

Neuropsychological Profiles of Adolescents with Bipolar Disorder and Adolescents with a High Risk of Bipolar Disorder



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SUMMARY

Purpose: In recent years evidence of an association between bipolar disorder (BD), and specific neuropsychological impairment and familial transmission of BD has been mounting. The aim of this study was to identify the clinical and neuropsychological features of BD in adolescents, to assess the clinical and neuropsychological parameters in adolescents with a high risk of familial transmission of BD, and to identify probable early markers of the disorder.

Materials and Methods: The study included 25 patients aged 12-18 years that were diagnosed as BD (case group), 25 adolescents without a mood disorder that had a parent and/or sibling diagnosed as BD, (risk group), and 25 typically developing adolescents (control group). To determine neuropsychological profiles the participants were administered the Wisconsin Card Sorting Test (WCST), Stroop Color Word Test (SCWT), and Continuous Performance Test (CPT), and to evaluate clinical and behavioral profiles the Children's Depression Inventory (CDI), Parent-Young Mania Rating Scale (P-YMRS), Youth Self-Report (YSR), and Conners' Parent Rating Scale (CPRS-48) were administered.

Results: The case group performed significantly lower on the WCST, SCWT, and CPT in terms of executive and attention functions, whereas there wasn't a difference between the risk group and control group. In addition, significantly more of the adolescents in the case and risk groups had clinical and behavioral problems than those in the control group.

Conclusion: The findings show that behavioral and clinical problems were more common in the risk group than in the control group, and that the frequency of attention and executive function impairment was similar in both of those groups. The findings suggest that BD itself may be associated with attention and executive function impairments, whereas a familial risk of BD may be associated with some behavioral problems. Follow-up and neuroimaging studies conducted with a larger number of participants, and neuropsychological test profiles may provide more detailed information about the neuropsychological profiles of individuals with a genetic risk for BD and may provide descriptive data about where and how the biological and psychometric deterioration initiate

Keywords: Bipolar disorder, neuropsychology, adolescent

INTRODUCTION

Bipolar disorder (BD) is a chronic illness with a course characterized by exacerbations and remissions. Although children and adolescents are infrequently diagnosed with BD, the number of such cases is increasing (Youngstrom et al. 2008). Among adult BD patients, 30%-40% experienced their first attack during adolescence (Loranger and Levine 1999). Studies show that the incidence of BD in children and adults

varies widely. The prevalence of BD type 1 among adults is 1.2%-1.6%, versus 0.1% among adolescents, whereas the prevalence of BD type 2 among adults is 4%, versus 1% among adolescents (Lewinsohn et al. 1995).

The traits associated with genes linked to illness, but that do not lead to clinical symptoms explicitly are referred to as endophenotypes. In other words, endophenotypes are genetically identified phenotypes that can be part of a complex illness.

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Endophenotypes occur at a higher rate in non-affected family members than in the general population and are independent of illness (Gottesman and Gould 2003). Endophenotypes can be biochemical, endocrinological, neurophysiological, neuro-anatomical, or neuropsychological. As they do not manifest as explicit clinical symptoms in many cases, they cannot be observed externally and specific techniques are required to detect them (Weinberger et al. 2001). Neuropsychological functions have been examined in patients diagnosed with endophenotype BD and non-affected family members. A study published in 2006 showed that twin sisters of BD patients exhibited similar cognitive functions and that genetic predisposition and cognitive impairment were related. In that study the researchers concluded that cognitive impairment can be a genetic risk for BD or it can be a candidate endophenotype (Christiansen et al. 2006).

Many studies on adults with BD agree that impaired executive functioning (Savitz et al. 2005; Glahn et al. 2004), attention (Burdick et al. 2006; Hasler et al. 2006), and verbal memory (Hasler et al. 2006; Glahn et al. 2004) were potential candidate endophenotypes. Arts et al.'s (2008) meta analysis analyzed neuropsychological functioning in adults with BD and their first-degree relatives, and reported that impaired executive functioning and verbal learning had a large effect size, whereas mental speed, visual memory, and continual attention had a mild effect and visual perception had little effect. A meta analysis of studies that analyzed patients with BD (45 studies, 1423 patients) and their first-degree relatives (17 studies, 443 participants) reported that both the patient group (large and mild effect size) and the first-degree relatives (little and mild effect size) had impaired reaction inhibition, set shifting, executive functioning, verbal memory, and continual attention, and that BD onset in early ages was associated with verbal memory impairment (Bora et al. 2009).

