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Bipolar and Antisocial Disorders Among Relatives of ADHD Children: Parsing Familial Subtypes of Illness

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Attention deficit hyperactivity disorder (ADHD) is a familial disorder that is highly comorbid with conduct disorder and sometimes co-occurs with bipolar disorder. This pattern of comorbidity is also seen among relatives of ADHD probands. A growing literature suggests that ADHD with antisocial comorbidity may be nosologically distinct from other forms of ADHD. A similar pattern has been observed for ADHD and bipolar disorder. Given these results, along with the observed comorbidity between conduct and bipolar disorders, we used data from our study of 140 ADHD and 120 control families to determine if conduct and bipolar disorders in ADHD boys should be considered alternative manifestations of the same familial disorder. The probands and their relatives were examined with DSM-III-R structured diagnostic interviews and were assessed for cognitive, achievement, social, school, and family functioning. Our results provide fairly consistent support for the hypothesis that antisocial- and bipolar-ADHD subtypes are different manifestations of the same familial condition. As predicted by this hypothesis, there was a significant three-way association between variables assessing the family history of each disorder. Moreover, when families were stratified into bipolar, antisocial, and other types, few differences emerged between the bipolar and antisocial families. Am. J. Med. Genet. (Neuropsychiatr. Genet.) 81:108–116, 1998.

INTRODUCTION

Family studies of attention deficit hyperactivity disorder (ADHD) have shown that the relatives of ADHD children are at high risk for ADHD, comorbid psychiatric disorders, school failure, learning disability, and impairments in intellectual functioning [Morrison and Stewart, 1971; Cantwell, 1972; Welner et al., 1977; Biederman et al., 1992; Faraone et al., 1993a,b; Faraone and Biederman, 1994a,b]. Additional lines of evidence from twin, adoption, and segregation analysis studies suggest that the familial aggregation of ADHD has a substantial genetic component. Twin studies find greater similarity for ADHD and components of the syndrome between monozygotic twins compared with dizygotic twins [Lopez, 1965; Goodman and Stevenson, 1989; Gillis et al., 1992; Stevenson et al., 1993; Waldeman et al., 1994; Gjone et al., 1996]. Their results suggest that the heritability of ADHD ranges from .88 to 1.0, suggesting a substantial role for genetic factors in its etiology. Adoption studies also implicate genes in the etiology of ADHD. The adoptive relatives of ADHD children are less likely to have ADHD or associated disorders than are the biological relatives of ADHD children [Morrison and Stewart, 1973; Cantwell, 1975]. Thus, a growing body of evidence shows that ADHD is a familial disorder and that transmission in families is mediated, at least in part, by genetic factors.

Our segregation analysis of ADHD [Faraone et al., 1992) confirmed the prior work of Deutsch et al. [1990], suggesting that a single gene of major effect might be involved in the etiology of ADHD. However, the differences in fit between genetic models was modest [Faraone et al., 1992]. Similar results have since been reported in a twin study by Eaves et al. [1993] and a pedigree study by Hess et al. [1995]. Several interpretations of these results are possible. If ADHD has more than one genetic cause, then the evidence for any single mode of transmission might be relatively weak. In this regard it is notable that Hauser et al. [1993] demonstrated that a rare familial form of ADHD is associated with generalized resistance to thyroid hormone, a disease caused by mutations in the thyroid receptor-β gene. Also, other studies have implicated by dopamine D2, D4 and the transporter genes [Comings et al.,

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1991; Cook et al., 1995; LaHoste et al., 1996]. These findings are consistent with either genetic heterogeneity or oligogenic inheritance.

The delineation of familial subtypes of ADHD would be beneficial to ADHD treatment and research. These subtypes may differ from other cases of ADHD in clinical phenomenology, intellectual functioning, and treatment response. This information would be useful to clinicians. Researchers would benefit from having a means to reduce the heterogeneity of ADHD in research studies. In particular, a highly familial form of ADHD would be more suitable for molecular genetic studies (i.e., linkage and association studies) than a less familial form [Faraone et al., 1995b].

