Archival Report

Biological Psychiatry: CNNI

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

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ABSTRACT

BACKGROUND: Given the partially shared genetic liability between schizophrenia and bipolar disorder, we aimed to assess whether 7-year-old children with a familial high risk of schizophrenia or bipolar disorder display specific deficits of sustained attention and interference control compared with each other and with control children.

METHODS: An observational cohort was identified through Danish registries and consisted of 522 children 7 years of age with no, one, or two parents with a diagnosis of schizophrenia or bipolar disorder. Control subjects were matched based on age, sex, and municipality. Sustained attention and interference control were assessed using Conners' Continuous Performance Test II and a modified Eriksen flanker task. Assessors were blinded to group membership of participants. The effect of higher genetic loading was not considered in the statistical models owing to low numbers.

RESULTS: At 7 years of age, children with a familial high risk of schizophrenia displayed deficits of sustained attention and subtle deficits in interference control compared with control children and children with a familial high risk of bipolar disorder. Children with a familial high risk of bipolar disorder displayed similar abilities of sustained attention and interference control as control children except in terms of a lower accuracy.

CONCLUSIONS: Our findings suggest distinct neurodevelopmental characteristics in middle childhood of sustained attention and interference control for children of parents with schizophrenia or bipolar disorder.

Keywords: Attention, Bipolar disorder, Endophenotypes, First-degree relatives, Interference control, Schizophrenia

https://doi.org/10.1016/j.bpsc.2018.04.012

Schizophrenia and bipolar disorder are severe mental disorders with a partially shared genetic liability and etiology (1,2). Individuals with schizophrenia or bipolar disorder exhibit cognitive impairments (3,4); however, cognitive deficits in individuals with schizophrenia tend to be more severe than in individuals with bipolar disorder (5,6). Given the genetic etiology of both disorders, it is relevant to assess cognitive abilities among children with a familial high risk of severe mental disorders. Individuals who develop schizophrenia in adulthood often display subtle cognitive impairments of sustained attention in childhood (7,8). Longitudinal cohort studies reported an increased risk of schizophrenia among children with poor academic performance (9,10), whereas both poor and excellent academic performance may precede the manifestation of bipolar disorder (11). Meta-analyses assessing adult first-degree relatives of individuals with schizophrenia (12,13) or bipolar disorder (14) reported evidence of cognitive impairments in the domains of executive function, verbal memory, and sustained attention in both disorders. However, to our knowledge, no studies to date have assessed cognitive function in prepubertal children with a familial high risk of bipolar disorder (FHR-BP) with a narrow age range.

Cognitive control is a crucial factor for functioning in daily life owing to its impact on academic and job performance, social functioning, and physical and mental health (15). One aspect of cognitive control, interference control, is the ability to suppress distracting information during cognitive processing to maintain adequate performance and focus on the task (16). Besides reducing interference from distractors, interference control involves the ability to suppress inadequate motor responses. The neurobiological mechanisms of cognitive control, including interference control, are linked to neural networks that involve the dorsolateral prefrontal cortex, anterior cingulate cortex, and parietal cortices (17). Sustained attention and interference control are two related concepts because sustained attention is considered a requirement for optimal interference control (18).

ISSN: 2451-9022

The development of interference control depends particularly on the maturation of the dorsal anterior cingulate cortex and the prefrontal cortex as well as on the dopaminergic connections and metabolism in these brain areas (19). The cognitive system matures in parallel with the motor system during development supported by abundant connections and interactions between the prefrontal cortex and the motor system (20–22). In light of the interrelated trajectories between cognitive and motor systems during development, the assessment of correlations between sustained attention and motor function in children with a familial high risk of schizophrenia (FHR-SZ) (23,24) may further enable identification of the complex phenotypic presentation of a genetic liability.

The overarching purpose of this study was thus to extend previous findings by assessing sustained attention and interference control in a large sample of 7-year-old children with FHR-SZ or FHR-BP. We hypothesized that children with FHR-SZ or FHR-BP compared with each other and with control children would display 1) deficits in sustained attention with longer reaction time (RT) as a function of time on task (vigilance), lower overall RT consistency, and lower between-block RT consistency during a task requiring attention and 2) deficits in interference control with reduced accuracy, higher RT, and greater coefficient of variation (CV) during a task requiring interference control.

METHODS AND MATERIALS

The Danish Data Protection Agency approved the study protocol. We received permission to draw data from registers from the Danish Ministry of Health. The Danish National Committee on Health Research Ethics received the protocol, and we attained a general evaluation, but owing to the lack of any intervention, further ethical approval was not regarded necessary. The parents of the participating children gave written informed consent.

