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Comparing cognition in parents with schizophrenia or bipolar disorder and their 7-year-old offspring

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ABSTRACT

Individuals with schizophrenia (SZ) or bipolar disorder (BP) display cognitive impairments, while their first-degree relatives perform at an intermediate level between the patient groups and controls. However, the environmental impact of having an ill relative likely varies with the type of kinship and some studies suggest that offspring may be particularly disadvantaged. The present study aimed to investigate the relationship between parent and child cognition in parents with SZ or BD and their 7-year-old offspring. A population-based cohort of 522 children (parental SZ, n = 202; parental BP, n = 120; controls, n = 200) and their parents underwent the same assessment battery covering a wide range of cognitive functions. We used Bayesian statistics to model performance. We found that performance on non-verbal tests was better in offspring than parents with SZ or BP, using the controls as reference. However, for verbal tests, there was little to no evidence for this pattern or even some evidence for the opposite in the BP group: relatively better performance in parents than offspring. The findings suggest that the offspring of parents with SZ or BP may be particularly disadvantaged in verbal abilities. Future studies will show whether this pattern persists throughout development.

1. Introduction

The most robust risk factor predicting severe mental disorders such as schizophrenia (SZ) and bipolar disorder (BP) is having a biological relative who is affected (Gottesman et al., 2010; Wray and Gottesman, 2012). The increased familial risk (genetic and environmental) extends beyond the specific disorder of the relative. About one-third of the offspring to individuals with a severe mental disorder will develop a severe mental disorder (Rasic et al., 2014). SZ and BP partially share clinical features (Keshavan et al., 2011), susceptibility genes (Lichtenstein et al., 2009) and environmental risk factors (Robinson and Bergen, 2021). However, SZ is associated with additional genetic and environmental risks that seem to impair neurodevelopment to a larger extent (Bora, 2015; Demjaha et al., 2012; Rapoport et al., 2012).

Despite the growing body of literature on the topic, the etiologies remain poorly understood. This is likely due to the large complexity and heterogeneity of the disorders. One strategy to overcome this has been to decompose the mental disorders and look at intermediate phenotypes. Cognitive functions, in particular, are simpler quantitative liability traits continuously distributed in the population, with SZ being over-represented in one extreme (low function) (Toulopoulou et al., 2007), and BP potentially being overrepresented in both extremes (Bora, 2015;

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Demjaha et al., 2012; MacCabe et al., 2010; Smeland et al., 2020). Individuals with SZ tend to exhibit severe and widespread cognitive impairments (Fioravanti et al., 2012; Reichenberg and Harvey, 2007). Individuals with BP, on average, display similar but milder cognitive impairments (Bortolato et al., 2015; Demjaha et al., 2012; Trotta et al., 2015). Familial high-risk studies have found that children of parents with SZ show widespread cognitive impairments already from infancy (Hameed and Lewis, 2016), whereas studies on cognitive functions in children of parents with BP present more divergent results (de la Serna et al., 2016; Klimes-Dougan et al., 2006). Larger studies directly comparing patients and their first-degree relatives show that first-degree relatives generally perform at an intermediate level between the respective patient group and controls across cognitive domains (see a list of references in Table S1). In these studies, first-degree relatives are treated as a whole despite the fact that the environmental impact of having an ill relative likely varies considerably with the type of kinship. Indeed, studies that have compared different types of first-degree relatives suggest that offspring may be more disadvantaged compared to siblings or parents when it comes to cognitive function, structural brain abnormalities and psychopathology (de la Serna et al., 2011; de Zwarte et al., 2019; Gillissie et al., 2022; Wang et al., 2010), and may have higher risk of developing a severe mental disorder (Aukes et al., 2012; Cowan et al., 2002; Gottesman et al., 2010; Rasic et al., 2014). This concern is further aggravated by the fact that offspring are underrepresented in the above studies (see Table S1).

In order to directly investigate the relationship between cognitive functioning in individuals with SZ or BP and their offspring, we assessed a wide range of cognitive functions, previously highlighted as being central to SZ and BP in a large representative population-based cohort of 7-year-old children and their parents (Krantz et al., 2023; Thorup et al., 2015). Importantly, both children and parents were administered the same cognitive tests. In addition, the children's age range was very narrow to reduce heterogeneity due to different developmental stages, and consequently the parents' age range was quite narrow. By investigating both SZ and BP, potential differences could be disentangled as disorder specific or spanning across the two diagnostic groups.