To examine the familial heterogeneity of ADHD, Biederman et al. [1990a,b, 1991a,b, 1992] and Faraone et al. [1991; 1997a,b] tested competing hypotheses about the association of ADHD with antisocial, mood, and anxiety disorders based on genetic models proposed by Pauls et al. [1986] and Reich et al. [1979]. Results of these analyses from our studies of DSM-III attention deficit disorder (ADD) [Biederman et al., 1990a] and DSM-III-R ADHD [Biederman et al., 1992] suggested that: (1) ADHD and major depression share common familial vulnerabilities [Biederman et al., 1991b]; (2) ADHD with conduct disorder may be a distinct familial subtype of ADHD [Faraone et al., 1991]; (3) ADHD with bipolar disorder may be a distinct familial subtype of ADHD [Faraone et al., 1997b]; and (4) ADHD is familially independent from anxiety disorders [Biederman et al., 1991a] and learning disabilities [Faraone et al., 1993a].

Thus, stratification by conduct and bipolar disorders may cleave the universe of ADHD children into more familially homogeneous subgroups. Major depression may be a nonspecific manifestation of different ADHD subforms (and may therefore be a variable manifestation of ADHD genotypes). In contrast, anxiety disorders and learning disabilities do not appear to be good candidates for resolving either variable expression or familial heterogeneity. Moreover, our literature reviews provide broad support for our conclusions about ADHD and conduct disorder [Faraone et al., 1995c], ADHD and bipolar disorder [Faraone et al., 1997b] and ADHD and depression [Faraone and Biederman, 1997].

In summary, our prior work has inferred the existence of three subtypes of ADHD based on psychiatric comorbidity: antisocial-ADHD, bipolar-ADHD and other-ADHD. The main goal of the present paper is to clarify if antisocial-ADHD and bipolar-ADHD are the same, or different subtypes of ADHD. This idea is consistent with both clinical studies, that show juvenile bipolar disorder to be associated with violence and antisocial behavior [Ryan and Puig-Antich, 1986; Kutcher et al., 1989; McElroy et al., 1992; Kovacs and Pollock, 1995; Wozniak et al., 1995; Biederman et al., 1997b], and an epidemiologic study [Lewinsohn et al., 1995] that found high rates of comorbidity between bipolar and disruptive behavior disorders. It is also notable that previous studies have documented the beneficial effects of the anti-manic medications lithium [Lena, 1980] and carbamazepine [Campbell et al., 1992] in conduct disordered children [Campbell et al., 1995]. Given that conduct disorders are very refractory to treatment, the validation of a subgroup of mood dysregulated, antisocial ADHD children would have implications for treatment.

Given these data suggesting an overlap between ADHD and conduct disorder, this paper tests the hypothesis that the antisocial- and bipolar-ADHD subtypes described in our prior reports are different manifestations of the same familial condition.

METHODS

We analyzed data from a family genetic study of ADHD that we have presented in previous publications [Biederman et al., 1992, 1993, 1996; Faraone et al., 1992, 1993]. The original sample included a total of 260 boys (140 ADHD and 120 normal controls) chosen from psychiatric and nonpsychiatric, pediatric settings (due to missing data, samples for some analyses are somewhat smaller as indicated in the Results section). Within each setting, ADHD boys and normal controls were included. These groups had 174 and 129 biological siblings, respectively. We obtained informed consent for all subjects prior to their enrollment in the protocol. All probands were Caucasian, non-Hispanic males between the ages of 6 and 17.

Probands and their siblings were assessed at baseline and then again 1 and 4 years later. We examined their parents at baseline only. All diagnostic assessments used DSM-III-R-based structured interviews. Psychiatric assessments of probands and siblings relied on the Kiddie SADS-E (Epidemiologic Version) [Orvaschel, 1985]. Diagnoses were based on independent interviews with the mothers and direct interviews of probands and siblings, except for boys younger than 12 years of age, who were not directly interviewed. Diagnostic assessments for parents were based on direct interviews with each parent using the Structured Clinical Interview for DSM-III-R (SCID) [Spitzer et al., 1990]. At baseline and year 1, the structured interviews assessed lifetime history of psychopathology; at year 4, these assessments reflected the interval since the prior assessment. We computed kappa coefficients of agreement by having three child psychiatrists diagnose subjects from audiotaped interviews made by the assessment staff. Based on 173 interviews, the median Kappa was 0.86. Over a 1-year interval, the median test-retest kappa between different interviewers was .64 [Faraone et al., 1995a].