Study Design and Participants

The Danish High Risk and Resilience Study–VIA7 was established in Denmark between January 1, 2013, and January 31, 2016 (25). This stratified cohort consisted of 522 Danish children 7 years of age with no, one, or two parents with a diagnosis of schizophrenia spectrum disorder or bipolar disorder. We identified the cohort using the Danish Civil Registration System (26) and the Danish Psychiatric Central Research Register (27). Schizophrenia spectrum disorder 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, and 298.99). Bipolar disorder was defined as ICD-10 codes F30 and F31 or ICD-8 codes 296.19 and 296.39. A control group was defined as population-based children of parents with no diagnoses of schizophrenia spectrum disorders or bipolar disorder. Control children were matched based on age, sex, and home address (municipality) (Supplemental Figure S1). The children underwent a battery of tests to assess motor, social, and neurocognitive function and psychopathology, which is described elsewhere (24,25,28). This article focuses on the capacity of sustained attention and interference control. Further information about the sample is provided in the Supplement.

Procedure

We assessed sustained attention using Conners' Continuous Performance Test, Second Edition (CPT II) (29), and interference control using a modified Eriksen flanker task (EFT) (30). (For further information concerning CPT II and EFT, see the Supplement). In addition, we used total standard scores from the Movement Assessment Battery for Children–Second Edition as an estimate of motor function (described in detail elsewhere) (24) when testing the relationship between sustained attention and motor function. All raters were blinded to the risk status of the children.

Outcome Measures for CPT II. We analyzed sustained attention with computer-based measures: vigilance (hit RT block change), overall RT consistency (hit RT standard error), between-block RT consistency (variability SE), RT (raw hit RT), and accuracy (omissions and commissions) (Table 1).

Outcome Measures for EFT. We measured RT, accuracy, and CV for congruent and incongruent trials. Accuracy was defined as the number of correct trials divided by the total number of trials, excluding omission trials, premature trials, and trials with RTs exceeding 3 SD from the mean. CV was defined as the SD divided by the mean for individuals for congruent and incongruent trials, respectively.

Statistical Analyses

A Priori Hypotheses. Outcome measures of CPT II were analyzed in a mixed model across groups, with a random effect of matched set (including singleton cases) and age and sex as covariates. In addition to these independent variables, we also considered all two-way and three-way interactions of group, sex, and age. Variables with a skewed distribution were logarithmically transformed and manually backward transformed with the antilogarithm. For the EFT outcome measures, we used the same mixed model as described above. However, we expanded the model with an unstructured covariance matrix, describing variance and correlation between the two outcomes for each child (congruent, incongruent). Covariates included age, sex, and condition (congruent or incongruent trials) as well as all three-way and two-way interactions of group, sex, age, and condition. Statistically nonsignificant interaction terms were eliminated via backward stepwise regression, with the constraint that the model at each step had to be hierarchically well formulated. The effect of sibling status ($n = 16$) and higher genetic loading ($n = 9$, including 7 children of two parents with schizophrenia, 1 child of two parents with bipolar disorder, and 1 child of one parent with schizophrenia and the other parent with bipolar disorder, which was categorized in the FHR-SZ group owing to hierarchy of ICD-10) were not considered in the statistical models owing to the low numbers. We considered p values $< .05$ as significant. All statistical analyses were conducted using SAS Version 9.4 (SAS Institute Inc., Cary, NC).

Explorative Analyses. The relationship between mean RT and accuracy for congruent and incongruent trials on a group

Table 1. Characteristics of Children and Definitions of CPT II and EFT Variables

Variable		Definition	Children With FHR-SZ	Children With FHR-BP	Control Subjects
CPT II[a]			*n* = 189	*n* = 116	*n* = 187
Sex, female, *n* (%)		Sex distribution	89 (47.09%)[b]	54 (46.55%)[b]	86 (45.99%)[b]
Age, years, mean (SD)		Age when child performed CPT II	7.932 (0.252)[c]	7.959 (0.22)[c]	7.893 (0.22)[c]
Vigilance, median (fractiles)	Hit RT block change	Slope of change in hit RT across different blocks (positive slope indicates slowing of RT as function of time on task)	0.0282 (−0.036, 0.11)	0.0193 (−0.059, 0.100)	0.0199 (−0.031, 0.104)
Overall RT consistency, median (fractiles)	Hit RT SE	Consistency of response time as measured by SE for responses target	17.093 (6.9, 41.3)	13.657 (6.08, 35.0)	14.505 (6.14, 39.08)
Between-block RT consistency, median (fractiles)	Variability SE	Measure of response time consistency calculated as SD of SE values for each subblock	35.590 (8.50, 94.96)	24.095 (6.17, 83.36)	30.801 (6.46, 94.68)
RT, ms, median (fractiles)	Raw hit RT	Average speed (RT) of correct responses across entire test	515.71 (378.8, 738.9)	480.48 (379.5, 699.5)	489.74 (352.0, 687.4)
Accuracy, %	Errors of omission, median (fractiles)	Number of nonresponses to target letters (non-X)	29 (6, 122)	22 (3, 79)	23 (3, 101)
	Errors of commission, mean (SD)	Number of responses to nontarget (X)	24.810 (6.243)	26.241 (4.993)	24.957 (5.620)
EFT			*n* = 192	*n* = 116	*n* = 192
Sex, female, *n* (%)		Sex distribution	89 (46.35%)[d]	55 (47.41%)[d]	87 (45.31%)[d]
Age, years, mean (SD)		Age when child performed EFT	7.942 (0.257)[e]	7.964 (0.226)[e]	7.896 (0.220)[e]
Reaction time, ms, median (fractiles)	Congruent trials	Mean RT of correct responses across EFT for all congruent trials	910.207 (540.2, 1510.2)	838.995 (569.6, 1193.3)	850.871 (590.3, 1380.7)
	Incongruent trials	Mean RT of correct responses across EFT for all incongruent trials	1253.874 (576.8, 2222.2)	1124.704 (616.52, 1851.9)	1138.720 (703.6, 2065.5)
Accuracy, %, mean (SD)	Congruent trials	Probability of correct responses for congruent trials	0.904 (0.080)	0.912 (0.081)	0.915 (0.077)
	Incongruent trials	Probability of correct responses for incongruent trials	0.769 (0.198)	0.798 (0.151)	0.812 (0.144)
CV, median (fractiles)	Congruent trials	SD of RT within subjects divided by mean RT within subjects for congruent trials	0.433 (0.252, 0.802)	0.382 (0.221, 0.792)	0.384 (0.223, 0.757)
	Incongruent trials	SD of RT within subjects divided by mean RT within subjects for incongruent trials	0.512 (0.296, 0.840)	0.490 (0.208, 0.881)	0.462 (0.253, 0.848)

