Longitudinal Trajectories of ADHD Symptomatology in Offspring of Parents With Bipolar Disorder and Community Controls

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ABSTRACT

Objective: To compare the psychopathology and longitudinal course of attention-deficit/hyperactivity disorder (ADHD) symptomatology and global functioning between the offspring with ADHD of parents with bipolar disorder and the offspring with ADHD of community control parents.

Method: One hundred twenty-two offspring with ADHD of parents with bipolar disorder and 48 offspring with ADHD of control parents from the Pittsburgh Bipolar Offspring Study (BIOS) were included. *DSM-IV* lifetime psychiatric disorders were ascertained through the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime version (K-SADS-PL). The outcome measures of ADHD symptoms were ascertained at intake and every other year for a period of 6 years using the ADHD section of the K-SADS-PL and the Disruptive Behavior Disorder rating scale (DBD). Global functioning was assessed using the Children's Global Assessment Scale (CGAS).

Results: The offspring with ADHD of parents with bipolar disorder showed higher lifetime prevalence of mood and anxiety disorders relative to the offspring with ADHD of control parents (P values ≤ .03). For both groups of offspring with ADHD, the hyperactivity, impulsivity, and total K-SADS-PL ADHD scores decreased over time (P values < .001) without differences between the 2 groups. There were no between- or within-group differences in the inattention scores over time. The DBD ADHD scores decreased with age in both groups (P values < .002) without differences between the 2 groups. For both groups of offspring with ADHD, the global functioning did not improve over time.

Conclusions: Offspring with ADHD of parents with bipolar disorder have more psychopathology relative to offspring with ADHD of control parents. However, there were no differences in the developmental courses of ADHD symptomatology between these 2 groups of ADHD youth.

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Epidemiologic and clinical data consistently show that bipolar disorder and attention-deficit/hyperactivity disorder (ADHD) are frequently comorbid in youth.[1–4] ADHD and bipolar disorder have in common several symptoms, including distractibility, talkativeness and increased motor activity, and mood symptoms such as irritability and mood lability.[3,5,6] Whether the relationship between ADHD and bipolar disorder is driven purely by the overlap of these symptoms or whether a significant etiologic relationship exists between the diagnostic entities is not clear. Recent studies show that each disorder increases risk for the other, supporting the hypothesis that these disorders may have some underlying biological features in common.[1,7] For example, in a recent meta-analysis of family genetic studies of ADHD and bipolar disorder, Faraone and colleagues[1] reported a high prevalence of ADHD among relatives of probands with bipolar disorder and a high prevalence of bipolar disorder among relatives of probands with ADHD. However, the above-noted studies need to be taken with caution because they used a broad definition of bipolar disorder, which may have exaggerated the relationship between ADHD and bipolar disorder, and they were cross-sectional.

Longitudinal studies of children with ADHD consistently show that ADHD symptoms decrease with age. More specifically, these studies demonstrate that the symptoms of hyperactivity and impulsivity decline over time, particularly during the transition from childhood to adolescence.[8–12] However, whether the same developmental trajectories of ADHD symptomatology will also be evident in youth with bipolar disorder and ADHD is unknown. If ADHD and bipolar disorder are 2 separate disorders, it is expected that the ADHD symptoms in youth with bipolar disorder will follow similar developmental trajectories as in children with only ADHD. Also, youth with ADHD show poor psychosocial functioning over time,[11] but whether the longitudinal course of global functioning will be the same for youth with bipolar disorder and ADHD is unknown.

Some studies indicate that offspring of parents with bipolar disorder are at high risk for both ADHD and bipolar disorder.[5,7] Thus, high-risk family studies of offspring of individuals with bipolar disorder are useful for studying the association between these 2 disorders.[5,7] The majority of the existing high-risk studies for bipolar disorder report an elevated rate of ADHD among offspring of parents with bipolar disorder compared to the children of parents with other psychiatric disorders or to those of healthy controls.[13–15] For instance, in a longitudinal study of adolescent offspring of parents with bipolar disorder and of healthy parents, Duffy and colleagues[16] recently reported an increased rate of ADHD in the offspring of parents with bipolar disorder (10.2%) relative to the offspring of control parents (1.6%). Petresco and colleagues[17] demonstrated that the offspring of bipolar mothers had higher prevalence of ADHD (11.6%) compared to the offspring of control mothers (4.7%). We also found high rates of ADHD in

