Prevalence and Genetic Architecture of Child Behavior Checklist–Juvenile Bipolar Disorder

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Background: *No consensus has been reached yet on how best to characterize children with juvenile bipolar disorder (JBD). Several groups have shown that children on the attention problems (AP), aggressive behavior (AGG), and anxious-depressed (AD) syndromes of the Child Behavior Checklist (CBCL) are likely to meet criteria for DSM-JBD. We aimed to use a large population-based twin sample to evaluate the prevalence and genetic architecture of the CBCL-JBD (deviant on AP, AGG, and AD) phenotype and compare these data to children who are deviant on just the CBCL-AP syndrome.*

Methods: *Structural equation modeling (SEM) was applied to CBCL data from 5418, 3562, and 1971 Dutch twin pairs at ages 7, 10, and 12 years.*

Results: *The CBCL-JBD phenotype occurs in ~ 1% of children at each age. Among the children who meet criteria for the CBCL-AP phenotype (~ 5%), between 13 and 20% also meet criteria for CBCL-JBD. The best SEM for CBCL-JBD includes additive genetic, shared and unique environmental factors. The best SEM for CBCL-AP includes dominant and additive genetic and unique environmental factors.*

Conclusions: *These data suggest that CBCL-JBD is common, and even more common among children who have severe attention problems. CBCL-JBD shows familial aggregation due to both genetic and shared environmental factors.*

Key Words: Child, bipolar affective disorder, CBCL, genetic model, ADHD, twin

The existence, prevalence and proper taxonomic designation of juvenile bipolar disorder (JBD) has been the focus of considerable debate. Central to the debate is the fact that little is known about the prevalence of the disorder due to the fact that few epidemiologic studies of JBD have been done (Coyle et al 2003). It has been suggested that the reason that few epidemiologic studies have addressed the prevalence of JBD is due to the fact that there is no agreement on how best to describe children who suffer from JBD. Although the DSM-IV provides explicit criteria for bipolar disorder in adults, experts in the field agree, that these criteria may not be applicable in children and adolescents (Coyle et al 2003; Geller and Luby 1997; Wozniak et al 1995). For a complete review of the debate surrounding the definition of the clinical phenotypes for juvenile mania, please see Leibenluft et al (2003). Carlson et al put it succinctly, "structured interviews provide only so much help" and such children as these, "do not fit the rules of DSM and are 'nosologic orphans' due to problems with the criteria" (Carlson et al 2004). Others point out how important the consideration of comorbidity to juvenile bipolar disorder may be. Tillman et al point out that the onset of attention-deficit hyperactivity disorder (ADHD) before mania and of oppositional defiant disorder (ODD) and conduct disorder (CD) after mania have both clinical and research implications for the study of JBD (Tillman et al 2003). In fact the National Institute of Mental Health (NIMH) Research Round Table on JBD pointed out that the relations between ADHD, ODD, major depressive disorder (MDD) and JBD need to be clarified in order to develop useful taxonomic approaches to this phenotype (Tillman et al 2003; National Institute of Mental Health 2001). There is consensus that standard diagnostic criteria for early onset BPD, that are developmentally appropriate and that exhibit high inter rater reliability and validity must be developed (Geller and Luby 1997; Giedd 2000). As Carlson et al states, the process of refining the DSM was conceptualized as an iterative endeavor and that such a process needs to be considered in the study of JBD (Carlson et al 2004). For such advancement to be achieved, research must move diagnostic processes beyond semantic description of disorder and base them on epidemiologic characteristics and biological processes.

One example of how to study the phenotype of JBD is to do so in relation to ADHD. The ADHD-JBD comorbid phenotype has been the source of considerable study and debate over the past decade (Leibenluft et al 2003). The general phenotype of a child described by this diagnosis is of ADHD with symptoms of aggressive out of control behavior, and affective instability. Although hotly debated, the symptoms of affective instability include manic-like behaviors that cycle rapidly over the course of a day. Definitional artifact makes it difficult to discern whether these symptoms are best described as "manic behaviors" or "severe hyperactivity of ADHD." The interface between ADHD and juvenile bipolar disorder is a complex one, and as a result leads to a great deal of debate on how to best conceptualize children with these symptom domains.

Biederman et al along with several other groups have described a profile on the Child Behavior Checklist (CBCL; Achenbach 1991) which occurs in children with JBD that is discrete from the CBCL profiles in children without either ADHD or JBD, and more importantly, is different from children with ADHD alone (Biederman et al 1995; Wals et al 2001; Carlson and Kelly 1998; Geller et al 1998; Hazell et al 1999; Dienes et al 2002). Figure 1 demonstrates that well children are typically below both the borderline (T score of 65) and clinical (T score of 70) scores for common psychopathologic conditions. Children suffering from JBD have been shown to have a CBCL profile that includes elevation about a T score of 70 on the Attention Problems (AP), Aggressive Behavior (AGG), and Anxious/Depressed (AD) syndromes. In contrast, ADHD children from Biederman's research are best represented by the second profile, one in which the child is elevated on the Attention Problems syndrome alone.