Very few studies have analyzed neuropsychological functions in pediatric and adult BD patients. Castillo et al. (2000) reported that 10 adult BD patients had impaired attention. Another study, which compared 57 children and adult BD patients to normal controls, reported that the BD patients had impaired continual attention that negatively affected academic performance (Doyle et al. 2005). A 2005 study that included 10 manic BD patients, 10 euthymic BD patients, and 10 controls reported that attention performance scores were lower in the patient group than in the control group, but that there wasn't a difference between the manic and euthymic patients (De Bello et al. 2004). In many of the studies on executive functioning, impairments were seen in this area. A study conducted using the Cambridge Neuropsychological Test Automated Battery reported that pediatric and adult BD patients had less set changing ability than controls (Dickstein et al. 2004). In a study based on the Wisconsin

Card Sorting Test (WCST) Doyle et al. (2005) reported that pediatric and adult BD patients had impaired executive functioning. A 2006 study that included 12 adults with BD that were evaluated using the Stroop Color Word Test (SCWT), Continuous Performance Test (CPT), and WCST reported that the patients had lower reaction inhibition scores than controls (Rucklidge 2006). Doyle et al. compared 57 young BD patients and healthy controls, and observed significant impairment in the BD patients based on the digit span test (Doyle et al. 2005). A study that compared 33 BD type 1 patients and healthy controls reported that the patient group had impaired working memory (Bearden et al. 2006). A meta analysis of neuropsychological impairment in pediatric and adult BD patients reported that the patients had impairment in all cognitive domains. The meta analysis included 10 selected studies and showed that impaired verbal memory had the greatest effect size. Moreover, impaired working memory, attention, executive functioning, and visual memory had a moderate effect size (Joseph et al. 2008).

Only a few studies have evaluated cognitive functions in pediatric BD patients simultaneously with that in their first-degree relatives. The first such study was conducted by Doyle et al. and included 170 children and adolescents diagnosed as BD, 118 of their non-affected siblings, and 79 healthy controls. The study investigated impairment in speed of processing, verbal learning, working memory, and problem solving. The best-defined familial risk was impaired problem solving skills (executive functioning). It was also reported that working memory seemed to be running in the family, although not as much as executive functioning (Doyle et al. 2009). Another study published in 2009 examined continuous attention in 28 BD patients aged 7-17 years, 26 non-BD adolescents that had first-degree relatives with BD (siblings of the adolescents with BD and children of the adults that had BD), and 24 healthy adolescents. It was reported that response time in the children and adolescents with first-degree relatives that had BD was longer, which was independent of existing psychopathology (Brotman et al. 2009). In summary, impaired attention and executive functioning were observed in people with a high risk of BD, and it is thought that additional research is required to determine if such impairment is an indicator of the development of BD (Jones and Bental 2008).

The aim of the present study was to identify differences in neuropsychological function between patients diagnosed as BD during adolescence and healthy controls, and to identify the endophenotypic indicators effective for adolescence BD by examining neuropsychological functions in individuals with a high risk of BD. The study was conducted based on 2 basic hypotheses:

1. Adolescents with BD have impaired attention and basic executive functioning, as compared to healthy adolescents, and the impairment can be observed in the form of lower neuropsychological test scores.

2. Adolescents with a familial risk of BD (adolescents with first-degree relatives that have BD) perform differently than healthy adolescents and adolescents with BD on neuropsychological tests.