Clinical Points

- Longitudinal prospective studies of offspring of parents with bipolar disorder are useful to study the association between attention-deficit/hyperactivity disorder (ADHD) and bipolar disorder.
- The offspring with ADHD of parents with bipolar disorder showed more psychopathology relative to offspring with ADHD of control parents, but there were no between-group differences in the developmental courses of ADHD symptomatology over time.
- The developmental trajectories of ADHD symptoms in the offspring with ADHD appear not to be influenced by history of parental bipolar disorder or lifetime prevalence of bipolar spectrum disorders in the offspring.

offspring with bipolar disorder and offspring of parents with bipolar disorder in the Pittsburgh Bipolar Offspring Study (BIOS).[13,18] However, these studies were limited by 1 or more of the following: lack of longitudinal prospective evaluation of the ADHD symptomatology, small sample sizes, not taking into account the effects of several factors that may have affected the outcome (eg, socioeconomic status, pubertal status, and children's comorbid disorders), and control groups consisting of offspring of healthy parents only.[16,19–21] This last limitation is important because we do not know whether the increased risk for ADHD in offspring of parents with bipolar disorder is due to the parental bipolar disorder or the parents' nonbipolar psychopathology. In fact, in BIOS, the effects of ADHD were no longer significant after adjusting for both biological parents' nonbipolar psychopathology.[13]

Most of the above studies were cross-sectional and did not compare the longitudinal course of ADHD in large samples of offspring of parents with bipolar disorder in comparison with offspring with ADHD of healthy or nonbipolar parents. Moreover, there is no evidence whether the phenomenology of ADHD in offspring of parents with bipolar disorder is similar to or different from that in offspring of nonbipolar or healthy parents. Thus, in this article, we sought to compare these 2 large groups of offspring based on the following 3 characteristics: (1) lifetime prevalence of comorbid psychiatric disorders, (2) the severity and developmental course of ADHD symptomatology, and (3) changes in global functioning over time. Based on the literature, we first hypothesized that offspring with ADHD of parents with bipolar disorder would show a higher lifetime prevalence of Axis-I psychiatric disorders, particularly bipolar spectrum disorders, than offspring with ADHD of community control parents. Second, we hypothesized that the severity of symptoms of ADHD would decrease with age and that the symptom trajectories of the offspring with ADHD of parents with bipolar disorder would be different from those of the offspring with ADHD of control parents. Finally, considering the expected rates of psychiatric comorbidity, we hypothesized that offspring with ADHD of parents with bipolar disorder would show significantly more impairment in global functioning over time than offspring with ADHD of control parents.

METHOD

Subjects

The methods for BIOS have been described in detail elsewhere.[13] Briefly, parents (probands) with bipolar disorder were recruited through advertisement (53%), adult bipolar disorder studies (31%), and outpatient clinics (16%) from November 2001 to July 2007. Parents were required to fulfill the *DSM-IV* criteria for bipolar I disorder (BP-I) or bipolar II disorder (BP-II). Exclusion criteria included current or lifetime diagnoses of schizophrenia, mental retardation, mood disorders secondary to substance abuse, medical conditions, or medications, and living more than 200 miles away from Pittsburgh, Pennsylvania. BIOS recruited 233 parents with bipolar disorder and their 388 offspring aged 6–18 years. Among these offspring, 122 subjects (31.4%) were diagnosed with ADHD via semistructured interview (see Measures, below).

Control parents consisted of healthy parents or parents with nonbipolar psychopathology from the community, group matched by age, sex, and neighborhood using the area code and first 3 digits of the telephone number and zip code of the parents with bipolar disorder. The control parents had the same exclusion criteria as the parents with bipolar disorder, and, in addition, they could not have bipolar disorder or have a first-degree relative with bipolar disorder. BIOS recruited 143 control parents and their 251 offspring. Among these offspring, 48 subjects (19.1%) were diagnosed with ADHD.

For this article, subjects were followed on average 6 years. The overall rate of retention was approximately 90%, with no significant differences between the 2 groups.

Measures

After Institutional Review Board (IRB) approval, consent from parents and assent from children were obtained. Parents were assessed for psychiatric disorders, family psychiatric history, and other demographic and clinical variables. Only instruments directly related to this article will be discussed. *DSM-IV* lifetime psychiatric disorders for parents were ascertained through the Structured Clinical Interview-*DSM-IV* (SCID)[22] plus the ADHD, disruptive behavior disorders, and separation anxiety disorder (SAD) sections from the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime version (K-SADS-PL).[23] Socioeconomic status was ascertained using the Hollingshead scale.[24]

Parents were interviewed about their children, and the children were directly interviewed for the presence of lifetime psychiatric disorders using the K-SADS-PL at intake and every other year.[23] As per the K-SADS-PL instructions, mood symptoms that were also in common with other psychiatric disorders (eg, hyperactivity) were not rated as present in the mood sections unless they intensified with the onset of abnormal mood. Comorbid diagnoses were not