The assessment personnel were blind to proband diagnosis (ADHD or control) and ascertainment site (psychiatric or pediatric). All follow-up assessments were made blind to prior assessments of the same subjects and their family members. We collected interview data about all siblings in both the ADHD and control families. Eighty-nine percent of the parents of psychiatrically referred boys and 93% of the parents of pediatrically referred boys were directly interviewed. Ninety-five percent of all uninterviewed cases were fathers. When a parent was unavailable for interviewing, information was obtained by administering the SCID about the absent spouse to the available spouse.

The interviewers were instructed to take extensive

notes about the symptoms for each disorder. These notes were reviewed by a committee of four board-certified child and adult psychiatrists. The committee was blind to the subjects' ascertainment group, ascertainment site, and all data collected from other family members. Diagnoses were considered positive if DSM-III-R criteria were unequivocally met. Diagnoses presented for review were considered positive only if a consensus was achieved that criteria were met to a degree that would be considered clinically meaningful. By "clinically meaningful" we mean that the data collected from the structured interview indicated that the diagnosis should be a clinical concern due to the nature of the symptoms, the associated impairment, and the coherence of the clinical picture. As suggested by Gershon et al. [1982], the diagnosis of major depression was made only if the depressive episode was associated with marked impairment. Since the anxiety disorders comprise many syndromes with a wide range of severity, we use two or more anxiety disorders to indicate the presence of a clinically meaningful anxiety syndrome [Biederman et al., 1990b].

In addition to psychiatric data we assessed: (1) cognitive functioning using subtests from the Wechsler Intelligence tests, the Wide Range Achievement Test, and the Gilmore Oral Reading test (interviewers were trained to administer these tests by a child clinical psychologist with extensive experience in the psychological assessment of children. The psychologist supervised the interviewers throughout the study); (2) social functioning with the Global Assessment of Functioning Scale of the DSM-III-R and the Social Adjustment Inventory for Children and Adolescents (SAICA); (3) dimensional measures of child syndromes as measured by the Child Behavior Checklist (CBCL) [Achenbach, 1991]; (4) Socio Economic Status (SES) [Hollingshead, 1975], and family intactness (divorce or separation of parents in family of origin). School dysfunction was assessed by documenting repeated grades, placement in special classes, or need for tutoring. These assessments were identical for baseline and follow-up assessments with one exception. At baseline, the Gilmore Oral reading test assessed reading ability but at the follow-up examinations we used the reading subtest of the WRAT-R. All cognitive, school, and psychosocial assessments at follow-up were blind to baseline data collected on the same subjects.

We collected complete psychiatric diagnostic information about all subjects at each assessment. However, in some cases, subjects could not complete the additional measures or, for the CBCL, were too young at the time of data collection. As a result, the numbers of siblings assessed using the CBCL, the neuropsychological measures and the SAICA were slightly lower than the overall sample size.

Following Sattler [1988], we estimated Full Scale IQ from the vocabulary and block design subtests and computed the Freedom From Distractibility IQ from the other subtests. The definition of Learning Disabilities under Public Law 94-142 requires a significant discrepancy between a child's potential and achievement [Federal Register, 1977]. We operationalized this with the procedure recommended by Reynolds [1984] that we have used elsewhere [Faraone et al., 1993a].