MATERIALS and METHODS

Sample

The study included 25 BD patients aged 12-18 years that were diagnosed as BD type 1, BD type 2, or BD-NOS (bipolar disorder not otherwise specified), according to DSM IV-TR, that were followed-up at Ondokuz Mayıs University, School of Medicine, Department of Pediatric and Adult Psychiatry, Outpatient Clinic (case group), 25 adolescents without a mood disorder that had a parent and/or sibling diagnosed as BD (risk group), and 25 typically developing adolescents (control group). The case group was rated in the euthymic phase (Childhood Depression Inventory [CDI] ≤ 19 points and Young Mania Rating Scale-Parent Version (P-YMRS) ≤ 13 points). To form the control group information was gathered from the personnel of Ondokuz Mayıs University and the epidemiological atmosphere of the university, and those with children aged 12-18 years were given an appointment with their children. Parents provided information about psychiatric illnesses in their children, and those without a psychological disorder were requested to sign an informed consent form and participate in the study. The participants with a comorbid autistic disorder or another pervasive developmental disorder, active psychotic symptoms, vision and/or hearing impairment, chronic medical illness (for example active asthma, multiple sclerosis, etc.), and mental retardation (Wechsler Intelligence Scale for Children or Wechsler Adult Intelligence Scale score < 80) were excluded from the study.

Clinical forms

Sociodemographic Data Form

The participants' sociodemographic data were collected using a sociodemographic data form prepared by the researchers. Data collected included personal identity information, address, telephone number, level of educational, family socioeconomic status, and family structure. The form also collected information about the course of illness (age at disease onset, number of hospitalizations, number of episodes, and pharmacological treatments) for those in the case group.

Schedule for Affective Disorders and Schizophrenia for School Age Children-Present and Lifetime Version (K-SADS-PL)

K-SADS-PL is a semi-structured interview designed to assess current and past psychopathology in children and adolescents according to the DSM-III-R and DSM-IV-TR (Kaufman et al. 1997). The Turkish version was reported to be reliable and valid for use in Turkey (Gökler et al. 2004).

Childhood Depression Inventory (CDI)

CDI is a self-report inventory that can be administered to children and adolescents aged 6-18 years. The highest score is 54 and the cut-point is 19. The Turkish version was reported to be reliable and valid for use in Turkey (Öy 1991).

Parent version of the Young Mania Rating Scale (P-YMRS)

P-YMRS is a 5-point Likert-type scale consisting of 11 questions that parents answer about the present mental state and state within the last 48 h of their children. The maximum score is 60 and the mean score for a manic episode is 25. Scores > 13 are indicative of potential mania or hypomania, whereas scores > 21 are an indicator of mania or hypomania (Youngstrom et al. 2004; Gracious et al. 2001). The Turkish version was reported to be reliable and valid for use in Turkey (Diler et al. 2008).

Youth Self-Report (YSR)

YSR consists of 2 parts: 17 competence items and 112 problem items. The competence items are about sports and non-sports activities young people are interested in and actively involved in, as well as their competence in these activities, and chores they perform at and away from home, and how well they perform them. The second part of the scale includes 112 problem items. The scale provides 2 different behavioral indication scores: internalizing and externalizing (Achenbach 1991). The Turkish version was reported to be reliable and valid for use in Turkey (Erol et al. 1998).

Conners' Parent Rating Scale (CPRS)

CPRS consists of 48 items: 5 for attention deficiency, 4 for hyperactivity, 5 for oppositional behavior, and 11 for behavioral disorders. The Turkish version was reported to be reliable and valid for use in Turkey (Dereboy et al. 1998).

Neuropsychological tests

Neuropsychological tests were selected based on their reliability and validity to measure cognitive functioning, and ease of use (time required for and method of administration), and clinician experience.

Wisconsin Card Sorting Test (WCST)

WCST was developed by Berg in 1948, and modified by Heaton et al. in 1981 and 1993 (Heaton et al. 1993). WCST measures frontal lobe function and is thought to be especially sensitive to the dorsolateral prefrontal cortex (DLPFC). The test has been associated with abstract examination, concept formation, conceptual examination, process memory, executive functioning, and attention; however, it was reported that the primary feature it measures is perseverative tendency (Karakaş 1996).