Table 1. Demographic and Clinical Characteristics of ADHD Offspring of Parents With Bipolar Disorder vs ADHD Offspring of Control Parents

Characteristic	ADHD Offspring of Parents With Bipolar Disorder (N = 122)	ADHD Offspring of Control Parents (N = 48)	Statistic	*P* Value[a] (Effect Size)
Demographic				
Age at intake, mean (SD), y	11.0 (3.4)	11.2 (3.5)	$t = 0.29$	.78 (0.06)
Age at the last assessment, mean (SD), y	16.8 (4.4)	16.8 (4.4)	$t = 0.01$	> .9 (0.01)
Had at least 1 follow-up assessment, n (%)	109 (89.3)	43 (89.6)	$\chi^2 = 0.05$	> .9 (0.01)
Number of follow-up assessments, mean (SD)	3.6 (1.4)	3.4 (1.2)	$t = 0.65$	.50 (0.15)
Years of follow-up, mean (SD), y	6.0 (2.8)	5.5 (2.8)	$t = 1.04$	.30 (0.18)
Female, n (%)	52 (42.6)	18 (37.5)	$\chi^2 = 0.37$	.54 (0.10)
Caucasian, n (%)	93 (76.2)	29 (60.4)	$\chi^2 = 4.25$	**.04 (0.34)**
Living with both biological parents, n (%)	43 (35.2)	19 (39.6)	$\chi^2 = 0.28$	.60 (0.09)
Socioeconomic status, mean (SD)	31.4 (13.9)	31.1 (12.2)	$t = 0.14$	.89 (0.02)
Lifetime ADHD diagnosis of parents, n (%)	38 (31.1)	2 (4.2)	Fisher exact test	**< .001 (0.77)**
Lifetime stimulant exposure, n (%)	73 (59.8)	23 (47.9)	$\chi^2 = 1.54$	.16 (0.24)
ADHD symptoms at intake, mean (SD)				
Disruptive Behavior Disorder score				
Inattention	17.0 (7.6)	13.1 (6.4)	$t = 3.02$	**.003 (0.54)**
Hyperactivity	8.6 (4.9)	5.9 (4.4)	$t = 3.29$	**.001 (0.57)**
Impulsivity	4.4 (2.9)	3.6 (2.5)	$t = 1.68$	.09 (0.29)
Total	30.1 (13.3)	22.6 (11.4)	$t = 3.32$	**.001 (0.59)**
K-SADS-PL score				
Inattention	22.5 (4.6)	22.1 (3.8)	$t = 0.52$	.60 (0.09)
Hyperactivity	13.1 (3.6)	12.4 (3.9)	$t = 0.98$	.33 (0.19)
Impulsivity	6.4 (2.2)	6.6 (2.1)	$t = 0.30$	.77 (0.09)
Total	42.0 (8.2)	41.0 (6.5)	$t = 0.68$	.50 (0.13)

[a]Bold indicates $P < .05$.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, K-SADS-PL = Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version.

assigned if they occurred exclusively during a mood episode. All diagnoses were made using the *DSM-IV* criteria. However, since the *DSM* does not clearly define bipolar disorder not otherwise specified (NOS), operationalized criteria for bipolar disorder NOS were utilized.[6,25] *Bipolar disorder NOS* was defined as the presence of clinically relevant bipolar disorder symptoms that did not fulfill the *DSM-IV* criteria for BP-I or BP-II. In addition, subjects were required to have a minimum of elated mood plus 2 associated *DSM-IV* symptoms or irritable mood plus 3 *DSM-IV* associated symptoms, along with a change in the level of functioning, duration of a minimum of 4 hours within a 24-hour period, and at least 4 cumulative lifetime days meeting the criteria.[25] Youth with bipolar disorder NOS show less severe clinical picture but similar longitudinal course than youth with BP-I.[4,25] Also, about 50% of youth with bipolar disorder NOS convert into BP-I or BP-II, supporting the hypothesis that bipolar disorder NOS is on a continuum with BP-I.[4]

Bachelors- or masters-level interviewers completed all assessments after intensive training for all instruments and after ≥ 80% agreement with a certified rater. The overall SCID and K-SADS-PL kappa values for psychiatric disorders were ≥ 0.8.

The ADHD symptoms were ascertained at intake and every other year using the ADHD section of the K-SADS-PL and the Disruptive Behavior Disorder rating scale (DBD), parent version.[26] The reliability and validity of the DBD have been established.[26] In contrast to the K-SADS-PL, the DBD does not take into account other disorders, and it is rated unfiltered ("rate what you see").