Data presented in mean and SD for normally distributed data or 2.5% and 97.5% fractiles for skewed data. Control subjects were population-based children of parents with no diagnoses of schizophrenia spectrum disorders or bipolar disorder.

CPT II, Conners' Continuous Performance Test, Second Edition; CV, coefficient of variation; EFT, Eriksen flanker task; FHR-BP, familial high risk of bipolar disorder; FHR-SZ, familial high risk of schizophrenia; RT, reaction time.

[a]CPT II manual defines the following measures as related to the concept of inattention: omissions, commissions, hit RT, hit RT SE, variability SE. The measures of impulsivity include commission and perseverations. Vigilance is captured by hit RT block change.

[b]The subgroups of children who completed CPT II did not differ with respect to sex (p = .98).

[c]Difference with respect to age between subgroups who completed CPT II (p = .048). Post hoc analysis showed that children with FHR-BP were slightly older than control subjects (mean difference = 0.066; 95% confidence interval, 0.012–0.12; p = .018), but there was no difference in age between children with FHR-SZ and control subjects (p = .10) and between children with FHR-SZ and children with FHR-BP (p = .34).

[d]The subgroups that completed EFT did not differ with respect to sex (p = .99).

[e]Difference with respect to age between subgroups who completed EFT (p = .03). Post hoc analysis showed that children with FHR-BP were significantly older than control subjects (p = .014), but there was no difference in age between children with FHR-SZ and control subjects (p = .053) and between children with FHR-SZ and children with FHR-BP (p = .43).

level was assessed in a Spearman correlation of speed and accuracy (speed-accuracy trade-off). Finally, we assessed the association among sustained attention, interference control (accuracy in incongruent trials in EFT), and motor ability [measured in the same sample with the total standard score from the Movement Assessment Battery for Children–Second Edition (24)] using a linear mixed model, in which sustained attention (between-block RT consistency, CPT II) served as the outcome variable.

RESULTS

Of the 522 children included in the entire Danish High Risk and Resilience Study–VIA7 cohort, 492 children completed CPT II (189 [38.4%] children with FHR-SZ, 116 [23.6%] children with FHR-BP, and 187 [38.0%] control children), and 500 children completed EFT (192 [38.4%] children with FHR-SZ, 116 [23.2%] children with FHR-BP, and 192 [38.4%] control children) (Table 1, Supplemental Figure S1, and Supplemental Table S1).

Table 2. Sustained Attention Among 7-Year-Old Children With FHR-SZ or FHR-BP and Control Subjects Measured by CPT II

	Estimated Ratio[a] or Mean Difference[b] (95% CI)	p Value
FHR-SZ Group vs. Control Group		
Vigilance[a]	1.295 (1.026, 1.635)	.03[c]
Overall RT consistency[a]	1.136 (1.035, 1.248)	.008[c]
Between-block RT consistency[a]	1.16 (1.008, 1.337)	.039[c]
RT[a]	1.035 (1.001, 1.069)	.044[c]
Omissions[a]	1.256 (1.07, 1.48)	.007[c]
Commissions[b]	−0.16 (−1.299, 0.982)	.785
FHR-BP Group vs. Control Group		
Vigilance[a]	1.069 (0.798, 1.433)	.65
Overall RT consistency[a]	0.950 (0.85, 1.062)	.36
Between-block RT consistency[a]	0.890 (0.755, 1.049)	.16
RT[a]	0.989 (0.951, 1.029)	.59
Omissions[a]	0.934 (0.7697, 1.130)	.48
Commissions[b]	1.24 (−0.075, 2.546)	.07
FHR-SZ Group vs. FHR-BP Group		
Vigilance[a]	1.211 (0.908, 1.615)	.19
Overall RT consistency[a]	1.196 (1.071, 1.336)	.002[c]
Between-block RT consistency[a]	1.304 (1.108, 1.535)	.002[c]
RT[a]	1.046 (1.005, 1.088)	.026[c]
Omissions[a]	1.345 (1.110, 1.630)	.003[c]
Commissions[b]	−1.394 (−2.696, −0.092)	.036[c]

Estimated ratio or mean difference of raw scores in CPT II between children with FHR-SZ (n = 189) or FHR-BP (n = 116) and control subjects (n = 187) adjusted for sex and age. No three-way or two-way interactions were significant. All variables were logarithmically transformed and manually backward transformed with the antilogarithm except for errors of commissions. Control group included population-based children of parents with no diagnoses of schizophrenia spectrum disorders or bipolar disorder.