Stroop Color Word Test (SCWT)

SCWT was developed as an experimental post by Stroop in 1935. SCWT has various forms. The Stroop Test BSRG (Basic Science Research Group) Form was used in the present study. The Turkish version was reported to be reliable and valid for use in Turkey (Karakaş 2002). Stroop Test BSRG is used to evaluate the ability to direct and sustain attention, depending on time and task, to ignore interfering stimuli, and to repress incongruent stimuli and incongruent reactions. It was reported that the most valid feature it measures is the interference effect (5th task with the 2nd stimulus card). The test is also used to evaluate reading speed, which is associated with attention (completion time for the first card) and naming a color (completion time for the 3rd and 4th stimulus cards) (Karakaş et al. 1999). In the present study the Stroop 1 time score (for attention) and the Stroop 5 time score (for the interference effect) were taken into consideration.

Continuous Performance Test (CPT)

CPT measures the ability to maintain attention and is based on monitoring changes that occur randomly within the flow of stimuli. During the test letters appear on a computer screen, and then disappear. In general, the omission score is associated with inattentiveness, whereas the commission score is associated with impulsivity (DeLongis 1991).

Wechsler Intelligence Scale for Children (WISC-R) and Wechsler Adult Intelligence Scale (WAIS-R)

WISC-R is an intelligence test for children aged 6-16 years that was developed by Wechsler (Wechsler 1974). The Turkish version was reported to be reliable and valid for use in Turkey (Savaşır and Şahin 1995). WAIS-R was developed by David Wechsler in 1955 (Wechsler 1955) for use with those aged ≥16 years. The test is administered on an individually basis. The Turkish version was reported to be reliable and valid for use in Turkey (Epir and İskit 1972).

Procedures

K-SADS-PL was administered to all of the participants by the interviewer (the first author); diagnoses and additional diagnoses were confirmed in both the case and risk groups.

WISC-R and WAIS were administered to the participants by a psychologist and the level of intelligence were determined. The parents of the participants and the same interviewer (first author) completed the sociodemographic data form. The participants were administered CDI and YSR, and their families were administered CPS and P-YMRS. Following completion of the scales, all the participants were administered WCST, Stroop Test BSRG Form, and CPT in the same order during 1 session about 50 min in duration by the same interviewer that performed the clinical evaluations.

Statistical analysis

Distribution of the scales' and neuropsychological tests' continuous variables was evaluated using the 1-sample Kolmogorov-Smirnov test. Variables with normal distribution were evaluated via parametric statistics. Variables not normally distributed were evaluated using non-parametric statistics. The chi-square (X^2) test or Fisher's Exact test was used to compare categorical data. When the distribution of scores or quantitative variables within groups was normal, mean $\pm$ SD values are presented in the tables, versus median and 25th-75th percentile values when the distribution was not normal. The Kruskal Wallis test was used for comparisons between the 3 groups. The level of statistical significance was set at $P = 0.05$. When there was significant difference between groups, double Mann-Whitney U tests were administered in post hoc analysis. As the 3 groups were compared in post hoc analysis and 3 Mann-Whitney U tests were administered, Bonferroni correction was applied and the level of significance was 0.05/3 (0.017). Prediction of independent variables over significant dependent variables was evaluated via regression analysis. All data were analyzed using SPSS v.15.0 for Windows (SPSS, Inc., Chicago, IL).

RESULTS

Sociodemographic data

The study included 75 participants; 25 in the case group, 25 in the risk group, and 25 in the control group. There weren't any significant differences in gender, mean age, mean level of education, mean parental age, or mean household income between the groups. The sociodemographic features of the groups are presented in Table 1.

Clinical data

Among the 25 patients in the case group, 12 (48%) had BD type 1, 10 (40%) had BD type 2, and 3 (12%) had BD-NOS. The other clinical features and comorbidities in the case group are presented in Table 2. Evaluation of comorbidity via K-SADS-PL showed that the frequency of comorbid attention deficit-hyperactivity disorder (ADHD) and generalized

anxiety disorder (GAD) was significantly higher in the case group than in the risk group.