In the K-SADS-PL, individual symptom items are rated on the Likert scales of 0 (no information), 1 (not present), 2 (subthreshold), and 3 (threshold). As per the K-SADS-PL instructions, children and their parents were first interviewed using the ADHD screening interview. This screen includes 4 ADHD items: "difficulty sustaining attention on tasks or play activities," "easily distracted," "difficulty remaining seated," and "impulsivity." If a child received a score of 3 on any of the above screen items, the K-SADS-PL supplement for ADHD was completed. There were significant correlations between the scores of the parent alone and the summary ratings of K-SADS-PL in each domain: inattention, hyperactivity, impulsivity, and total ADHD scores ($r_s = 0.76–0.86$, *P* values ≤ .01). Therefore, for this article, we used the current summary ratings of 18 *DSM-IV* ADHD symptoms for the analysis: 9 items for the inattention symptoms, 6 items for the hyperactivity symptoms, and 3 items for the impulsivity symptoms. The inattention, hyperactivity, and impulsivity scores were generated from the sums of inattention, hyperactivity, and impulsivity items, respectively, and the total score was generated from the sum of inattention, hyperactivity, and impulsivity items.

The DBD consists of 41 *DSM-IV* items (ADHD = 18, oppositional defiant disorder = 8, conduct disorder = 15). Each item is rated on a 4-point scale (0 = not at all, 1 = just a little, 2 = pretty much, and 3 = very much). For this article, we only used the ADHD symptoms that are composed of 9 inattention, 6 hyperactivity, and 3 impulsivity items. The inattention, hyperactivity, impulsivity, and total scores were generated using the same method described above with

Table 2. Lifetime Axis I Psychiatric Disorders of ADHD Offspring of Parents With Bipolar Disorder vs ADHD Offspring of Community Control Parents

Lifetime Axis I Psychiatric Disorder, n (%)	ADHD Offspring of Parents With Bipolar Disorder (N = 122)	ADHD Offspring of Control Parents (N = 48)	Statistic	*P* Value[a] (Effect Size)
Bipolar spectrum disorders	36 (29.5)	2 (4.2)	Fisher exact test	**< .001 (0.74)**
BP-I	9 (7.4)	0 (0.0)	Fisher exact test	.06 (0.55)
BP-II	4 (3.3)	1 (2.1)	Fisher exact test	> .9 (0.07)
Bipolar disorder not otherwise specified	23 (18.9)	1 (2.1)	Fisher exact test	**.003 (0.61)**
Any depression	69 (56.6)	13 (27.1)	$\chi^2 = 11.99$	**.001 (0.61)**
Dysthymic disorder	6 (4.9)	0 (0.0)	Fisher exact test	.19 (0.45)
Major depressive disorder	39 (32.0)	7 (14.6)	$\chi^2 = 5.27$	**.02 (0.42)**
Any anxiety disorders	61 (50.0)	15 (31.2)	$\chi^2 = 4.90$	**.03 (0.39)**
Generalized anxiety disorder	24 (19.7)	4 (8.3)	Fisher exact test	.11 (0.34)
Separation anxiety disorder	28 (23.0)	8 (16.7)	$\chi^2 = 0.82$	.37 (0.16)
Social phobia	15 (12.3)	7 (14.6)	$\chi^2 = 0.16$	.69 (0.07)
Specific phobia	28 (23.0)	7 (14.6)	$\chi^2 = 1.48$	.23 (0.22)
Panic disorder	11 (9.0)	1 (2.1)	Fisher exact test	.18 (0.32)
Obsessive-compulsive disorder	8 (6.6)	2 (4.2)	Fisher exact test	.73 (0.11)
Posttraumatic stress disorder	10 (8.2)	5 (10.4)	$\chi^2 = 0.21$	.65 (0.08)
Disruptive behavior disorders	63 (51.6)	18 (37.5)	$\chi^2 = 2.76$	.10 (0.28)
Oppositional defiant disorder	60 (49.2)	17 (35.4)	$\chi^2 = 2.63$	.11 (0.28)
Conduct disorder	23 (18.9)	7 (14.6)	$\chi^2 = 0.43$	.51 (0.12)
Tic disorders	5 (4.1)	2 (4.2)	Fisher exact test	> .9 (0.01)
Transient tic disorder	1 (0.8)	1 (2.1)	Fisher exact test	.49 (0.11)
Chronic tic disorder	2 (1.6)	2 (4.2)	Fisher exact test	.32 (0.16)
Tourette's disorder	2 (1.6)	0 (0.0)	Fisher exact test	> .9 (0.25)
Elimination disorders	34 (27.9)	6 (12.5)	$\chi^2 = 4.52$	**.03 (0.39)**
Enuresis	32 (26.2)	5 (10.4)	$\chi^2 = 5.06$	**.03 (0.42)**
Encopresis	6 (4.9)	1 (2.1)	Fisher exact test	.68 (0.16)
Substance use disorders	21 (17.2)	6 (12.5)	$\chi^2 = 0.57$	.45 (0.13)