We used two data-analytic strategies to test the hypothesis that antisocial-ADHD and bipolar-ADHD are two manifestations of the same underlying condition. First, we used loglinear analysis to determine if, using the proband as the unit of analysis, there was a three-way association between family history of antisocial disorders (conduct or antisocial personality disorder), family history of ADHD, and family history of bipolar disorder. A statistically significant finding would be supportive of our hypothesis. Second, we compared antisocial, bipolar and other families (as defined at the baseline assessment) on a comprehensive battery of psychiatric, neuropsychological, and psychosocial outcomes at the 4-year follow-up. When this three-way comparison was significant, we examined pairwise comparisons between families. Our hypothesis predicted that there should be no significant differences between the antisocial and bipolar families. Families were defined as bipolar if either the proband or a parent had bipolar disorder. Among the remaining families, those having a proband or parent with an antisocial disorder were classified as antisocial. The remaining were defined as other-ADHD families.

Because the nonindependence of siblings from the same family leads to inaccurate estimates of statistical significance, we adjusted our analyses by using Huber's [1967] formula as implemented in STATA [Stata Corporation, 1997] to produce robust statistical tests for both linear and logistic regression. We used .05 as the level of statistical significance for all analyses.

RESULTS

The loglinear analyses assessed the three-way stratification given in Table I. These analyses found significant associations between family history of ADHD and family history of antisocial disorder ($z = 4.0$, $P < .001$), family history of ADHD and family history of bipolar disorder ($z = 3.8$, $P < .001$), and family history of bipolar disorder and family history of antisocial disorder ($z = 3.3$, $P = .001$). Each of these associations had a similar interpretation: having a family history of one disorder make it more likely that the proband had a family history of the other disorder.

The loglinear analyses also found a significant three-way association between the three family history variables ($z = 2.7$, $P = .008$). This three-way association indicates that the pairwise associations between any

TABLE I. Stratification of Probands by Family History of ADHD, Antisocial Disorders, and Bipolar Disorder

	Family history of conduct disorder or antisocial personality			
	No		Yes	
	Family history of bipolar disorder		Family history of bipolar disorder	
Family history of ADHD	No	Yes	No	Yes
No	149	4	36	8
Yes	25	5	24	6

two family history variables depend on whether the third family history variable is positive or negative. For example, for probands that did not have a family history of antisocial disorders, the odds ratio for the association between ADHD family history and bipolar family history was 11.9, indicating a robust association. For other probands, the odds ratio was 1.1 indicating no association.

Table II compares probands from the bipolar, antisocial and other ADHD families (defined using baseline data as described in Methods) on rates of psychiatric disorders at the 4-year follow-up. Probands from the bipolar and antisocial families each had higher rates of conduct and bipolar disorders compared with probands from other ADHD families. The only differences between probands from the bipolar and antisocial families were the greater rates of bipolar disorder, major depression, and separation anxiety in the former group.

Table III presents clinical T-scores from the Child Behavior Checklist. There were no differences between probands from the bipolar and antisocial families, but compared to probands from other ADHD families, both groups were significantly more deviant on measures of delinquency and aggressive behavior.

Table IV presents the psychosocial outcome of the probands at the 4-year follow-up. There was only one difference between probands from the bipolar and antisocial families: the former group reported having more problems with the opposite sex. Compared with controls, both groups showed more evidence of impaired relationships with parents. Notably, the highest rates of hospitalization were observed in the probands from bipolar families, but the difference with probands from antisocial families did not reach significance.

The neuropsychological outcome of probands is given in Table V. There was only one difference among the three ADHD subtypes: probands from antisocial families were more likely to have been placed in special classes compared with probands from other ADHD families.

Table VI presents the psychiatric diagnoses of siblings at the 4-year follow-up. There was only one difference between the siblings in bipolar and antisocial

TABLE II. Lifetime Prevalence of Year-4 Diagnoses in Familial-Typed ADHD Probands