Adapted scales data

There were significant differences in P-YMRS and CDI scores between the groups. Post-hoc analysis showed that P-YMRS and CDI scores in the case group were higher than those in the control and risk groups. There were significant differences in all CPRS subscale score between the groups. Post-hoc analysis showed that CPRS behavior, impetuosity, anxiety, and psychosomatic scores in the case group were significantly higher than those in the risk group, and that CPRS impetuosity, learning, and psychosomatic scores were significantly higher in the case group than those in the control group. YSR, which the participants answered independently, showed significant differences in all sub scales between sub scale behavior scores. Post-hoc analysis showed that all YSR subscale scores and YSR total score were significantly higher in the case group than in the control group. YSR social problems, thought problems, attention problems, crime-oriented behavior, aggressive behaviors, expression, and total problem scores were significantly higher in the risk group than those in the control group.

Neuropsychological test data

There were significant differences in all WCST sub-dimension scores between the groups, except for the reaction number score for completing the first category. Post-hoc analysis showed that in the case group all WCST sub-dimension scores, except for the reaction number score for completing the first category, were significantly different than those in the control and risk groups. There weren't any significant differences in the WCST sub-dimension scores between the risk and control groups. Assessment of Stroop 1 and Stroop 5 completion times, and CPT omission and commission scores via the Kruskal-Wallis test showed that there were significant differences between groups. Further analysis showed that scores in the case group were significantly higher than in the control group, but that the scores did not differ significantly between the risk and control groups. Neuropsychological test data are summarized in Table 3.

Additional analysis

Controlling for the effect of IQ

According to WISC-R and WAIS, the mean IQ score was 91.8 ± 8.5 in the case group, 98.6 ± 11.4 in the risk group, and 98.3 ± 6.6 in the control group; the difference between groups was significant ($f = 4.3$; $P = 0.001$). In order to exclude the effect of IQ on neuropsychological tests results the difference between IQ scores was eliminated by excluding consecutive participants from each of the 3 groups. As such,

2 participants in the case group, 2 in the risk group, and 3 in the control group were excluded, and then the differences in neuropsychological test scores between the groups were reassessed. Following this reassessment, the differences in WCST sub-dimensions, CPT, and Stroop 1 time scores between the groups persisted, whereas the difference in Stroop 2 time scores was no longer significant.

The Effect of ADHD on neuropsychological processes

In order to assess the effect of comorbid ADHD on neuropsychological test results, after controlling for the effect of IQ in the case and risk groups (as described above), case and risk groups were divided into those with and without comorbid ADHD. WCST, Stroop Test BSRG and CPT scores in the case and control groups, as well their ADHD subgroups were assessed using the Mann-Whitney U test. The assessments showed that the WCST number of trials, number of correct trials, number of non-perseverative trials, and failure to maintain set sub-dimension scores, and the Stroop 1 time and CPT omission sub-dimension scores were significantly different between the subgroups with and without ADHD, and between the case and risk groups ($P < 0.05$). In order to determine which indicators (attention or mood disorder) best predicted the occurrence of the significant differences, a model was formed from the CPRS impetuosity subscale score, which measures attention, and CDI and P-YMRS scores, which measure mood, and then multiple regression analysis was conducted. The multiple regression analysis findings showed that the strongest predictor of the 2 WCST sub-dimension scores, namely the number of trials ($R^2 = 0.27$; $F(3,64) = 8.15$; $P < .001$) and the number of non-perseverative trials [$R^2 = 0.18$; $F(3,64) = 4.72$; $P < 0.05$] was P-YMRS score, whereas the strongest predictor of (2) Stroop 1 time [$R^2 = 0.21$; $F(3,64) = 5.83$; $P < 0.001$] and CPT number of omissions [$R^2 = 0.38$; $F(3,64) = 13.1$; $P < .001$] scores was the CPRS impetuosity subscale score.

DISCUSSION

As previously reported, the present findings show that attention and executive functioning in adolescents with BD is impaired. In addition, the present findings show that adolescents with a risk of familial BD did not have impaired attention and executive functioning, even if they did have behavioral and clinical problems. The WCST, Stroop Test BSRG, and CPT were used in the present study to evaluate attention and executive functioning. The literature is inconclusive about which features the WCST measures; abstract examination, conceptual examination, working memory, executive functions, or attention. Factor analysis grouped WCST subscale scores under 3 factors; the first factor is factor perseveration tendency and the second is conceptualization/examination

(Karakaş et al. 1996). In the present study there were significant differences in all the WCST subscale scores that were indicative of the perseveration tendency factor and all subscores that were indicative of the conceptualization/examination factor between the case and control groups.