[a]Bold indicates $P < .05$.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, BP-I = bipolar I disorder, BP-II = bipolar II disorder.

respect to the K-SADS-PL ADHD scores. Parents of children aged 6 to 18 years completed the DBD at baseline and at each follow-up assessment.

Global overall functioning was assessed by interviewers using the Children's Global Assessment Scale (CGAS) at intake and every other year. The CGAS is measured in 3 domains: current (prior month before the interview), most severe past (lifetime), and highest past year. For this article, we used the current functioning measure. The reliability and validity of the CGAS have been established.[27]

Statistical Analyses

Between-group demographic and clinical characteristics were evaluated using *t*, χ^2, and Fisher exact tests as appropriate. Effect sizes for continuous and categorical variables (d and h, respectively) were calculated as described by Cohen.[28]

Linear growth curve models were used to compare the K-SADS-PL and DBD ADHD symptoms between the 2 offspring groups. We also estimated the effect of age on the change of ADHD symptoms and whether these age effects differed across the groups. Because the response variables are not normally distributed, a generalized linear mixed model was used. Group, age, and age by group interactions were kept in the model as fixed effects, while intercept was set as a random effect. These analyses were repeated adjusting for between-group significant demographic characteristics and whether the offspring met criteria for lifetime bipolar spectrum disorder. All of the *P* values are based on 2-tailed tests. Statistical analyses were performed in SAS 9.3 and SPSS 20.

RESULTS

Demographic and Clinical Characteristics

A total of 122 offspring with ADHD of parents with bipolar disorder and 48 offspring with ADHD of control parents (38 from parents with nonbipolar psychopathology and 10 from healthy parents) were included for the analyses (Table 1). Subjects were followed on average 5.9 ± 2.9 years. There was no between-group difference in the length of the follow-up time.

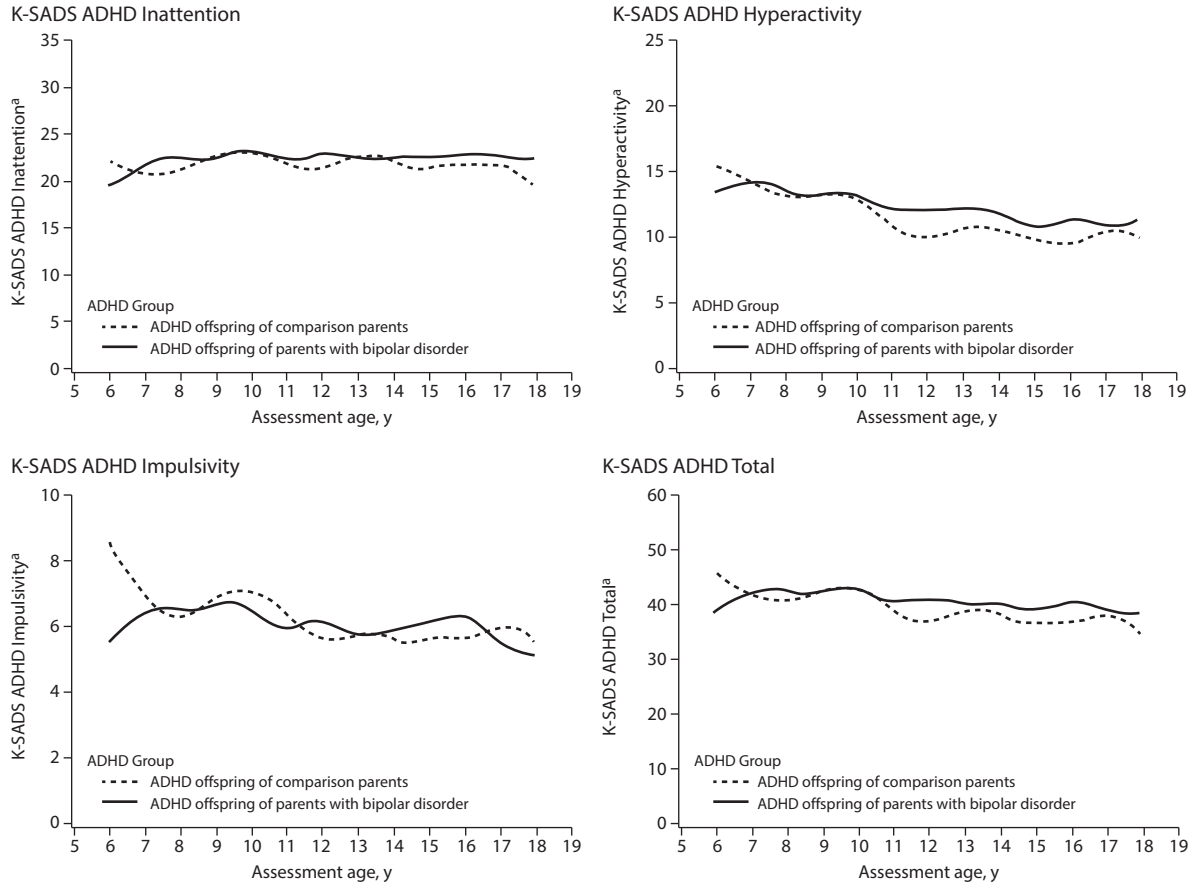
The offspring with ADHD of parents with bipolar disorder were more frequently Caucasian ($P = .04$), and their parents showed greater lifetime (intake and during the follow-up) prevalence of ADHD relative to the control parents of offspring with ADHD (31.1% vs 4.2%, respectively, $P < .001$). There were no other between-group demographic differences including socioeconomic status and lifetime stimulant exposure.