Investigating the relationship between the parent's and the offspring's cognition already from an early age could provide important clues on some of the processes through which these individuals go on to develop mental disorders. For instance, if the familial high-risk (FHR) children display relatively poor cognitive functioning combined with a weaker association between parent and child cognition, it could indicate that environmental factors may be shifting the children below their expected level of functioning, potentially enhancing their risk further for developing mental disorders. Importantly, different cognitive functions may vary in their degree of susceptibility to such influences (National Institute of Child and Human Development Early Child Care Research, 2000), for instance verbal abilities could be more malleable to environmental input.

Thus, the aim of this study was twofold. First, we assessed whether the FHR children's cognitive functions deviated from their parents' using the control families as reference. Second, we assessed whether the strength of the associations between parent and child cognition was different in the three groups, potentially providing an explanation to differences and similarities in the identified cognitive profiles of children and their parents.

2. Methods

This study relied on data from The Danish High Risk and Resilience Study – VIA 7, a nationwide cohort established in Denmark between January 2013 and January 2016. The cohort consists of 522 children aged 7 with no, one, or two parents registered with a diagnose of either SZ or BP in the Danish registers (Thorup et al., 2015). 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. In addition, executive functions as measured with classical neuropsychological tests, like the ones used in this study, are expected to emerge at age 6 (Anderson, 2001). Furthermore, although the stability of intelligence measurements increases with age, it is expected to be quite high already in early childhood (Mortensen et al., 2003; Schuerger and Witt, 1989).

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). SZ was defined as schizophrenia, delusional disorder, or schizoaffective disorder (ICD-10-codes: F20, F22, and F25) and BP as ICD 10-code: F30 and F31. The cohort was drawn from the total population of 7-year-old children in the study period who had parents diagnosed with SZ or BP together with population-based control (PBC) children. PBC families were matched 1:1 (on the child's age, sex, and municipality) to families with a parent with SZ to avoid that such extraneous factors would affect the results. The families with a parent with BP were matched at the group level to the other two groups. Index parents were defined as the affected parent or the matched PBC parent. The gender of the index parent in the SZ group defined the gender of the index parent in the PBC family. Demographic characteristics of the cohort are presented in Table 1. Cross-sectional comparisons between FHR children and their controls as well as parents with SZ or BP and their controls have already been published elsewhere (Greve et al., 2022; Hemager et al., 2018).

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 Health Authority 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 child assessors were blinded to the risk 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 were conducted in the homes of the participating families in surroundings suitable for assessment.

2.3. Clinical measures

The Children's Global Assessment Scale (CGAS) (Shaffer et al., 1983) was used to assess the current level of functioning of the children. Levels of social functioning for the index 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.

2.4. Neurocognition

The battery of cognitive tests was chosen in order to make intergenerational comparison possible. Intelligence was estimated using The Reynolds Intellectual Screening Test (RIST) (Reynolds and Kamphaus, 2009), 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 assessed

Table 1
Characteristics of children participating in the Danish High Risk and Resilience Study - VIA 7 and their biological parents. Index parents refer to the biological parents with a diagnosis of schizophrenia spectrum disorder or bipolar disorder. In the population-based control group the index parents refer to the matched biologic parents without any of these disorders.