Doyle et al. (2005) studied pediatric BD patients using the WCST and observed significant differences in complete category, number of perseverative errors, and number of non-perseverative errors subscale scores, as compared to controls. Another study based on the WCST reported that there were differences in the complete category, number of perseverative errors, and failure to maintain set scores (Meyer et al. 2004). It was also reported that BD patients with a comorbid behavioral disorder exhibited a greater tendency for perseveration than healthy controls (Olvera et al. 2005). In contrast, other studies based on WCST assessment of pediatric BD patients reported that there weren't significant differences between patients and controls. A 2003 study did not observe significant impairment based on any tests of attention and executive functions in children and adolescents with BD (Robertson et al. 2003). Similarly, Ruclindge et al. (2006) and Henin et al. (2007) noted impairment in neuropsychological functioning in adolescents with BD based on a different test, but such impairment was not indicated based on WCST scores.

It was reported that the most valid measure assessed via the Stroop Test BSRG is the interference effect (5th task with the 2nd stimulus card). In the present study Stroop 1 and Stroop 5 completion time scores differed significantly between the case and control groups. The literature is inconsistent regarding Stroop Test performance in pediatric BD patients. Doyle et al. (2005) observed significant differences in SCWT scores in pediatric BD patients and healthy controls. One study published in 2006 reported that BD patients with comorbid ADHD had lower SCWT total scores than healthy controls, but that there wasn't a significant difference in SCWT interference effect sub-test scores (Rucklidge 2006). In contrast, Olvera et al. (2005) reported that SCWT scores did not differ significantly between BD patients with a comorbid behavioral disorder and healthy controls. In the light of these data and the present findings, we conclude that the ability to maintain attention and ignore incongruent stimuli is impaired in BD patients.

CPT measures the ability to maintain attention and to follow changes that occur randomly within the flow of stimuli. The present study CPT errors of omission and errors of commission subscale scores in the case group and control group differed significantly. Based on CPT assessment in pediatric BD patients, Doyle et al. (2005) reported that BD patients made more errors of omission than healthy controls, and Rucklidge et al. (2006) reported that BD patients with comorbid ADHD made more errors of omission and commission than both BD patients without ADHD and ADHD patients

without comorbidity. In contrast, Henin et al. (2007) did not observe significant differences in CPT performance, but did note differences in performance on other neuropsychological tests that measure attention.

In the present study the WCST, Stroop Test BSRG, and CPT scores in the risk group did not differ significantly from those in the control group. Few studies have examined cognitive functions in pediatric BD patients and their first-degree relatives. The first such study was conducted in 2009 and included 170 children and adolescents diagnosed as BD, 118 of their non-affected siblings, and 76 healthy controls. That study used the WCST, Stroop Test BSRG, and CPT, as in the present study, and they used a different neuropsychological test that measures memory, verbal fluency, and planning. The researchers reported significant differences in WCST number of perseverative errors and non-perseverative errors subscale scores, CPT errors of commission and omission scores, and Stroop color subtest scores between and the healthy controls (Doyle et al. 2009). Another study that assessed only continuous attention reported that the response time in children and adolescents that had first-degree relatives with BD was independent of psychopathology (Brotman et al. 2009). In the present study there weren't any significant differences in neuropsychological test results between the control and risk groups. The difference between the present findings and those reported by Doyle et al. could be because they included children and adolescents that had siblings with BD, whereas the present study included adolescents with both siblings and parents with BD in the risk group (a heterogeneous group). Moreover, the age range in Doyle et al.'s study was 7-18 years, versus 12-18 years in the present study. As such, significant differences might have been observed in the present study had it included more participants with a wider age range.