CI, confidence interval; CPT II, Conners' Continuous Performance Test, Second Edition; FHR-BP, familial high risk of bipolar disorder; FHR-SZ, familial high risk of schizophrenia; RT, reaction time.

[a]Estimated ratio.

[b]Mean difference.

[c]p value $<$ .05.

Sustained Attention (CPT II)

Overall RT consistency differed across groups ($F_{2,352}$ = 6.19, p = .0023) and sex ($F_{1,298}$ = 13.42, p = .0003), with no effect of age ($F_{1,459}$ = 0.00, p = .98) or any of the two-way or three-way interactions. Post hoc tests specified that children with FHR-SZ had 13.6% lower overall RT consistency compared with control children (95% confidence interval [CI], 3.5%–24.8%; p = .026). Furthermore, children with FHR-SZ displayed 19.6% lower overall RT consistency than children with FHR-BP (95% CI, 7.1%–33.6%; p = .002). Children with FHR-BP did not differ from control children (mean difference = −5%; 95% CI, −15% to 6.2%; p = .36). Moreover, boys exhibited 17.6% lower overall RT consistency compared with girls (95% CI, 7.8%–28.2%; p = .0003) (Table 2 and Figure 1).

Between-block RT consistency differed across groups ($F_{2,345}$ = 5.43, p = .005) and sex ($F_{1,286}$ = 15.99, $p < .0001$) but not with respect to age ($F_{1,450}$ = 0.05, p = .83). None of the two-way or three-way interactions were significant. Post hoc tests specified that children with FHR-SZ had 16% lower between-block RT consistency (or 16% higher variability SE) compared with control children (95% CI, 0.8%–33.7%; p = .039). Furthermore, children with FHR-SZ displayed 30% lower between-block RT consistency (or 30% higher variability SE) than children with FHR-BP (95% CI, 10.8%–53.5%; p = .002). Children with FHR-BP did not differ from control children (mean difference = −11%; 95% CI, −24.5% to 4.9%; p = .16) (Table 2). Moreover, boys exhibited 29.3% lower between-block RT consistency (or 29.3% higher variability SE) than girls (95% CI, 14%–47%; $p < .0001$). Vigilance did not differ across groups ($F_{2,287}$ = 2.52, p = .08), age ($F_{1,368}$ = 0.43, p = .51), or sex ($F_{1,255}$ = 0.34, p = .56) or any significant

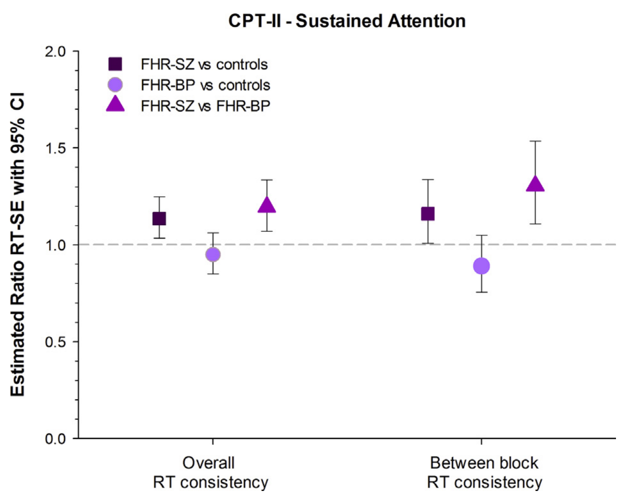

Figure 1. Sustained attention—Conners' Continuous Performance Test, Second Edition (CPT II). Estimated ratio for reaction time (RT) standard error (SE) for overall RT consistency and between-block RT consistency between children with familial high risk of schizophrenia (FHR-SZ) versus control subjects (dark purple squares), children with familial high risk of bipolar disorder (FHR-BP) versus control subjects (light purple circles), and children with FHR-SZ versus children with FHR-BP (purple triangles). The reference level (dashed horizontal line) represents no difference between the FHR groups and the contrast group, which concerns either control subjects (squares and circles) or children with FHR-BP (triangles). Error bars indicate 95% confidence interval (CI).