Biederman's work was reported on a sample of children

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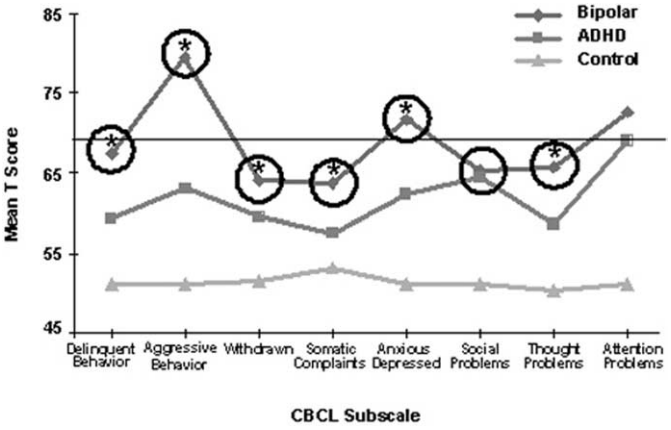

Figure 1. CBCL subscales and their relationship to ADHD and bipolar phenotypes. CBCL, Child Behavior Checklist; ADHD, attention deficit-hyperactivity disorder. * Significantly different between children with bipolar disorder and ADHD versus children with ADHD alone (Biederman et al 1995). Circles indicate subscales also elevated in children of bipolar mothers (Wals et al 2001; Galanter et al 2003).

diagnosed as having JBD using DSM interviews (Biederman et al 1995). A powerful confirmation of the utility of these findings was published by Wals et al who studied children of bipolar mothers (Wals et al 2001). Figure 1 demonstrates that although Biederman was studying children already diagnosed as JBD and Wals et al was studying children of bipolar mothers, the CBCL profile was similar. The utility of this CBCL-JBD phenotype is supported by the work of Carlson and Kelly (Carlson and Kelly 1998) who reported a profile in their sample of inpatients, who were also highly impaired, and appeared to be symptomatically similar to those described by Wals and Biederman. Geller and colleagues (Geller et al 1998) also demonstrated similar findings in their research on children with bipolar disorder. Finally, Galanter et al used this same profile in their work determining treatment response in the Multimodal Treatment Study of Children with Attention-Deficit/Hyperactivity Disorder (MTA) study (Galanter et al 2003). In the Galanter study, Diagnostic Interview Schedule for Children (DISC) interview and CBCL data were used to generate a "DISC-MANIA Proxy" and a "CBCL-MANIA Proxy." They report that in expertly diagnosed ADHD children from the MTA study, 10% meet the DISC MANIA Proxy and 11% meet the CBCL-MANIA proxy, and that these two groups were quite similar on their CBCL profiles and nearly identical to the profiles seen in the Biederman, Carlson, Geller, and Wals analyses (Galanter et al 2003). Thus, the CBCL-JBD phenotype has been reported across samples, across countries, and across methodologies (family studies of child bipolar disorder, of ADHD, family studies of children of bipolar mothers). Mick et al's 2003 meta-analysis of the CBCL studies found considerable agreement between research sites indicating the bipolar children are highly aggressive, mixed with depression, and comorbid with ADHD (Mick et al 2003).

The present study sought to shed light on the CBCL-JBD phenotype by estimating its prevalence and its genetic architecture in a large general population twin sample of 7, 10 and 12 year old twins.

Methods and Materials

Subjects and Procedure

The data of the present study are derived from a large ongoing longitudinal study, which examines the genetic and environmental influences on the development of problem behavior in families with 3- to 12-year-old twins. The families are volunteer members of the Netherlands Twin Register, kept by the Department of Biological Psychology at the Free University in Amsterdam (Boomsma et al 2002; Boomsma 1998). Starting in 1987 families with twins were recruited a few months after birth. Currently, 40-50% of all multiple births are registered by the Netherlands Twin Registry. For the present study, we included data of 7, 10, and 12 year old twin pairs. Parents of twins were asked to fill in questionnaires about problem behavior for the eldest and youngest twin at ages 7, 10, and 12 years. After two months a reminder was sent to the nonresponders, and after four months those who still did not respond were telephoned. From ages 3 to 7, and ages 7 to 10 and from 10 to 12 the continued participation was 80%. Families who do not participate at one year (e.g. at age 10) may participate at a subsequent year.