Based on WCST, Stroop Test BSRG, and CPT results in the present study, the BD patients had impaired executive and attention functions. Although WCST can measure the performance of other frontal regions, it is primarily used for measuring dorsolateral prefrontal cortex (DLPFC) performance (Karakaş 2002). Stroop test performance was reported to be associated with such regions as the orbitofrontal cortex (OFC), which is responsible for maintaining set under a disruptive effect, the anterior cingulate cortex (ACC), right DLPFC, and right lateral prefrontal cortex (Karakaş et al. 1999). Rezai et al. (1993) showed that CPT performance was associated with the mesial frontal cortex, with the left side being more dominant. Imaging studies suggest that DLPFC functioning in patients with BD is an indicator of impairment. Although some studies did not report significant results (Adler et al. 2007), many others reported that BD patients had intensity and a decrease in the size of neuronal and glial cells in the DLPFC (Frey et al. 2007; Rajkowska et al. 2001; Yurgelun-Todd et al. 2000). Another study reported

a decrease in gray and white matter volume in , as compared to healthy controls (Cecil et al. 2002). Wilke et al. reported a decrease in left ACC volume in children and adolescents with BD (Wilke et al. 2004). In addition to these structural imaging studies, a functional study reported that a working memory test in children and adolescents with familial BD showed increased activation in the left DLPFC, bilateral ACC, left thalamus, and right inferior frontal gyrus, and in healthy normal controls increased activity in the cerebellar vermis was observed (Chang et al. 2004). Consequently, the present findings confirm that there is impaired frontal region functioning in BD patients.

ADHD is the most common comorbidity seen in children diagnosed as BD (Singh et al. 2006). In the present study 56% of the case group and 16% of the risk group had comorbid ADHD, which is in agreement with the literature. In order to assess the effect of comorbid ADHD on neuropsychological test results, after the IQ of the participants in the case and risk groups was controlled for via consecutive case exclusion, common data of neuropsychological test result differences between the subgroup with comorbid ADHD and the subgroup without comorbid ADHD, and the neuropsychological test result differences between the case and risk groups were analyzed via multiple regression analysis based on the CPRS inattentiveness subscale score, which indicates the level of attention, and CDI and P-YMRS scores, which indicate mood. Based on the results, it was concluded that WCST sub-dimension scores were affected by mood, whereas SCWT and CPT scores were affected by attention. As the present study was a cross-sectional clinical study and it can be thought that the inclusion of patients without comorbidities will not reflect real clinical data. As such, comorbid ADHD had an effect on neuropsychological test results, foremost Stroop Test BSRG and CPT. Additional research that compares patients with and without comorbid ADHD to each other, as well as to controls with and without ADHD may yield more useful neuropsychological findings.

The present study has some limitations. The case group included all BD types (BD type 1, BD type 2, and BD-NOS). As the number of cases was limited, neuropsychological factors among the BD types were not completely analyzed. Studies that include a larger patient population will more definitively show clinical and neuropsychological differences between the types of BD. Another important limitation is use of a heterogeneous group consisting of sons, daughters and siblings. Studies that include only siblings or only sons and daughters will facilitate identification of more endophenotypic indicators in the BD risk group. All the patients in the present study's case group were receiving pharmacological treatment. Although one study that analyzed the neuropsychological effects of medication in pediatric BD patients reported that such use did not impair attention, executive functioning, or

process memory (Pavuluri et al. 2006), the present study did not analyze the effect of medication on neuropsychological factors. Additional larger scale studies will more likely illuminate the effects of medication on BD.

The main findings of the present study are summarized as follows:

1. More of the participants in the case group had clinical and behavioral problems while in a euthymic state than the controls, based on structured scales administered to both the patients and their families.
2. More adolescents in the risk group had behavioral and clinical problems than in the control group, based on the scales they were administered.
3. The BD patients had impaired attention and executive functions, as previously reported.
4. Although the adolescents in the risk group had behavioral and clinical problems, their attention and executive functions were not impaired, which may indicate that BD itself impairs attention and executive functions, whereas the genetic risk for BD is associated some behavioral problems.

The neuropsychological features of adolescents with a risk of BD have not been sufficiently studied. Additional larger scale follow-up and imaging studies that employ more neuropsychological tests will more clearly delineate the neuropsychological profiles of the BD risk group and provide more data concerning where and how biological and psychometric impairment begins.

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