Table 3. Interference Control Among 7-Year-Old Children With FHR-SZ or FHR-BP and Control Subjects Measured by Eriksen Flanker Task

	Estimated Ratio[a] or Mean Difference[b] (95% CI)	*p* Value
FHR-SZ Group vs. Control Group		
Boys		
RT mean congruent[a]	1.2028 (1.009, 1.434)	.0395[c]
RT mean incongruent[a]	1.274 (1.059, 1.532)	.01[c]
Accuracy congruent[b]	−0.02 (−0.09, 0.05)	.55
Accuracy incongruent[b]	−0.12 (−0.26, 0.02)	.087
CV congruent[a]	1.152 (1.12, 1.25)	.0012[c]
CV incongruent[a]	1.141 (1.06, 1.23)	.0009[c]
Girls		
RT mean congruent[a]	1.192 (1.002, 1.419)	.048[c]
RT mean incongruent[a]	1.179 (0.980, 1.418)	.08
Accuracy congruent[b]	−0.02 (−0.08, 0.05)	.563
Accuracy incongruent[b]	−0.16 (−0.29, −0.02)	.029[c]
CV congruent[a]	1.098 (1.00, 1.20)	.046[c]
CV incongruent[a]	1.112 (1.01, 1.22)	.024[c]
FHR-BP Group vs. Control Group		
Boys		
RT mean congruent[a]	0.875 (0.698, 1.097)	.25
RT mean incongruent[a]	0.915 (0.724, 1.158)	.46
Accuracy congruent[b]	−0.04 (−0.123, 0.04)	.309
Accuracy incongruent[b]	−0.24 (−0.42, −0.07)	.006[c]
CV congruent[a]	0.99 (0.90, 1.09)	.83
CV incongruent[a]	1.02 (0.92, 1.11)	.80
Girls		
RT mean congruent[a]	0.894 (0.702, 1.140)	.37
RT mean incongruent[a]	0.845 (0.656, 1.109)	.19
Accuracy congruent[b]	−0.05 (−0.14, 0.04)	.249
Accuracy incongruent[b]	−0.29 (−0.48, −0.11)	.002[c]
CV congruent[a]	1.04 (0.93, 1.16)	.47
CV incongruent[a]	1.036 (0.93, 1.15)	.51
FHR-SZ Group vs. FHR-BP Group		
Boys		
RT mean congruent[a]	1.374 (1.106, 1.707)	.004[c]
RT mean incongruent[a]	1.392 (1.109, 1.746)	.004[c]
Accuracy congruent[b]	0.02 (−0.06, 0.10)	.57
Accuracy incongruent[b]	0.12 (−0.04, 0.29)	.15
CV congruent[a]	1.164 (1.06, 1.28)	.003[c]
CV incongruent[a]	1.127 (1.03, 1.24)	.013[c]
Girls		
RT mean congruent[a]	1.333 (1.057, 1.681)	.015[c]
RT mean incongruent[a]	1.396 (1.097, 1.779)	.007[c]
Accuracy congruent[b]	0.03 (−0.05, 0.11)	.45
Accuracy incongruent[b]	0.14 (−0.04, 0.32)	.12
CV congruent[a]	1.05 (0.95, 1.17)	.99
CV incongruent[a]	1.07 (0.97, 1.19)	.19

Estimated ratio of mean RT between children with FHR-SZ (n = 192) or children with FHR-BP (n = 116) and control subjects (n = 192) adjusted for sex, age, condition (congruency), and significant group-by-sex-by-congruency interaction and all two-way interactions. Mean difference of accuracy between children with FHR-SZ or children with FHR-BP and control subjects adjusted for sex, age, condition (congruency), and age-by-group-by-condition interaction and age-by-sex-condition interaction and all two-way interactions. Estimated ratio of CV between children with FHR-SZ or FHR-BP and control subjects adjusted for sex, age, and condition (congruency). All variables were logarithmically transformed and manually backward transformed with the antilogarithm except for accuracy. Control group included population-based children of parents with no diagnoses of schizophrenia spectrum disorders or bipolar disorder.

CI, confidence interval; CV, coefficient of variation; FHR-BP, familial high risk of bipolar disorder; FHR-SZ, familial high risk of schizophrenia; RT, reaction time.

[a]Estimated ratio.

[b]Mean difference.

[c]p value $<$ .05.

two-way or three-way interactions (Table 2). Furthermore, children with FHR-SZ displayed longer RT and more omissions compared with control children and children with FHR-BP (Table 2 and Figure 1).

Interference Control (Eriksen Flanker Task)

For RT mean, only one interaction (group-by-sex-by-condition) reached significance ($F_{2,493}$ = 3.59, p = .028), whereas effects of group ($F_{2,438}$ = 2.83, p = .06), condition (congruency) ($F_{1,493}$ = 2.90, p = .089), age ($F_{1,521}$ = 3.23, p = .073), and sex ($F_{1,475}$ = 0.09, p = .76) were not significant. Post hoc tests indicated that children with FHR-SZ displayed slower RT mean compared with control children in congruent trials and boys with FHR-SZ in incongruent trials as well as compared with children with FHR-BP for both congruencies (Table 3 and Figure 2A).