With respect to ADHD symptoms at intake, there were no between-group differences in K-SADS-PL ADHD scores. The DBD inattention, hyperactivity, and total ADHD scores were significantly higher in the offspring with ADHD of parents with bipolar disorder relative to the offspring with ADHD of control parents (*P* values ≤ .003).

Lifetime Comorbid Axis I Disorders

As shown in Table 2, the offspring with ADHD of parents with bipolar disorder showed a significantly higher lifetime (intake and during the follow-up) prevalence of bipolar

Figure 1. Developmental Trajectories of ADHD Symptoms Based on K-SADS-PL[a]



[a]Y axis: lines represent observed means of ADHD symptoms over time.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, K-SADS-PL = Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version.

spectrum disorders, any depression, any anxiety disorders, and elimination disorders relative to the offspring with ADHD of control parents (*P* values, ≤.03; effect sizes, 0.39–0.74). The increased rates of bipolar spectrum disorders and any depression in the offspring with ADHD of parents with bipolar disorder were accounted for by significantly higher rate of bipolar disorder NOS (*P* = .003; effect size, 0.61; odds ratio [OR] = 10.9; 95% confidence interval [CI] = 1.4–83.3) and major depressive disorder (*P* = .02; effect size, 0.42; OR = 2.8; 95% CI = 1.1–6.7), respectively. The offspring with ADHD of parents with bipolar disorder also showed greater lifetime prevalence of enuresis than the offspring with ADHD of control parents (*P* = .03; effect size, 0.42; OR = 3.1; 95% CI = 1.1–8.4).

Severity and Developmental Course of ADHD Symptomatology

K-SADS-PL (Figure 1). For both groups of offspring, the hyperactivity, impulsivity, and total ADHD scores significantly decreased over time (all *P* values < .001). There were no significant between-group differences in any of these scores. Similar results were obtained after adjusting for offspring's race and lifetime bipolar spectrum disorders and parents' lifetime ADHD. There were no between- or within-group statistical differences in the ADHD inattention scores over time.

DBD (Figure 2). For both groups of offspring, the inattention, hyperactivity, impulsivity, and total ADHD scores significantly decreased with age (all *P* values < .002). There were no between-group differences in any of these scores. Similar results were obtained after adjusting for offspring's race and lifetime bipolar spectrum disorders and parents' lifetime ADHD.