	Bipolar family type (n = 26)		Antisocial family type (n = 46)		Other (n = 68)		
	N	%	N	%	N	%	*P*-value
Antisocial disorders							
Conduct disorder	14	56*	21	48*	3	5	0.000
Oppositional disorder	23	88	34	76	45	68	0.130
Mood disorders							
Major depression (severe)	20	77*,***	19	44**	22	35	0.002
Bipolar	19	73*,***	8	17	4	6	0.000
Dysthymia	2	8	8	19	9	15	0.526
Anxiety disorders							
Multiple (⩾2) anxieties	14	56	15	34	21	33	0.107
Panic disorder	1	4	3	7	2	3	0.674
Agoraphobia	8	33	9	21	11	17	0.272
Overanxious disorder	12	48	20	45	28	44	0.955
Simple phobia	10	42	10	23	15	24	0.194
Social phobia	10	40	7	16	18	28	0.094
Separation anxiety	14	56*,****	12	28	17	27	0.021
Generalized anxiety	0	0	0	0	0	0	n/a[a]
Obsessive compulsive disorder	2	8	6	14	7	11	0.808
Substance disorders							
Any alcohol/drug abuse/dep	6	29	7	17	6	10	0.123
Alcohol abuse	4	17	4	9	6	10	0.606
Alcohol dependence	4	17*	5	12*	0	0	0.009
Drug abuse	2	8	5	12	2	3	0.251
Drug dependence	2	8	3	7	1	2	0.288
Other disorders							
Tic disorder	3	12	10	22	10	15	0.462
Enuresis	6	24	20	43	23	36	0.264
Encopresis	1	4	6	14	5	8	0.363
Language disorder	5	21	15	33	18	28	0.540
Stuttering	2	8	3	7	6	10	0.876
Psychosis	1	4	2	5	3	5	0.989

*$P \leqslant 0.01$ vs. other.
**$P \leqslant 0.05$ vs. other.
***$P \leqslant 0.01$ vs. antisocial.
****$P \leqslant 0.05$ vs. antisocial.
[a]n/a, not applicable.

TABLE III. Child Behavior Checklist Scores at Year 4 in Familial-Typed ADHD Probands

	Bipolar family type (n = 19)		Antisocial family type (n = 34)		Other (n = 57)		
Clinical T-scores	Mean	S.D.	Mean	S.D.	Mean	S.D.	*P*-value
Withdrawn	55.1	5.5	54.6	6.3	54.3	7.2	0.920
Somatic complaints	56.1	8.7	56.1	7.9	54.1	6.3	0.360
Anxious/depressed	59.7	8.5	57.7	7.5	57.6	8.2	0.576
Delinquent behavior	61.7	10.4*	57.6	9.0*	53.6	4.9	0.000
Aggressive behavior	65.8	12.8*	60.5	9.6**	56.4	6.6	0.000
Social interaction problems	60.3	10.4	59.1	8.3	58.5	9.9	0.763
Thought problems	55.5	7.9	53.9	5.2	54.5	7.2	0.708
Attention problems	64.0	8.3	62.4	8.4	61.2	8.8	0.460

*$P < .01$ vs. other.
**$P < .05$ vs. other.

families: the former group had significantly higher rates of agoraphobia than the latter. There were, however, many differences between these two groups and the siblings from other ADHD families. The siblings in bipolar and antisocial families had significantly higher rates of conduct, oppositional defiant, major depressive, and substance use disorders. Both groups had higher rates of bipolar disorder but only the comparison between the bipolar and other families was significant.

To determine if assortative mating could account for the familial coaggregation of antisocial and bipolar disorders, we examined the association of these diagnoses in parents. The rate of bipolar disorder among fathers was 7.5% if the mother had antisocial personality and 3.7% otherwise, but the difference was not significant ($\chi^2(1) = 1.2$, $P = .28$). Similarly, the rate of bipolar disorder among mothers was 11% if the father had antisocial personality and 4% otherwise, but the difference was not significant ($\chi^2(1) = 1.1$, $P = .31$).