	FHR-SZ	FHR-BP	PBC
Children, N	202	120	200
Female, N (%)	93 (46.0)	56 (46.7)	93 (46.5)
Age at inclusion, mean (SD)	7.84 (0.22)	7.87 (0.20)	7.81 (0.20)
Living with both biological parents, N (%)	82 (40.6)	63 (52.5)	169 (84.5)
Living with index parent, N (%)	124 (61.39)	84 (70.00)	189 (94.50)
Children's Global Assessment Scale (CGAS), N, mean (SD)	199 68.07 (15.40)	118 73.55 (14.91)	197 77.71 (13.47)
Rapid Visual Processing (RVP) A', N, mean (SD)	187 0.89 (0.06)	116 0.90 (0.06)	193 0.91 (0.05)
Intra Extra Dimensional Set Shift (IED) EDS errors, N, mean (SD)	195 18.24 (9.89)	118 18.86 (10.32)	198 19.27 (10.14)
Spatial Working Memory (SWM) Total errors, N, mean (SD)	194 51.49 (15.84)	118 49.17 (17.15)	198 47.03 (15.35)
TOMAL-2 Word Selective Reminding (WSR) Immediate recall raw score, N, mean (SD)	191 38.62 (5.68)	117 39.47 (4.87)	198 39.08 (4.91)
The Delis–Kaplan Executive Function System (D-KEFS) semantic fluency, N, mean (SD)	192 24.35 (6.23)	115 25.37 (6.49)	195 26.21 (6.46)
The Delis–Kaplan Executive Function System (D-KEFS) phonemic fluency, N, mean (SD)	193 13.01 (6.53)	115 14.15 (6.26)	195 14.18 (6.04)
Letter Number Sequencing (LNS) Raw score, N, mean (SD)	196 12.44 (4.06)	117 13.92 (3.81)	198 13.73 (3.62)
Coding Raw score, N, mean (SD)	199 26.3 (7.76)	118 28.68 (7.14)	199 29.43 (7.32)
Brief Smell Identification Test (BSIT), N, mean (SD)	199 6.32 (1.98)	116 6.46 (2.02)	197 6.71 (1.92)
RIST index, N, mean (SD)	200 102.18 (11.33)	119 104.2 (9.29)	198 105 (9.84)
Index Parents, N	199	117	204
Female, N (%)	110 (55.28)	65 (55.56)	115 (56.37)
Age, mean (SD)	38.1 (6.08)	40.85 (7.1)	40.64 (4.79)
Employed or studying, N (%) ($N = 497$)	93 (49.7)	61 (56.0)	185 (92.0)
Education, N ($N = 484$)	178	109	197
– Primary/lower secondary, N (%)	54 (30.3)	10 (9.2)	8 (4.1)
– 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)
Personal and Social Performance scale (PSP), N, mean (SD)	158 66.13 (15.71)	102 68.91 (14.09)	194 84.27 (9.89)
Rapid Visual Processing (RVP) A', N, mean (SD)	150 0.89 (0.06)	101 0.90 (0.06)	179 0.92 (0.05)
Intra Extra Dimensional Set Shift (IED) Total errors adjusted, N, mean (SD)	156 10.21 (9.81)	102 9.32 (9.12)	193 9.33 (9.68)
Spatial Working Memory (SWM) Total errors, N, mean (SD)	156 24.46 (16.78)	102 22.84 (17.63)	193 16.44 (15.06)
TOMAL-2 Word Selective Reminding (WSR) Immediate recall raw score, N, mean (SD)	152 54.16 (10.91)	97 56.55 (9.34)	184 54.8 (9.76)
The Delis–Kaplan Executive Function System (D-KEFS) semantic fluency, N, mean (SD)	151 46.02 (11.12)	97 47.68 (9.41)	181 48.67 (8.97)
The Delis–Kaplan Executive Function System (D-KEFS) phonemic fluency, N, mean (SD)	151 39.73 (13.6)	100 42.97 (12.23)	190 41.66 (11.67)
Letter Number Sequencing (LNS) Raw score, N, mean (SD)	153 18.52 (3.12)	102 19.63 (3.39)	190 19.69 (3.07)
Coding Raw score, N, mean (SD)	157 64.1 (15.88)	103 66.13 (12.72)	190 72.66 (14.41)
Brief Smell Identification Test (BSIT), N, mean (SD)	153 9.99 (1.42)	101 10.21 (1.44)	190 10.24 (1.4)
RIST index, N, mean (SD)	158 101.1 (10.02)	103 104 (8.14)	192 103.9 (8.08)

FHR-SZ: Children with familial high risk for schizophrenia spectrum disorders.
FHR-BP: Children with familial high risk for bipolar disorder.
PBC: Population-based controls.
Results on child neurocognition have already been presented in Hemager et al. (2018) and LNS, Coding and RIST scores for parents have already been presented in Greve et al. (2022).

with Coding from the WISC-IV and in parents with Coding from the WAIS-IV (Wechsler, 2003, 2004). Verbal fluency was assessed using condition one (phonemic fluency) and two (semantic fluency) from the Delis-Kaplan Executive Function System (D-KEFS) (Delis et al., 2001). Flexibility/set shifting was assessed with Intra-Extra Dimensional Set Shifting task (IED), visual working memory with the Spatial Working Memory (SWM) and sustained attention with the Rapid Visual Information Processing (RVP), all from the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Cognition, 2012). Verbal memory was measured using Word Selective Reminding - Immediate Recall (WSR) from the Test of Memory and Learning – Second Edition (TOMAL-2) (Reynolds and Voress, 2007). To assess odor identification, the Brief Smell Identification Test (BSIT, Version A, Danish version) (Doty, 2001) was used. 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 a psychologist (ANG), a specialist in child neuropsychology (JRMJ), and a specialist in clinical child psychology (NH).

2.5. Data analysis

We used Bayesian multilevel multivariate outcome techniques to model at the same time the parent and child performance on specific tests and the correlation between the two. This approach includes all available information, such as repeated measures of performance, number of trials, and uncertainty in the performance estimates. Hereby, we obtained a more precise estimate of the uncertainty in the correlations between parents and children, avoiding undue confidence, and accounting for the attenuation effect (Haines et al., 2023).