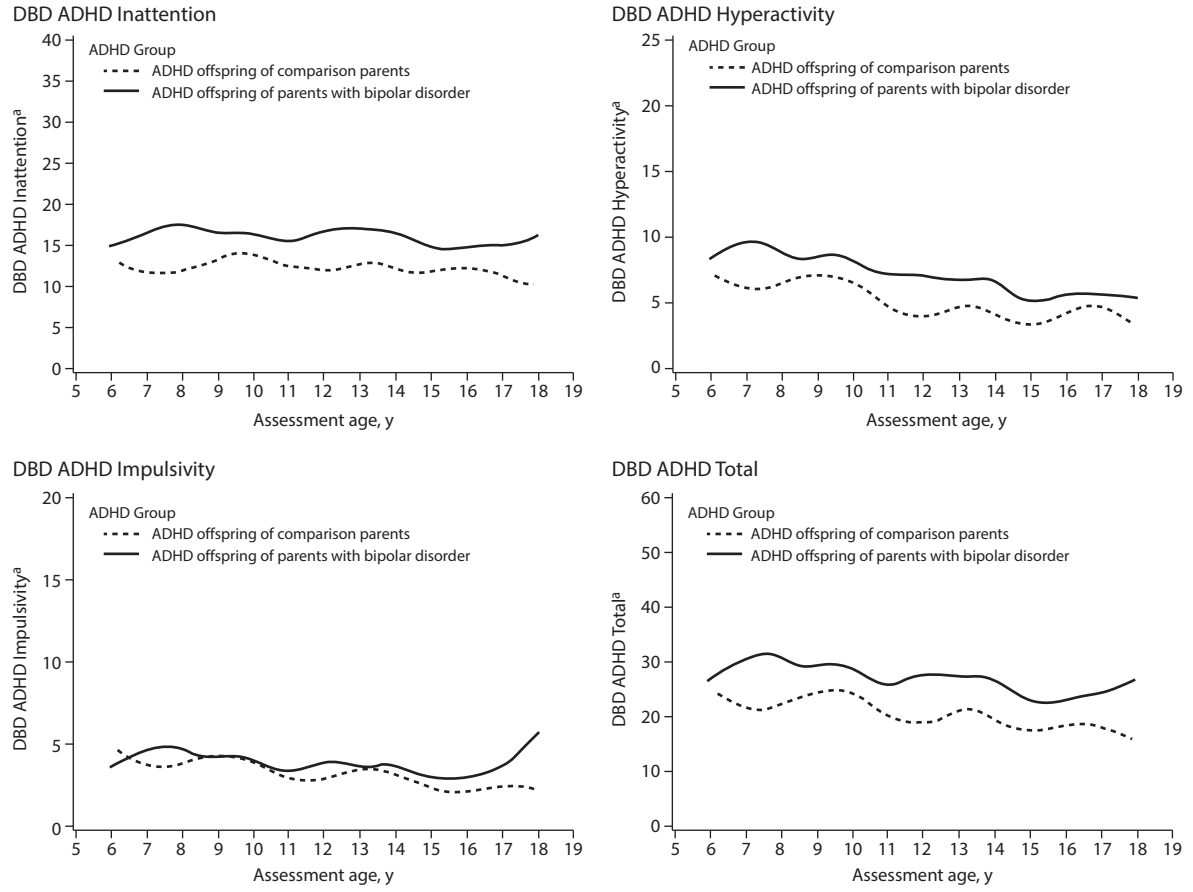
Longitudinal Course of Global Functioning

CGAS (Figure 3). For both groups of offspring, there were no between- or within-group statistical differences in the CGAS scores over time. Although not statistically significant, the CGAS scores were consistently lower over time in the offspring with ADHD of parents with bipolar disorder relative to the offspring with ADHD of control parents.

DISCUSSION

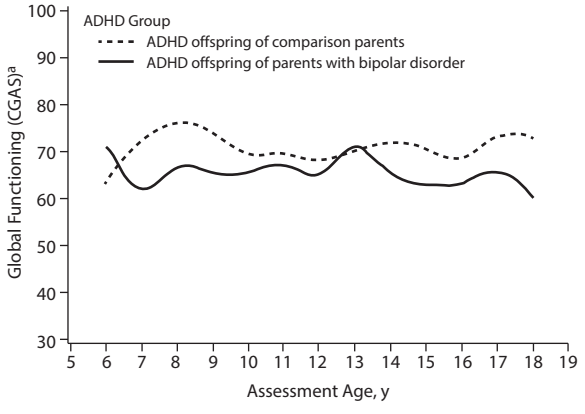
To our knowledge, the present study is the first to compare lifetime psychiatric comorbidity rates and longitudinal clinical course of ADHD between offspring of parents with

Figure 2. Developmental Trajectories of ADHD Symptoms Based on DBD[a]



[a]Y axis: lines represent observed means of ADHD symptoms over time.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, DBD = Disruptive Behavior Disorder rating scale.