TABLE IV. Psychosocial Outcome at Year 4 in Familial-Typed ADHD Probands

	Bipolar family type (n = 19)		Antisocial family type (n = 32)		Other (n = 48)		
	Mean	S.D.	Mean	S.D.	Mean	S.D.	*P*-value
Social adjustment inventory scale							
School behavior	3.0	.9	2.8	.6	2.7	.7	0.226
Spare time activities	2.4	.8	2.3	.6	2.2	.6	0.665
Spare time problems	2.3	.9	2.2	.8	2.0	.7	0.514
Activity with peers	2.3	.8	2.2	.8	2.4	.9	0.757
Problems with peers	2.4	.9	2.2	.7	2.1	.8	0.436
Boy/girl relationship	2.1	.9	2.4	1.0	2.7	.9	0.090
Problems with opposite sex	2.1*,***	.9	1.4	.5	1.4	.7	0.004
Activity with siblings	1.7	1.1	2.2	.8	2.1	.8	0.204
Problems with siblings	2.4	1.9	1.9	.7	2.3	1.2	0.317
Relationship with mother	1.9**	.8	1.9**	.6	1.6	.6	0.047
Relationship with father	2.4**	1.7	2.3*	.9	1.8	.7	0.027
Problems with parents	2.1	1.0	2.1	.8	1.8	.6	0.087
Global assessment Functioning scale	50.0*	9.2	52.2	8.1	55.0	6.8	0.020
CBCL social T-scores							
Social T-score	56.1	23.9	48.9	20.3	54.0	23.7	0.468
Activities T-score	46.5	9.2	51.4	17.2	50.8	14.7	0.479
School T-score	49.4	23.7	45.3	18.4	42.5	10.7	0.257
Family environment							
Cohesion	44.0**	20.5	43.8*	19.5	54.5	16.3	0.011
Expression	51.6	18.3	52.1	14.2	52.3	13.3	0.985
Conflict	57.1	10.8	56.4	12.1	53.7	10.6	0.375
Treatment history	N	%	N	%	N	%	
Counseling	23	96	35	81	48	79	0.161
Medication	11	46	29	67	33	54	0.188
Combination (meds/counseling)	16	67	28	65	39	64	0.971
Hospitalization	5*	21	3	7	1	2	0.008

*$P < .01$ vs. other.
**$P < .05$ vs. other.
***$P < .01$ vs. antisocial.
****$P < .05$ vs. antisocial.

TABLE V. Neuropsychological Outcome at Year 4 in Familial-Typed ADHD Probands

	Bipolar family type (n = 20)		Antisocial family type (n = 37)		Other (n = 54)		
	Mean	S.D.	Mean	S.D.	Mean	S.D.	*P*-value
WISC-R subscales							
Vocabulary	10.5	2.4	11.5	3.6	11.6	2.5	0.307
Block design	11.9	3.7	11.4	3.7	11.5	3.6	0.880
Digit symbol	9.5	3.5	10.2	3.7	9.4	3.1	0.503
Digit span	8.9	2.4	9.7	3.7	9.7	3.0	0.547
Oral arithmetic	10.0	3.1	10.0	3.0	10.7	3.2	0.475
Estimated full scale IQ	105.1	12.2	107.4	16.4	107.7	12.4	0.752
Freedom from distractibility	97.3	14.7	95.7	25.1	100.0	14.6	0.591
Achievement scores							
Wide Range Achievement Test arithmetic	94.3	18.6	92.3	20.7	93.9	16.5	0.890
Wide Range Achievement Test reading	102.5	15.1	100.6	21.8	102.7	12.2	0.831
Learning disability	N	%	N	%	N	%	
Arithmetic Learning Disability	4	20	5	14	11	20	0.717
Reading Learning Disability	0	0	5	14	5	9	0.223
Any Learning Disability	4	20	6	17	16	30	0.335
School failure	N	%	N	%	N	%	
Repeat grade	8	33	16	36	25	40	0.815
Tutoring	21	84	37	82	58	89	0.556
Special class	15	58	28	61**	24	38	0.034

*$P < .01$ vs. other.
**$P < .05$ vs. other.
***$P < .01$ vs. antisocial.
****$P < .05$ vs. antisocial.

DISCUSSION

Our results provide fairly consistent support for the hypothesis that the antisocial- and bipolar-ADHD subtypes we have described in our prior reports are different manifestations of the same familial condition. As predicted by this hypothesis, there was a significant three-way association between variables assessing the family history of each disorder. Moreover, when families were stratified into bipolar, antisocial, and other types, few differences emerged between the bipolar and antisocial families.