For 822 same sex twin pairs, zygosity was based on blood group polymorphisms (n = 424) or DNA (n = 398). For the remaining twins, zygosity was determined by questionnaire items, filled by the mother, about physical similarity and frequency of confusion of the twins by family and strangers (Goldsmith 1991). The classification of zygosity was based on a discriminant analysis, relating the questionnaire items to zygosity based on blood/DNA typing in a group of same-sex twin pairs. The zygosity was correctly classified by questionnaire in nearly 95% of the cases (Rietveld et al 2000).

A family was excluded when one of the twin pair had a disease or handicap that interfered severely with normal daily functioning (about 2%). Table 1 gives an overview of the number of families with complete twin pairs. An earlier comparison of the parental Socioeconomic Status (SES) distribution with those obtained for the general Dutch population showed a slightly higher frequency of the middle and higher SES-groups (for details see Rietveld et al (2003a). Attrition rates as well as a detailed discussion on the representation of the sample at each age are discussed in detail elsewhere (van Beijsterveldt et al 2003).

Measures

At ages 7, 10, and 12 years problem behavior was measured with the CBCL/4-18 (Achenbach 1991), a questionnaire of 118 items developed to measure problem behavior in 4 to 18 years old children. Again parents were asked to rate the behavior of the child of the preceding 6 months on a 3-point scale.

For the CBCL/4-18 eight syndrome scales were composed according to the 1991 profile (Achenbach 1991). In the present study, subjects with more than three missing items per syndrome were not included in the analyses. This occurred in less than

Table 1. Sample Description (Age, Gender, Zygosity)

	Number of Pairs		
Twin Type	Age 7	Age 10	Age 12
Monozygotic (MZ) Males	905	598	360
Dizygotic (DZ) Males	879	542	308
Monozygotic (MZ) Females	1023	726	410
Dizygotic (DZ) Females	838	538	303
Dizygotic Opposite Sex Male Eldest	927	587	313
Dizygotic Opposite Sex Female Eldest	846	524	277
TOTAL	5418	3515	1971

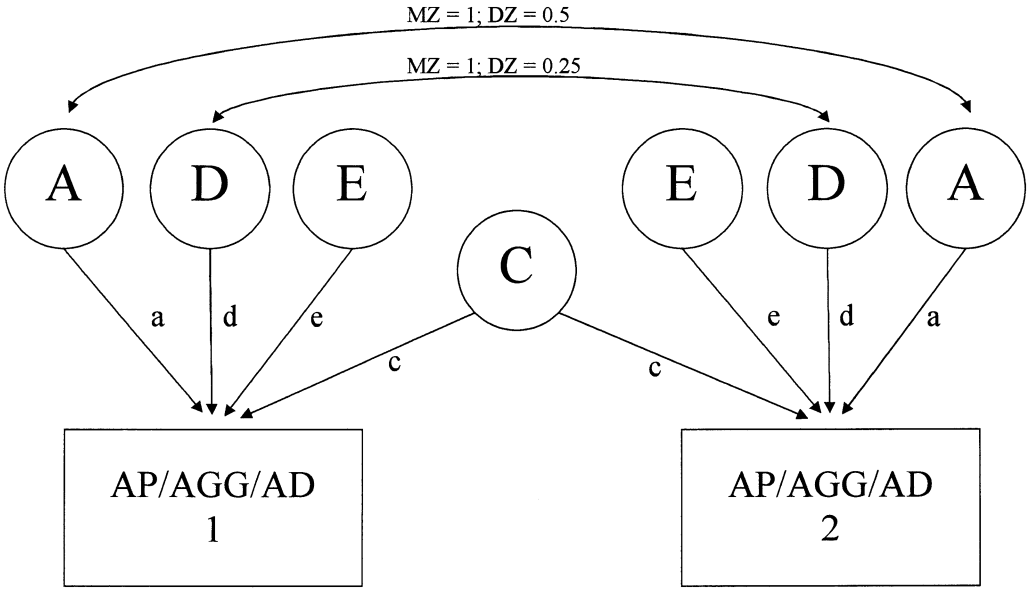

Figure 2. Genetic Model. A, addictive genetic; D, dominance genetic; E, unique environment; C, shared environment; AP, attention problems; AGG, aggressive behavior; AD, anxious-depressed; CBCL, Child Behavior Checklist; JBD, juvenile bipolar disorder. AP/AGG/AD1 = CBCL-JBD score of twin 1; AP/AGG/AD2 = CBCL-JBD score of twin 2.

2.5% of the received questionnaires filled out by the mother when the twins were aged 7, 10 and 12 years.

Statistical Analyses

The generalized linear modeling procedure (GLM) (SPSS, 2001) was used to test for mean differences between sex and age. For each age, the AP/AGG/AD scores of mother reports were analyzed as the dependent variables, with sex and age as between subjects factors. Analyses were conducted separately for the oldest and youngest of the twin pair, because due to their genetic relatedness their data are not independent.