The different tests had different outcome measures, involving different likelihood functions (see Supplementary Material). In all cases, the outcome was conditioned on group (PBC, BP, SZ), age and sex, i.e. we included the parent's and the child's age and sex in all analyses. Estimates were allowed to vary by participant (random intercepts) and participants were clustered by group (Valton et al., 2020). Individual level estimates assumed a potential shared variance between each child and their parent (correlation), which was estimated separately by group. Detailed description and evaluation of the individual models are

reported in the Supplementary Material. In order to make the parents' and children's performance on the individual tests comparable in the patient groups, the group level estimates from the models were standardized relative to the mean (SD) performance of the parents and children in the control group, respectively, i.e. the average score and SD of the PBC parents on the specific test was used as reference for assessing parental performance in the patient groups and similarly for the children, the PBC children's average score and SD on the specific test was used as reference for assessing offspring performance in the FHR groups. These deviations from the PBC parents and children were then directly compared to test whether they differed (for further details see Supplementary Material p. 35).

The analysis code can be found here: https://osf.io/q4y9d/?view_only=4ed8434e2f9348d889355bb68edcc54d

Estimates from the models are reported as mean and 95 % Compatibility Intervals (CI) of the posterior estimates. We calculated evidence ratios (ER) for the relevant estimates in the form of the posterior probability of the directed hypothesis (e.g. child performance is relatively better than parent performance) against the posterior probability of all the alternatives. ERs below 3 were considered anecdotal, and the higher the ER the more reliable the evidence, with ERs up to 10 considered moderate evidence and ERs above 10 considered strong evidence in favor of the hypothesis. Note that these values are for guidance only and do not represent clear cutoffs. ERs below $^1/_3$ suggest some evidence in favor of the opposite hypothesis and ERs below $^1/_{10}$ suggest strong evidence. We also reported the credibility of the estimated parameter distribution, that is, the probability that the true parameter value is above 0 if the mean estimate is positive, or below 0 if it is negative. Note that credibility and ER differently express the same information, with ER being defined as: $\frac{Credibility}{1-Credibility}$

3. Results

3.1. Comparison of parents' and children's cognitive performance in the SZ and BP groups

There was strong evidence that the performance of the children was relatively better than the parents' performance on non-verbal tests (Coding, SWM, RVP, IED) in the SZ group. The same was the case in the BP group for Coding and SWM, while for RVP and IED, the evidence was moderate and weak, respectively. For verbal tests (WSR, LNS, D-KEFS semantic/phonetic fluency, BSIT, RIST), there was no or only weak evidence that performance in the children was better than the parent performance in the SZ group (ERs $\leq$ 3). For the BP group, we saw a similar pattern for LNS and semantic fluency, while there was moderate to strong evidence that parents performed relatively better than their children on WSR, BSIT, RIST and phonetic fluency (ERs $\leq$ $^1/_3$). See detailed results in Table 2 and Fig. 1. Analysis of a reduced dataset (without younger siblings or offspring and parents where both parents were affected) yielded similar results (see Table S2). Follow-up analyses showed strong evidence for the observed differential parent-child performance on verbal vs. non-verbal tests in both groups (SZ: M = −0.54 [CI: −1.36; 0.25], ER = 11; BP: M = −1.2 [CI: −2.03; −0.35], ER = 363), with children performing relatively better than the parents on nonverbal compared to verbal tests. Task performance in the familial high-risk children with and without a participating parent was similar (see Fig. S21).

3.2. Association between parents and children's cognitive performance

For PBC, there was moderate to strong evidence for a positive association between parent and child cognition on all tests, with the average correlation coefficient ranging from 0.10 to 0.71, depending on the test. For the BP group, there was weak to strong evidence for a positive association between parent and child cognition for all tests except semantic fluency. The average correlation coefficient ranged from 0 to 0.57. For the SZ group, there was moderate to strong evidence for a positive association between parent and child cognition for all tests except WSR. The average correlation coefficient ranged from 0.04 to 0.51.

For RIST, IED and RVP, there was no evidence that the strength of the association differed between the patient groups and PBC. For semantic fluency and BSIT, there was moderate to strong evidence that the correlation was weaker in BP than in PBC. For WSR, Coding, LNS and phonetic fluency, there was weak to moderate evidence that the correlation was weaker in the SZ than in the PBC group. For SWM, there was moderate to strong evidence that the correlation was stronger in the patient groups compared to PBC. See detailed results in Table 3. Analysis

Table 2
Standardized mean differences (95 % CI) in cognitive performance compared to the reference group (column 2 – 5). Positive and negative values indicate that the average performance is better or worse than in the population-based controls (PBC), respectively. Column 6 and 7: mean differences (95 % CI) in standardized cognitive performance between parents and children within the bipolar group (BP difference) and the schizophrenia group (SZ difference). Positive and negative values indicate that the performance of the children is relatively better or worse than the parents', respectively. WSR: Word Selective Reminding - Immediate Recall; LNS: Letter-Number Sequencing; PHON: phonemic fluency; SEM: semantic fluency; BSIT: Brief Smell Identification Test; RIST: The Reynolds Intellectual Screening Test; SWM: Spatial Working Memory; IED: Intra-Extra Dimensional Set Shifting; RVP: Rapid Visual Information Processing; BP: bipolar disorder; SZ: schizophrenia.