If the antisocial- and bipolar-ADHD subtypes were familially distinct disorders, we should have found high rates of antisocial disorders only in the former families and high rates of mood disorders only in the latter families. But this was not so; both types of family had elevated rates of antisocial and mood disorders in both probands and siblings. Moreover, there were few psychopathologic or functional differences between the two types of families.

One aspect of our results was inconsistent with the unity of bipolar-ADHD and antisocial-ADHD subtypes: rates of bipolar disorder in siblings differed significantly between bipolar-ADHD families and other-ADHD families, but not between antisocial-ADHD families and other-ADHD families. Yet, the difference between bipolar and antisocial families (24% vs. 9%) was not significant, possibly due to the relatively small subsamples of siblings.

In contrast to the loglinear analyses, which allow us to safely infer a three-way familial association between ADHD, bipolar disorder and conduct disorder, the comparisons of familial subtypes rely on accepting the null hypothesis of no difference between bipolar and antisocial families. These latter findings are statistically weaker inasmuch as they could be due to the relatively low power afforded by the subsamples of bipolar and antisocial families.

Nevertheless, our work is consistent with data from other investigators who have suggested that childhood onset bipolar disorder might be a subform of bipolar disorder with a high familial loading [Strober, 1992; Todd et al., 1993; Neuman et al., 1997]. For example, in another report from this sample [Faraone et al., 1997b], we reported a 16% rate of bipolar disorder among relatives of bipolar, ADHD probands, which was more than twice as high as the mean risk to first degree relatives of 7% reported in Tsuang and Faraone's [1990] review of 17 family studies of adult bipolar probands. Thus, comorbid bipolar ADHD is highly familial. Notably, studies of adults have reported an association between childhood onset bipolar disorder and ADHD [Sachs et al., 1993].

The results from this paper along with our prior work suggest that ADHD boys with bipolar or antisocial features are categorically different from other ADHD boys. Although we conclude that these boys have a variant form of ADHD, it might be equally accurate to describe them as having a variant of conduct or bipolar disorders. For example, Strober [1992] and Todd et al. [1993] proposed that childhood onset bipolar disorder might be a subform of bipolar disorder with a high familial loading. It may be that childhood onset

TABLE VI. Lifetime Prevalence of Diagnoses at Year 4 in Siblings of Familial-Typed ADHD Probands

	Bipolar family type (n = 36)		Antisocial family type (n = 59)		Other (n = 82)		
Psychopathology	N	%	N	%	N	%	*P*-value
ADHD	12	35**	23	39*	15	18	0.012
Antisocial disorders							
Conduct disorder	9	26*	10	17*	1	3	0.000
Oppositional disorder	19	54*	20	34	17	21	0.002
Mood disorders							
Major depression (severe)	10	29*	14	25*	6	8	0.004
Bipolar	8	24*	5	9	2	3	0.002
Dysthymia	0	0	3	5	4	5	0.183
Anxiety disorders							
Multiple (⩾2) anxieties	11	31	13	22	20	25	0.658
Panic disorder	2	6	1	2	2	3	0.486
Agoraphobia	7	21	3	5	10	13	0.522
Overanxious disorder	7	20	18	31	19	24	0.885
Simple phobia	9	26	14	24	14	18	0.286
Social phobia	7	20	13	22	12	15	0.381
Separation anxiety	9	25	8	14	15	19	0.645
Generalized anxiety	1	3	5	9*	0	0	0.010
OCD	0	0	0	0	1	1	0.564
Substance disorders							
Any alcohol/drug abuse/dep	9	31*	15	29**	8	12	0.009
Alcohol abuse	5	15	11	19	5	6	0.092
Alcohol dependence	6	18*	7	12**	2	3	0.004
Drug abuse	3	9	4	7	4	5	0.513
Drug dependence	6	18*	4	7	1	1	0.001
Other disorders							
Tic disorder	1	3	1	2	1	1	0.543
Enuresis	8	24	12	21	16	20	0.636
Encopresis	1	3	4	7	3	4	0.956
Language disorder	4	11	7	12	15	19	0.313
Stuttering	2	6	3	5	2	3	0.329
Psychosis	0	0	2	4	1	1	0.812

*$P \leqslant 0.01$ vs. other.
**$P \leqslant 0.05$ vs. other.
***$P \leqslant 0.01$ vs. antisocial.

bipolar disorder and bipolar-ADHD are the same disorder. Notably, both are highly familial disorders and relatives of bipolar ADHD boys are at high risk for childhood onset mania.