The test for fixed effects of accuracy revealed significant differences across groups ($F_{2,494}$ = 3.06, p = .048), condition (congruency) ($F_{1,492}$ = 4.23, p = .04), and age ($F_{1,498}$ = 4.09, p = .044) but no significant effect of sex ($F_{1,498}$ = 2.70, p = .10). The group-by-age-by-condition interaction ($F_{2,492}$ = 3.93, p = .020), the sex-by-age-by-condition interaction ($F_{1,492}$ = 3.91, p = .049) and the group-by-condition interaction ($F_{2,492}$ = 4.02, p = .019) reached significance, whereas the remaining two-way interactions were not significant. Post hoc tests indicated evidence of an interference effect among girls with FHR-SZ who displayed significantly lower accuracy during incongruent trials (mean difference = −0.16; 95% CI, −0.29 to −0.015; p = .029) compared with girls in the control group. Moreover, children with FHR-BP also displayed an interference effect with lower accuracy during incongruent trials compared with control children (Table 3 and Figure 2B).

We tested for speed-accuracy trade-off between RT and accuracy for congruent and incongruent trials, but correlations between RT and accuracy did not reach significance in the overall sample (Spearman correlation; r = −.021, p = .64 for congruent trials; r = .034, p = .44 for incongruent trials). No significant correlations were detected for children with FHR-SZ (r = .03, p = .71 for congruent trials; r = .05, p = .45 for incongruent trials), control children (r = −.074, p = .52 for congruent trials; r = .007, p = .33 for incongruent trials), or children with FHR-BP (r = −.026, p = .78 for congruent trials; r = −.005, p = .95 for incongruent trials).

RT variability (measured as CV) differed across groups ($F_{2,337}$ = 9.51, p < .0001), condition (congruency) ($F_{1,499}$ = 388.00, p < .0001), sex ($F_{1,274}$ = 7.22, p = .008), and age

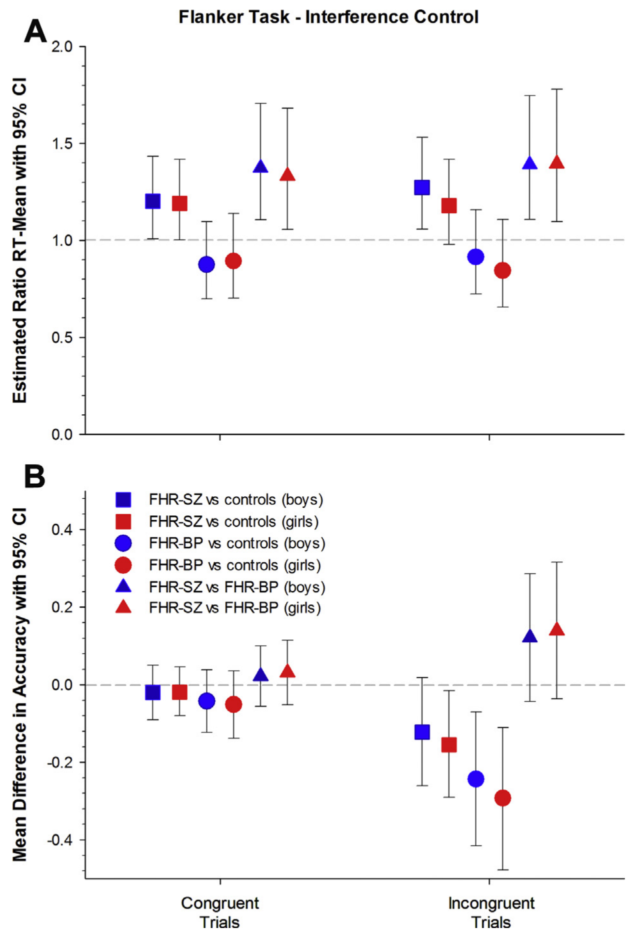

Figure 2. Flanker task—interference control. Estimated ratio for mean reaction time (RT) **(A)** and mean difference for accuracy in congruent and incongruent trials **(B)** between children with familial high risk of schizophrenia (FHR-SZ) versus control subjects (red and blue squares), children with familial high risk of bipolar disorder (FHR-BP) versus control subjects (red and blue circles), and children with FHR-SZ versus children with FHR-BP (red and blue triangles). Error bars indicate 95% confidence interval (CI). The reference level (dashed horizontal line) represents no difference between the FHR groups and the contrast group, which concerns either control subjects (squares and circles) or children with FHR-BP (triangles).

($F_{1,458}$ = 4.52, p = .034). No interactions were significant. Post hoc tests estimated that children with FHR-SZ had 12.6% higher RT variability compared with control children (95% CI, 6.4%–19.21%; $p < .0001$). Children with FHR-SZ had 10.78% higher RT variability compared with children with FHR-BP (95% CI, 3.6%–18.41%; p = .003), whereas no difference was detected between children with FHR-BP and control children (estimated ratio = 1.66; 95% CI, −4.92% to 8.70%; p = .63). RT variability was higher in the incongruent condition, younger children exhibited a significantly higher CV than older children, and boys showed higher RT variability than girls (Table 3).