TEST	BP CHILD	BP PARENT	SZ CHILD	SZ PARENT	BP DIFFERENCE	SZ DIFFERENCE
WSR	0.09 (−0.13; 0.33)	0.19 (−0.02; 0.42)	−0.09 (−0.28; 0.10)	−0.14 (−0.33; 0.04)	−0.10 (−0.39; 0.20) ER = 0.3; 0.25	0.06 (−0.19; 0.32) ER = 2; 0.67
CODING	−0.16 (−0.39; 0.07)	−0.52 (−0.72; −0.33)	−0.56 (−0.75;−0.37)	−0.77 (−0.96; −0.58)	0.36 (0.09; 0.64) ER = 210; 1	0.22 (−0.04; 0.49) ER = 18; 0.95
LNS	0.02 (−0.27; 0.31)	0.05 (−0.35; 0.47)	−0.60 (−0.86; −0.34)	−0.68 (−0.97; −0.38)	−0.03 (−0.48; 0.41) ER = 0.8; 0.46	0.08 (−0.28; 0.45) ER = 2; 0.67
SEM	−0.29 (−0.63; 0.02)	−0.25 (−0.62; 0.11)	−0.54 (−0.79; −0.29)	−0.68 (−1.04; −0.34)	−0.05 (−0.53; 0.44) ER = 0.7; 0.42	0.15 (−0.26; 0.55) ER = 3; 0.77
PHON	−0.12 (−0.40; 0.14)	0.11 (−0.14; 0.36)	−0.37 (−0.60; −0.15)	−0.33 (−0.57; −0.09)	−0.23 (−0.55; 0.09) ER = 0.1; 0.08	−0.05 (−0.34; 0.25) ER = 0.6; 0.37
BSIT	−0.35 (−0.79; 0.09)	−0.12 (−0.53; 0.35)	−0.49 (−0.82; −0.16)	−0.47 (−0.80; −0.12)	−0.24 (−0.84; 0.34) ER = 0.3; 0.23	−0.02 (−0.49; 0.43) ER = 0.9; 0.47
RIST	−0.07 (−0.28; 0.13)	0.05 (−0.20; 0.28)	−0.32 (−0.51; −0.13)	−0.41 (−0.66; −0.16)	−0.12 (−0.38; 0.15) ER = 0.2; 0.18	0.09 (−0.17; 0.35) ER = 3; 0.76
SWM	−0.14 (−0.34; 0.07)	−0.39 (−0.57; −0.20)	−0.29 (−0.43; −0.15)	−0.63 (−0.76; −0.49)	0.25 (0.02; 0.47) ER = 52; 0.98	0.33 (0.16; 0.51) ER >1000; 1
IED	0.05 (−0.14; 0.26)	−0.04 (−0.23; 0.17)	0.05 (−0.09; 0.20)	−0.16 (−0.33; −0.001)	0.09 (−0.19; 0.37) ER = 3; 0.73	0.21 (−0.002; 0.43) ER = 37; 0.97
RVP	−0.26 (−0.48; −0.04)	−0.46 (−0.68; −0.22)	−0.44 (−0.63; −0.24)	−0.62 (−0.83; −0.42)	0.19 (−0.10; 0.50) ER = 9; 0.90	0.19 (−0.07; 0.45) ER = 12; 0.92

