Archival Report

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

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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).

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