updated Metanalysis of the Scientific Evidence, 12(1), p. 64.

Fry, A.F., Hale, S., 1996. Processing speed, working memory, and fluid intelligence: evidence for a developmental cascade. Psychol. Sci. 7 (4), 237–241.

Fry, A.F., Hale, S., 2000. Relationships among processing speed, working memory, and fluid intelligence in children. Biol. Psychol. 54 (1–3), 1–34.

Gantriis, D., et al., 2019. Home visits in the Danish High Risk and Resilience Study–VIA 7: assessment of the home environment of 508 7-year-old children born to parents diagnosed with schizophrenia or bipolar disorder. Acta Psychiatr. Scand. 140 (2), 126–134.

Georgiades, A., et al., 2017. In: Psychometric Characteristics of the MATRICS Consensus Cognitive Battery in a Large Pooled Cohort of Stable Schizophrenia Patients, 190, pp. 172–179.

Greve, A.N., et al., 2021. A nationwide cohort study of nonrandom mating in schizophrenia and bipolar disorder. Schizophr. Bull. 47 (5), 1342–1350.

Hameed, M.A., Lewis, A.J., 2016. Offspring of parents with schizophrenia: a systematic review of developmental features across childhood. Harv.Rev.Psychiatry 24 (2), 104–117.

Haworth, C.M., et al., 2010. The heritability of general cognitive ability increases linearly from childhood to young adulthood. Mol. Psychiatry 15 (11), 1112.

Heinrichs, R.W., Zakzanis, K.K., 1998. Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. Neuropsychology 12 (3), 426.

Heinrichs, R.W., Zakzanis, K.K.J.N., 1998. In: Neurocognitive Deficit in Schizophrenia: A Quantitative Review of the Evidence, 12(3), p. 426.

Hemager, N., et al., 2018. Assessment of neurocognitive functions in 7-year-old children at familial high risk for schizophrenia or bipolar disorder: the Danish High Risk and Resilience Study VIA 7. JAMA Psychiatry 45 (8), 844–852.

Hemager, N., et al., 2019. Visual attention in 7-year-old children at familial high risk of schizophrenia or bipolar disorder: the Danish high risk and resilience study VIA 7. J. Affect. Disord. 258, 56–65.

Jonas, K., et al., 2022. The course of general cognitive ability in individuals with psychotic disorders. JAMA Psychiatry. https://doi.org/10.1001/jamapsychiatry.2022.1142.

Lezak, M.D., et al., 2004. Neuropsychological Assessment. Oxford University Press, USA.

Lichtenstein, P., et al., 2009. Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. Lancet 373 (9659), 234–239.

Morosini, P., et al., 2000. Development, reliability and acceptability of a new version of the DSM-IV Social and Occupational Functioning Assessment Scale (SOFAS) to assess routine social funtioning. Acta Psychiatr. Scand. 101 (4), 323–329.

Mors, O., et al., 2011. The Danish psychiatric central research register. Scand.J.Public Health 39 (7 suppl), 54–57.

Nordsletten, A.E., et al., 2016. In: Patterns of Nonrandom Mating Within and Across 11 Major Psychiatric Disorders, 73(4), pp. 354–361.

Owens, S.F., et al., 2012. Prefrontal deviations in function but not volume are putative endophenotypes for schizophrenia. Brain 135 (7), 2231–2244.

Pedersen, C.B., et al., 2006. The Danish civil registration system. Dan. Med. Bull. 53 (4), 441–449.

Rasic, D., et al., 2013. Risk of mental illness in offspring of parents with schizophrenia, bipolar disorder, and major depressive disorder: a meta-analysis of family high-risk studies. Schizophr. Bull. sbt114.

Reichenberg, A., Harvey, P.D., 2007. Neuropsychological impairments in schizophrenia: integration of performance-based and brain imaging findings. Psychol. Bull. 133 (5), 833.

Reichenberg, A., et al., 2010. Static and dynamic cognitive deficits in childhood preceding adult schizophrenia: a 30-year study. Am. J. Psychiatry 167 (2), 160.

Reynolds, C., Kamphaus, R.J.L., 2003. Reynolds Intellectual Assessment Scales (RIAS). Psychological Assessment Resources, FL.

Reynolds, C.R., Kamphaus, R., 2009. Development and application of the Reynolds Intellectual Assessment Scales (RIAS). In: Practioner's Guide to Assessing Intelligence and Achievement. John Wiley & Sons, Inc, Hoboken, NJ.

Rutter, M., Silberg, J., 2002. Gene-environment interplay in relation to emotional and behavioral disturbance. Annu. Rev. Psychol. 53 (1), 463–490.

de la Serna, E., et al., 2016. Neuropsychological characteristics of child and adolescent offspring of patients with bipolar disorder. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 65, 54–59.

Shaffer, D., et al., 1983. A children's global assessment scale (CGAS). Arch. Gen. Psychiatry 40 (11), 1228–1231.

Sharma, A., et al., 2017. Neuropsychological study of IQ scores in offspring of parents with bipolar I disorder. Cogn.Neuropsychiatry 22 (1), 17–27.

Spearman, C., 1961. "General Intelligence" Objectively Determined and Measured.

Szöke, A., et al., 2008. Longitudinal studies of cognition in schizophrenia: meta-analysis. Br. J. Psychiatry 192 (4), 248–257.

Szöke, A., et al., 2008. In: Longitudinal Studies of Cognition in Schizophrenia: Meta-analysis, 192(4), pp. 248–257.

Thorup, A.A., et al., 2015. The Danish High Risk and Resilience Study–VIA 7-a cohort study of 520 7-year-old children born of parents diagnosed with either schizophrenia, bipolar disorder or neither of these two mental disorders. BMC Psychiatry 15 (1), 233.

Torres, I., et al., 2007. In: Neuropsychological Functioning in Euthymic Bipolar Disorder: A Meta-analysis, 116, pp. 17–26.

Toulopoulou, T., et al., 2015. Reciprocal causation models of cognitive vs volumetric cerebral intermediate phenotypes for schizophrenia in a pan-European twin cohort. Mol. Psychiatry 20 (11), 1386.

Trotta, A., et al., 2015. Do premorbid and post-onset cognitive functioning differ between schizophrenia and bipolar disorder? A systematic review and meta-analysis. Psychol. Med. 45 (2), 381–394.

Vinkhuyzen, A.A., et al., 2012. In: Reconsidering the Heritability of Intelligence in Adulthood: Taking Assortative Mating and Cultural Transmission Into Account, 42 (2), pp. 187–198.

Wechsler, D., 2003. WISC-IV: Administration and Scoring Manual. Psychological Corporation.

Wechsler, D., 2004. WISC-IV: Wechsler Intelligence Scale for Children, Integrated: Technical and Interpretive Manual. Harcourt Brace and Company.

Wechsler, D., 2008. In: Wechsler Adult Intelligence Scale–Fourth Edition (WAIS–IV), 22. NCS Pearson, San Antonio, TX, p. 498.

Zanelli, J., et al., 2022. Dynamic and static cognitive deficits in schizophrenia and bipolar disorder after the first episode. Schizophr. Bull. 48 (3), 590–598.