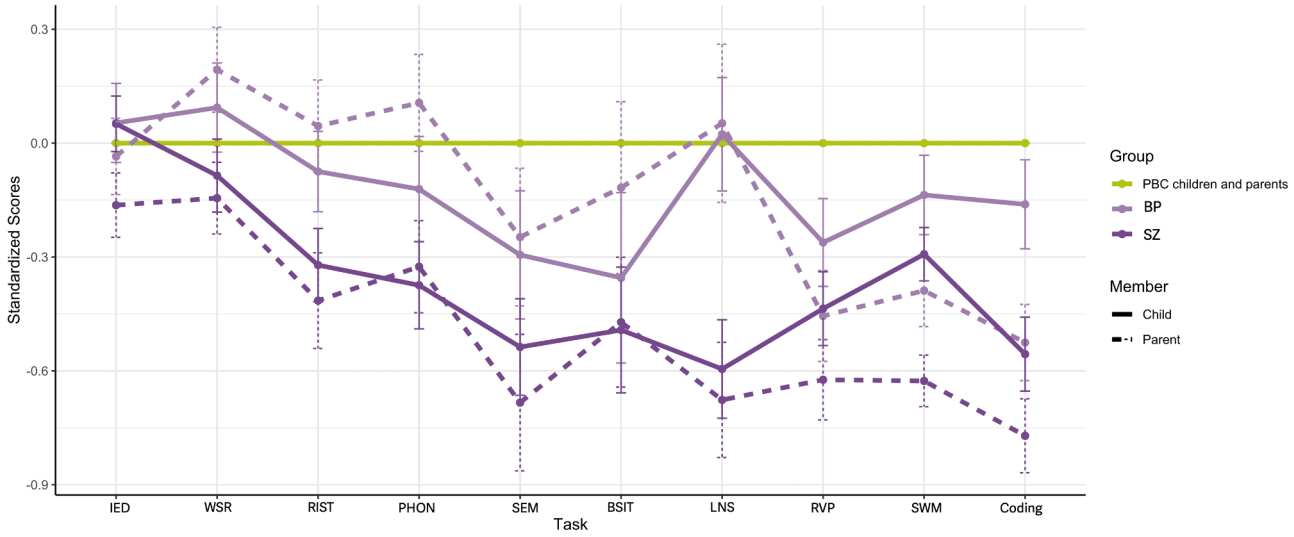

Fig. 1. Standardized estimates in parents and children by task and group. Group level estimates are standardized relying on the control group estimates. The error bars indicate one standard error of the mean (i.e., a standard deviation of the posterior estimate of the mean). The green line indicates the reference baseline – the estimate of the control groups. IED: Intra-Extra Dimensional Set Shifting; WSR: Word Selective Reminding - Immediate Recall; RIST: The Reynolds Intellectual Screening Test; PHON: phonemic fluency; SEM: semantic fluency; BSIT: Brief Smell Identification Test; LNS: Letter-Number Sequencing; RVP: Rapid Visual Information Processing; SWM: Spatial Working Memory; PBC: population-based controls; BP: bipolar disorder; SZ: schizophrenia.

of the reduced dataset yielded similar results (see Table S3).

4. Discussion

The aim of this large population-based cohort study was to investigate the relationship between cognition in parents with SZ or BP and their 7-year-old offspring. Overall, we found that children follow the parents' cognitive profile with some deviation on specific cognitive functions. Specifically, we found a difference in performance on nonverbal tests of processing speed, sustained attention, spatial working memory and to some extent cognitive flexibility, where children performed relatively better than their parents with SZ or BP. This finding is consistent with the idea that these functions are some of the most severely affected in SZ and BP (Bo et al., 2017; Reichenberg, 2010; Trotta et al., 2015). Note that despite the relatively better performance in offspring than parents, their performance on most of these nonverbal tests was still significantly poorer in SZ offspring compared to PBC offspring, while no such differences were seen for BP offspring compared to PBC offspring (Hemager et al., 2018). For verbal tests, there was little to no evidence of a relatively better performance in the children, - in fact we found some evidence for the opposite pattern, i.e., that parents with BP performed relatively better than their children. This included tests of verbal memory, verbal working memory, semantic/phonetic fluency, odor identification and estimated intelligence. This pattern is in contrast to previous studies, where first-degree relatives typically performed better than patients (see list of references in Table S1). However, previous studies were performed on a mix of first-degree relatives and our findings are consistent with studies of offspring suggesting that they may be more disadvantaged than other types of first-degree relatives (Aukes et al., 2012; Cowan et al., 2002; de la Serna et al., 2011; de Zwarte et al., 2019; Gillissie et al., 2022; Gottesman et al., 2010; Rasic et al., 2014; Wang et al., 2010). It could be argued that the reduced differences seen in the current study were simply due to the fact that the most ill parents did not participate in the testing, thus increasing the overall parent performance in the patient groups. However, performance was highly similar in children whose parents participated or not. Another potential reason for differences is that some of the studies performed on first-degree relatives only include participants without mental disorders (Gillissie et al., 2022). This likely skews the picture of the general performance of first-degree relatives in a positive direction. Conversely, some of the children in this study will go on to develop a severe mental disorder. However, a previous study found no differences in cognitive performance in 7-year-old children that went on to develop SZ as compared to their 7-year-old siblings that did not develop SZ (Cannon et al., 2000), suggesting that this is unlikely to explain the findings.