Relationship Between Sustained Attention, Interference Control, and Motor Performance

We tested the relationship between sustained attention (between-block RT consistency), motor function [total standard score from Movement Assessment Battery for Children–Second Edition (24)], and interference control (accuracy in incongruent trials). Sustained attention was positively related with better motor function ($F_{1,466}$ = 17.15, $p < .0001$) and interference control ($F_{1,460}$ = 8.10, p = .0046). The effect of group ($F_{2,340}$ = 3.68, p = .026) reached significance and revealed reduced sustained attention among children with FHR-SZ compared with children with FHR-BP (p = .0072). The effect of sex ($F_{1,296}$ = 6.86, p = .009) was significant and indicated a reduced performance of sustained attention among boys compared with girls. No effect of age ($F_{1,433}$ = 0.39, p = .53) and none of the two-way or three-way interactions reached significance.

DISCUSSION

We confirmed our hypothesis that children 7 years of age with FHR-SZ would display deficits in sustained attention on CPT II, with a lower overall RT consistency and a lower between-block RT consistency compared with control children and children with FHR-BP. Moreover, children with FHR-SZ showed deficits in interference control compared with control children: slower RT for boys in both conditions and for girls in the congruent condition and lower accuracy during incongruent trials for girls. Both girls and boys with FHR-SZ displayed a greater CV for both conditions. Children with FHR-SZ compared with children with FHR-BP displayed slower RT for both sexes and a greater CV for boys. In contrast, children with FHR-BP displayed skills similar to control children in all the measures of sustained attention and interference control (with the exception of lower accuracy during incongruent trials in EFT). Our data provide evidence of a clear distinction regarding sustained attention ability between children with FHR-SZ and children with FHR-BP. CPT II measures differed between the two familial risk groups, indicating different abilities of attentional neurocognitive functioning between children with FHR-SZ and children with FHR-BP, suggesting distinct developmental characteristics for sustained attention at 7 years of age.

Our results of impaired sustained attention are consistent with the New York High-Risk Project, which reported deficits of sustained attention among 7- to 12-year-old children of parents with schizophrenia measured with CPT (31). However, both the Edinburgh High Risk Study cohort that examined 16- to 25-year-old first-degree relatives of individuals with schizophrenia (32,33) and the Harvard and Hillside Adolescent High Risk Studies that examined 12- to 25-year-old first-degree relatives of individuals with schizophrenia (34) did not report differences in sustained attention compared with control subjects. However, our study differs from the previous high-risk studies in a narrow age range in childhood, as it does not conceal the effect of cognitive maturation across childhood and puberty and because of our large sample size taken from a registry-based sample. Finally, our results contribute to the discussion of whether cognitive deficits are risk factors that reflect the underlying vulnerabilities in a neurodevelopmental process of psychosis (35) because our findings emphasize the essential role of cognitive impairments in schizophrenia, as they occur already in childhood among offspring of individuals with schizophrenia.

Previous studies among first-degree relatives of individuals with bipolar disorder reported both attention abilities (36,37) and attention deficits (14,38) comparable to control subjects (39). In adult first-degree relatives of individuals with bipolar disorder, a meta-analysis reported a small effect size of impaired sustained attention (omission errors on a CPT task) and a medium effect size in response inhibition (Stroop task) ($N = 443$) (14). Taken together, our results and previous studies point toward a decline of sustained attention and interference control only at a later stage during development for children with FHR-BP, but not yet in childhood. Longitudinal cohort studies suggest that individuals who later develop mania (40) or bipolar disorder (11) display either similar cognitive skills (IQ) compared with control subjects (40) or alternatively excellent or extremely poor school performance (11), thus indicating different subgroups before the manifestation of the disorder (41,42). Equally, neurodevelopmental models for schizophrenia (43) and bipolar disorder (44) claim different trajectories of symptoms and deficits during neurodevelopment (motor, cognitive, and social impairments in childhood for individuals who develop schizophrenia, whereas anxiety and sleep problems are present in childhood for individuals who develop bipolar disorder).

Sustained attention and cognitive control have shown correlations with symptoms of attention deficit (45–47); therefore, attention-deficit symptoms may have contributed to performance differences. However, one cannot disregard the notion that the same underlying (biological/genetic) factors may influence both measures. Thus, controlling for behavior may overadjust group differences (48). Our main interest, however, was to further map the characteristics and patterns of problems in the domains of attention and cognitive control.

Sustained attention and interference control are two related concepts, as sustained attention is considered a prerequisite for the capacity of interference control (18). Our findings suggest that interference control is relatively immature at 7 years of age, as reflected in the discrepancy between congruent and incongruent trials. This finding is coherent with the fact that the anterior cingulate cortex and prefrontal cortex as well as their dopaminergic connections mature relatively late during development, reaching maturity only after puberty and into early adulthood (19). Our explorative analysis showed that interference control was positively correlated with sustained attention. As sustained attention and interference control are related, deficits in sustained attention may delay the development of interference control.

The close and abundant connections between the motor and cognitive systems during development (22) (which is illustrated in the explorative analysis documenting a relationship among sustained attention, motor function, and interference control) could explain why children with FHR-SZ exhibit both cognitive (7) and motor (23) deficits during development, whereas children with FHR-BP do not exhibit motor deficits (24), sustained attention deficits, or prominent deficits of interference control. Furthermore, children with FHR-SZ had prolonged RTs, which could not be explained by a speed-accuracy trade-off mechanism, but may suggest impaired response interference and delayed developmental motor abilities.