Figure 3. Developmental Trajectories of Global Functioning Based on CGAS[a]



[a]Y axis: lines represent observed means of CGAS scores over time.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, CGAS = Children's Global Assessment Scale.

bipolar disorder and offspring of community control parents. As compared with the offspring with ADHD of control parents, the offspring with ADHD of parents with bipolar disorder demonstrated more severe ADHD symptomatology at intake and a higher lifetime prevalence of bipolar spectrum disorders, depression, anxiety disorders, and elimination disorders. For both groups of offspring, the hyperactivity, impulsivity, and total ADHD scores ascertained through the K-SADS-PL and DBD equally decreased over time. Also, there were no differences in global functioning over time.

Before discussing the above results in detail, it is important to consider the limitations of this study. Similar to other studies, the main informants were the mothers. In addition, the psychopathology in the biological coparents was mostly ascertained by interviewing the main informant. However, there were no differences between the bipolar and control parent groups in the rate of mothers serving as main informants and in the proportion of direct and indirect interviews of biological coparents in BIOS.[13] Given that this is a high-risk study for bipolar disorder, the results may not be generalizable to other populations. Finally, collateral information (eg, information provided by teachers) regarding ADHD symptomatology was not measured.

As expected, and consistent with previous findings,[2,29,30] our analyses showed that ADHD was associated with a broad range of lifetime Axis I psychiatric disorders in both groups of offspring. For example, in large longitudinal studies, Biederman and colleagues showed that youth with ADHD had elevated risk of lifetime mood and anxiety disorders and disruptive behavior disorders as compared with controls.[29,30]

The offspring with ADHD of parents with bipolar disorder did not show a significantly higher lifetime prevalence of BP-I relative to the offspring with ADHD of control parents. This finding is in line with a recent review of prospective high-risk studies of the offspring of parents with bipolar disorder, which showed that ADHD does not appear to increase the risk for bipolar disorder.[31] However, using a strict definition of bipolar disorder NOS, we found a significantly higher rate of this subtype of bipolar disorder in the offspring with ADHD of parents with bipolar disorder than in the offspring with ADHD of control parents, suggesting the possibility of a significant relationship between ADHD and bipolar disorder.

It is important to note that the DBD ADHD scores at intake were higher in the offspring with ADHD of parents with bipolar disorder relative to the offspring with ADHD of control parents. However, there were no between-group differences in the K-SADS-PL ADHD scores. The discrepancy in these results might be accounted for by the way ADHD symptoms were ascertained. The K-SADS-PL symptoms were based on summary ratings that include information by parents, children, the interviewers, and the child psychiatrist who supervised the case. In contrast, the DBD questionnaire was based on information by only parents.

With respect to continuity and change in ADHD symptomatology over time, our results are consistent with the findings of previous studies that symptoms of ADHD decrease with age. In a study by Hart and colleagues,[9] hyperactive and impulsive symptoms of ADHD significantly declined with age, whereas inattentive symptoms did not. Biederman and colleagues[10] demonstrated that hyperactivity, impulsivity, and inattention symptoms decreased with age. It is worth noting that the above-noted studies were based on clinic samples, and symptom trajectory studies of ADHD using nonreferred samples are limited.

Contrary to our hypothesis, ADHD symptoms ascertained through the K-SADS-PL and DBD did not differ over time between the offspring with ADHD of parents with bipolar disorder and the offspring with ADHD of control parents. Similar results were obtained after controlling for a range of possible confounding variables such as offspring's race and lifetime bipolar spectrum disorders and parents' lifetime ADHD. There are no other studies of this nature in the literature with which to compare our results. Thus, further replication studies are necessary.

Finally, with respect to the longitudinal course of global functioning, although there were no statistically significant differences between the offspring with ADHD of parents with bipolar disorder relative to the offspring with ADHD of control parents, the CGAS scores were consistently lower over time in the offspring with ADHD of parents with bipolar disorder. This may be accounted for by the higher lifetime prevalence of comorbid psychiatric disorders in the latter offspring group. Of note, the CGAS scores were generally between 60 and 70 in both groups of offspring over time, which indicates that both groups experienced functional impairments in 1 or more areas at baseline and follow-up assessments, although the severity of ADHD symptoms decreased over time.

In summary, the results of this study indicate that ADHD in offspring of parents with bipolar disorder is associated with more severe ADHD symptomatology at intake and a higher lifetime prevalence of a broad range of Axis I psychiatric disorders, including mood and anxiety disorders, relative to offspring with ADHD of community control parents. However, after taking into account confounding factors, our results do not suggest that there are differences in the developmental course of ADHD symptomatology between these 2 groups of offspring. Further longitudinal studies are warranted to evaluate whether there are neurobiological, cognitive, and treatment response differences between offspring with ADHD of parents with and without bipolar disorder.

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