Interestingly, despite varying widely, all the tests, where we failed to see the expected pattern of performance (i.e. a better performance in the children than the parents) had a verbal component. This suggests that cognitive functions that to a larger extent rely on verbal processing may be more malleable to environmental input. Alternatively, these tests may conflate the specific cognitive functions with general verbal abilities that again are more closely tied to the environmental input. Of note, this similarity was not simply due to the fact that parent performance was better on verbal tests since performance was equally poor on some of the verbal and non-verbal tests in the SZ group. In addition, although the evidence was not strong, the associations between parent and child performance in the patient groups tended to be weaker on most verbal tests, suggesting that the children in these groups may have shifted unsystematically in a negative direction from their cognitive potential. A similar pattern was less evident on the non-verbal tests. However, this could be due to the strength of the associations generally being weaker on the non-verbal tests compared to the verbal tests also in the control group.

Rather surprisingly, we found some evidence that children to parents with BP performed relatively poorer than their parents on several of the verbal tests. This is especially interesting as case-control comparison in these children yielded no differences in performance (Hemager et al., 2018) and suggests that the current study design is more sensitive to potential differences. Parent performance was in general good on these tests compared to the PBC parents. Indeed, previous studies have found that BP or mania are associated with increased intellectual ability in childhood (Koenen et al., 2009) and adolescence (MacCabe et al., 2010) and their children may thus simply perform poorer because they have a lower genetic load than their parents. Alternatively, despite their good cognitive functioning, parents with BP may find it more difficult to create an appropriate, stimulating environment for their children in order to fulfill their cognitive potential, due to their mental disorder (van der Ende et al., 2016). In fact, the parents' level of functioning was lower compared to the PBC.

The association between parent and child performance on the spatial

Table 3
Correlations between parent and child cognition in the three groups (column 2 – 4) and group differences in the strength of these correlations (column 5 – 6). Positive values in column 5 and 6 indicate that the relationship is weaker in the respective patient group. WSR: Word Selective Reminding - Immediate Recall; LNS: Letter-Number Sequencing; PHON: phonemic fluency; SEM: semantic fluency; BSIT: Brief Smell Identification Test; RIST: The Reynolds Intellectual Screening Test; SWM: Spatial Working Memory; IED: Intra-Extra Dimensional Set Shifting; RVP: Rapid Visual Information Processing; PBC: population-based controls; BP: bipolar disorder; SZ: schizophrenia.

TEST	PBC	BP	SZ	PBC – BP	PBC – SZ
WSR	0.13 (−0.06; 0.31) ER = 9; 0.90	0.17 (−0.08; 0.41) ER = 11; 0.91	0.04 (−0.15; 0.23) ER = 2; 0.65	−0.04 (−0.35; 0.26) ER = 0.7; 0.39	0.09 (−0.17; 0.35) ER = 3; 0.76
CODING	0.22 (0.04; 0.41) ER = 120; 0.99	0.30 (0.05; 0.5) ER = 117; 0.99	0.14 (−0.04; 0.32) ER = 15; 0.94	−0.08 (−0.37; 0.23) ER = 0.4; 0.30	0.08 (−0.17; 0.34) ER = 3; 0.74
LNS	0.71 (0.34; 0.98) ER > 1000; 1	0.57 (0.15; 0.93) ER = 234; 1	0.51 (0.09; 0.93) ER = 110; 0.99	0.14 (−0.38; 0.65) ER = 2; 0.70	0.20 (−0.35; 0.73) ER = 3; 0.75
SEM	0.50 (0.12; 0.85) ER = 117; 0.99	0.00 (−0.50; 0.50) ER = 1; 0.50	0.42 (0.05; 0.76) ER = 63; 0.98	0.50 (−0.13; 1.11) ER = 15; 0.94	0.08 (−0.41; 0.59) ER = 2; 0.62
PHON	0.42 (0.22; 0.61) ER > 1000; 1	0.39 (0.12; 0.63) ER = 266; 1	0.30 (0.10; 0.49) 799; 1	0.03 (−0.28; 0.36) ER = 1; 0.57	0.12 (−0.15; 0.40) ER = 4; 0.80
BSIT	0.69 (0.11; 0.99) ER = 72; 0.99	0.28 (−0.63; 0.94) ER = 3; 0.76	0.48 (−0.57; 0.97) ER = 8; 0.89	0.41 (−0.48; 1.4) ER = 4; 0.81	0.21 (−0.56; 1.30) ER = 2; 0.67
RIST	0.39 (0.18; 0.57) ER > 1000; 1	0.48 (0.22; 0.70) ER > 1000; 1	0.38 (0.20; 0.55) ER > 1000; 1	−0.09 (−0.40; 0.23) ER = 0.4; 0.27	0.00 (−0.26; 0.27) ER = 1; 0.51
SWM	0.10 (−0.05; 0.26) ER = 9; 0.90	0.38 (0.19; 0.56) ER > 1000; 1	0.27 (0.08; 0.43) ER = 499; 1	−0.27 (−0.51; −0.02) ER = 0.02; 0.02	−0.16 (−0.39; 0.09) ER = 0.1; 0.09
IED	0.10 (−0.06; 0.26) ER = 8; 0.89	0.09 (−0.13; 0.31) ER = 4; 0.79	0.09 (−0.01; 0.27) ER = 5; 0.82	0.01 (−0.26; 0.29) ER = 1; 0.53	0.01 (−0.22; 0.26) ER = 1; 0.54
RVP	0.27 (0.08; 0.45) ER = 499; 1	0.24 (0.02; 0.45) ER = 54; 0.98	0.26 (0.08; 0.43) ER = 499; 1	0.03 (−0.25; 0.33) ER = 1; 0.57	0.01 (−0.24; 0.27) ER = 1; 0.53