Moreover, although epidemiological studies find no gender differences in the prevalence of bipolar disorder [Tsuang and Faraone, 1990], Todd et al. [1993] reported that the bipolar relatives of childhood onset bipolar probands were more likely to be male than female. In a prior report from this sample [Faraone et al., 1997b], we found that the bipolar relatives of bipolar-ADHD probands were 75% male and 25% female and in a different sample we previously reported a predominance of males among childhood onset bipolar children, most of whom had ADHD [Wozniak et al., 1995]. A meta-analysis of this issue based on 2,168 patients from 34 studies showed that, in cases with prepubertal onset, bipolar disorder is nearly four times more common in males compared with females [Faedda et al., 1995].

Furthermore, as we reported elsewhere [Faraone et al., 1997], the "bipolar" subjects in our study met full diagnostic criteria for bipolar disorder with severe impairment, but most had severe irritable, not euphoric, mood. Only one had a classic, biphasic illness and nine had a mixed manic and depressive presentation. These subjects had a chronic, rather than episodic condition. These clinical features are similar to what others have reported from child bipolar samples [Carlson, 1984, 1995; Weller et al., 1995], yet differ from typical adult mania.

The atypical picture of bipolar disorder among ADHD boys may indicate that they will grow up to become atypical bipolar adults. Indeed, their mixed presentation, chronicity, and rapid cycling suggests that they may become the adults described by McElroy et al. [1992] as having dysphoric or mixed mania. Follow-up studies are needed to resolve this issue.

In summary, these converging findings, along with the data presented in this report, suggest that further nosological work investigate the validity of a male predominant syndrome that exhibits childhood onset atypical bipolar disorder, antisocial symptoms, ADHD, and high familial risks for ADHD, bipolar disorder, and antisocial disorder. If the validity of this subtype is

confirmed, it may be worthwhile for genetic studies to examine it separately from other forms of ADHD, bipolar, and antisocial disorders.

Our results must be interpreted in the context of methodological limitations. Although we included both psychiatrically and pediatrically referred samples, we do not know to what degree our findings will generalize to siblings of nonreferred ADHD children in the community. In addition, although raters were blind to the diagnosis of the children, parents were not. Another potential source of bias stems from the lack of direct interviews with children younger than 12. This method for assessment of psychopathology in the children may have led to under-representation of psychopathology in this group, especially for "internalizing" disorders such as anxiety and depression.

Our research approach also used a nonhierarchical approach to diagnosis. Thus, ADHD was not required to be the referral diagnosis, nor was it required to dominate the clinical picture. We only required that subjects met DSM-III-R criteria for the disorder. Since we used a nonhierarchical approach, our diagnostic procedure did not rule out a comorbid disorder if its symptoms "could be accounted for" by ADHD. Of course, from a clinical perspective, it might be argued that the extreme nature of bipolar features makes the diagnosis of ADHD moot. However, we favor the nonhierarchical approach for two reasons.

First, as Caron and Rutter [1991] noted, use of the wrong hierarchical principle may lead to invalid diagnoses. Until we know more about the etiologies and pathophysiologies of child psychiatric disorders, the application of hierarchical methods may be premature. If we routinely discount symptoms because another disorder is present, we may discard valuable nosologic information. Fortunately, psychometric studies suggest that simple diagnostic criterion overlap cannot account for the comorbidity and familial cotransmission of ADHD and comorbid disorders [Milberger et al., 1995].

Despite these limitations, our data suggest that antisocial- and bipolar-ADHD subtypes are different manifestations of the same familial condition. This suggests that genetic linkage studies might be able to combine the two types of families without increasing the genetic heterogeneity of linkage samples.

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