Previous studies suggested that deficits of sustained attention represent an endophenotype for schizophrenia (49,50). Our study extends and further confirms previous findings in a large group of children with FHR-SZ and contrasts their performance to children with FHR-BP, who did not display impaired sustained attention. This finding indirectly supports the notion that deficits in sustained attention could be regarded as a specific endophenotype for schizophrenia for three reasons. First, we have demonstrated a clear distinction in sustained attention between children with FHR-SZ and children with FHR-BP. Second, our data indicate that offspring of individuals with schizophrenia, to a greater extent than in the general population, display deficits in sustained attention. Third, these are state-independent deficits in sustained attention in individuals with schizophrenia (3).

The potential clinical implications of this study could be early identification of attention deficits in children of parents with schizophrenia, ideally before they start school. Once identified, attention problems may be addressed through adaptation in teaching settings to prevent a negative impact on academic performance. This is relevant because the combination of this vulnerability with a decreased interference control may lead to secondary behavioral and emotional consequences.

Our study has major strengths, including the novelty of assessing the specificity of sustained attention deficits in three different populations and of assessing interference control in children with a familial risk of severe mental disorders within a large sample with a narrow age range. Furthermore, the raters were blinded to the familial risk status of the children, which minimized the risk of assessor bias. Our study, however, has several limitations that need to be addressed in future research. First, owing to the cross-sectional nature of the first wave of the study, we were unable to predict whether children with cognitive deficits will continue to deviate from the general population throughout development. It is possible that these deviations are transitory and may normalize during development (51). Only longitudinal studies may address these issues. In addition, owing to the nature of the behavioral data, we were not able to identify the underlying neurobiological mechanisms of interference control; however, the patterns across diagnostic groups contribute to enhancing the understanding of the specific deficits and give rise to potential interventions. Moreover, parents in the control group did not have a diagnosis of schizophrenia spectrum disorder or bipolar disorder, but they could have other mental or somatic disorders, as in the general population. Despite the fact that the control group was composed to reflect a general parental population, it is a limitation that the children in the three groups could have been influenced by the potential of disorders their parents may have other than schizophrenia or bipolar disorder. The advantage of this approach, however, is a higher generalizability of the findings, as would not be the case in a more selected population.

Children 7 years of age with FHR-SZ showed deficits in sustained attention and subtle deviations of interference control compared with control children; these deficits were largely absent in children with FHR-BP. Moreover, children with FHR-SZ differed significantly from children with FHR-BP in all CPT II measures of sustained attention. Our findings reflect distinct neurodevelopmental characteristics before puberty for children at risk of severe mental disorders. By assessing offspring of individuals with either schizophrenia or bipolar disorder, this study contributes to the understanding of their respective neurodevelopmental cognitive vulnerability in middle childhood. Furthermore, our results suggest that deficits of sustained attention may be regarded as possible endophenotypes for schizophrenia. Finally, our results demonstrate that deficits of sustained attention correlate positively with motor abilities, which could reflect the tight interplay of the motor and cognitive systems during development (22).

ACKNOWLEDGMENTS AND DISCLOSURES

This work was supported by the Mental Health Services of the Capital Region of Denmark, the Beatrice Surovell Haskell Fund for Child Mental Health Research of Copenhagen (Grant No. J.NR 11531), Aarhus University, Central Denmark Region, and The Lundbeck Foundation Initiative for Integrative Psychiatric Research (*i*PSYCH) (Grant Nos. R102-A9118 and R155-2014-1724). Sources of funding had no involvement in this work.

AAET, JRJ, OM, MN, and KJP developed the study design, provided methodological advice, and supervised the conduct of the study. MN, OM, AAET, KJP, and BKB obtained funding. BKB, AAETT, JRJ, DE, KSS, CJC, NH, DG, and AG collected data. HE provided the Flanker task. AP, SV, and BKB were responsible for data management. BKB, LTS, SV, AP, and KJP conducted the statistical plans and analysis. BKB and KJP wrote the first draft. All authors contributed to data interpretation, commenting on and editing the report, and approved the final version of the manuscript. All authors are accountable for the work.

We thank all the children and families who participated in the Danish High Risk and Resilience Study-VIA7 study. We thank Carsten Bøcker Pedersen and Marianne Giørtz Pedersen for retrieving the register extract; Camilla Tjott for training and supervision in the assessment of Movement Assessment Battery for Children–Second Edition; Mette Skjærbæk, Maja Gregersen, Anne Søndergaard, Anne Ranning, Heidi Jensen, Marianne Melau, Cecilie Gregersen, Henriette Stadsgaard, Kate Kold Zahle, and Maria Toft Henriksen for helping with data collection; Manon Chaine and Jessica Ohland for help with data management; and Preben Bo Mortensen, Thomas Werge, David Hougaard, and Anders Børglum for collaboration in *i*PSYCH.

The authors report no biomedical financial interests or potential conflicts of interest.

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Received Jan 10, 2018; revised and accepted Apr 23, 2018.

Supplementary material cited in this article is available online at https://doi.org/10.1016/j.bpsc.2018.04.012.

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