working memory test was stronger in the patient groups. This may be due to the fact that a large proportion of the PBC parents made very few errors (< 10) on the task (PBC: 42 %; BP: 25 %; SZ: 17 %). This may make it difficult to differentiate parent performance in this group and consequently the association between parent and child performance will be weakened. Similarly, the associations between parent and child performance on IED were weak in all three groups. Here, a large proportion of parents also made very few (< 5) errors (PBC: 53 %; BP: 47 %; SZ: 46 %). Similar problems were seen for the verbal memory test, where performance in children and parents were skewed towards high scores.

In this study, we used the same or highly similar tests to assess parent and child performance on different cognitive functions. However, using the same measurement tool does not necessarily imply that we are measuring the same cognitive abilities. There are some potential concerns to consider. In particular, the development of cognitive functions might limit the comparability. For example, the development of executive functions is closely related to frontal lobe maturation, which occurs throughout childhood, adolescence and even into early adulthood (Capilla et al., 2004; Korzeniowski et al., 2021). The frontal lobes are; however, not functionally silent during childhood (Capilla et al., 2004), which would have rendered assessment (and any comparison) of functioning at this age fruitless. That being said, the maturation of the brain does not follow a simple pattern. For instance, white matter increases linearly in the frontal lobes between age 4 and 13, while synaptic pruning occurs into adulthood with frontal gray matter volume increases seen into adolescence, after which it decreases (Giedd et al., 1999). Metabolic changes related to maturation are also seen until the second decade of life (Chugani et al., 1987). Thus, the different co-occurring maturation processes could affect cognitive performance in non-linear ways. One way to mitigate this issue is to test children within a narrow age-span and thus an expected similar developmental stage, as was done in this study. Most studies using classical neuropsychological tests, such as Wisconsin Card Sorting Task, agree that executive functions emerge at age 6 and gradual improvements are seen from 6 to 10 and comparable adult performance is seen at age 12 (Anderson, 2001; Capilla et al., 2004). Since this study uses classical neuropsychological tests, age 7 is a relevant age to assess performance as executive functions are expected to have emerged (although not fully developed). In addition, fMRI studies suggest that although the intensity varies, cerebral activations during executive task performance (e.g. working memory, verbal fluency, and response inhibition) are similar in children and adults (Casey et al., 1997; Gaillard et al., 2000; Klingberg et al., 2002), i.e. they seem to recruit the same brain areas despite different developmental stages. This lends further support to the parent – child comparison being meaningful.

Our study has a number of strengths: First, data comes from a representative and large nationwide cohort. Second, only young offspring were included prior to the expected age of onset of severe mental disorders, and within a very narrow age range to reduce heterogeneity due to different developmental stages. Third, all assessors of the children were blinded to the risk status in the family. Fourth, a large neuropsychological test battery was used with well-validated tests to assess a wide range of cognitive functions. Finally, and importantly, the same cognitive tests were used for parents and children. Despite these strengths, our findings should also be interpreted in the context of some limitations. First, due to the cross-sectional study design, we were not able to include a developmental perspective. Second, the narrow age range of the children precludes information on different developmental stages. A future study relying on longitudinal data is planned that will address this concern. Third, the study relies on the assumption that it is meaningful to compare standardized scores of parents and children despite actual performance being quite different. This is a requirement for all norm-based tests that span a wide age range. Finally, we cannot exclude that illness related factors such as medication, symptoms, or disease related changes in cognition in the parents may have contributed to the weakened association between parent and child performance in the patient groups.

4.1. Conclusions and perspectives

In conclusion, we found that while performance on non-verbal tests was relatively better in offspring than parents with SZ or BP, performance on verbal tests was similar in offspring and parents or even slightly better in parents with BP. In addition, the associations between parent and child performance in the patient groups tended to be somewhat weaker on most verbal tests. The findings suggest that offspring may be particularly disadvanteged on verbal abilities. Future studies should inveastigate whether the identified pattern persists throughout

development.

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CRediT authorship contribution statement

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Declaration of competing interest

None.

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Supplementary materials

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