We next computed the prevalence of the CBCL-JBD phenotype by taking those children deviant with a T-score greater than 70 on all three of the AP, AGG, and AD subscales.

We then used the square-root transformed sum of AP, AGG and AD scores as a continuous trait in the genetic analyses. These analyses were conducted in Mx using maximum likelihood estimation of parameters (Neale 1997). First, PRELIS 2 was used to obtain the variance-covariance matrices for CBCL-JBD and for CBCL-AP in the oldest and youngest twin, separately for each age-sex-by-zygosity group. These matrices were used as input for the genetic analyses. Structural equation modeling was employed to obtain estimates and confidence intervals of the genetic and environmental contributions to the observed variances and covariances. Technical details of genetic model-fitting analyses are reviewed elsewhere (Neale and Cardon 1992). Figure 2 summarizes the fundamental univariate genetic model that underlies the analyses. This model was used to estimate the additive genetic (A, additive effects of genes at multiple loci), dominance genetic (D, interaction of genetic effects at the same loci), common or shared environment (C, shared among members of the same household), or nonshared environment (E, unique to the individual) effects. The circles represent the latent, unmeasured factors. Correlations between latent factors were 1.0 for MZ and .5 (for A) and .25 (D) for DZ pairs. The environment shared by two members of a pair (C) is assumed not to depend on the zygosity of the twins. The unique or nonshared environment is by definition, uncorrelated between two members of a pair. Estimates of the unique environmental effects also include measurement error (Plomin 1997; Boomsma et al 2002). The classical twin design which includes mono- and dizygotic twins cannot simultaneously estimate the effects of genetic dominance and common environment shared by family members. Based on the pattern of twin correlations a choice needs to be made to evaluate an ADE or ACE model. Next, significance of the C or D can be tested by dropping this parameter.

Sex differences were tested by constraining the parameters to

Table 2. Means (and Standard Deviations) for CBCL Subscales and Summed CBCL-JBD Measure

		AP		AGG		A-D		JBD	
Age	Twin	Male	Female	Male	Female	Male	Female	Male	Female
7	Younger	3.40 (3.16)	2.44[a] (2.62)	7.64 (6.20)	5.56[a] (5.17)	2.12 (2.72)	2.25 (2.73)	13.15 (10.22)	10.25[a] (8.86)
	Older	3.41 (3.08)	2.53[a] (2.71)	7.96 (6.23)	5.91[a] (5.39)	2.63 (2.79)	2.41 (2.88)	13.63 (10.27)	10.85[a] (9.26)
10	Younger	3.36 (3.19)	2.36[a] (2.55)	6.87 (6.09)	4.81[a] (4.71)	2.49 (3.01)	2.65 (3.36)	12.72 (10.55)	9.81[a] (9.01)
	Older	3.44 (3.23)	2.50[a] (2.69)	7.14 (6.30)	5.20[a] (4.96)	2.63 (3.29)	2.78 (3.37)	12.21 (10.88)	10.48[a] (9.39)
12	Younger	2.92 (3.06)	2.04[a] (2.34)	5.83 (5.63)	4.24[a] (4.43)	2.14 (3.12)	2.36 (2.88)	10.89 (10.07)	8.65[a] (8.16)
	Older	3.24 (3.27)	2.11[a,b] (2.40)	6.52 (6.10)	4.38[a,b] (5.43)	2.42 (3.27)	2.40[b] (3.06)	12.18 (10.93)	8.89[a,b] (8.36)

CBCL, Child Behavior Checklist; JBD, juvenile bipolar disorder; AP, attention problems; AGG, aggressive behavior; A-D, anxious-depressed.
[a] $p < .001$ for difference between males and females.
[b] $p < .001$ for difference across ages.

Table 3A. Prevalence of the CBCL-AP and CBCL-JBD Phenotypes

	Male		Female	
Age	CBCL-AP	CBCL-JBD	CBCL-AP	CBCL-JBD
7	4.8%	.8%	5.6%	.8%
10	4.1%	.9%	5.2%	.9%
12	4.6%	1.2%	6.6%	.9%

be equal for boys and girls. When sex differences appeared to be significant, a scalar sex-limitation model was tested. In this model a difference in total variance between boys and girls is allowed, but the relative contributions of genetic and environmental influences are the same for boys and girls. Different models were evaluated on the basis of their goodness-of-fit (chi-squared statistic: χ^2). The associated degrees of freedom (*df*) equal the number of statistics minus the number of estimated parameters. The difference in χ^2 between models is also distributed as a χ^2, with *df* equal to difference in *df* between the full (e.g. ACE) and the reduced (e.g. AE) model. Comparison of models was also done by the use of Akaike's Information Criterion (AIC; Akaike 1987), which is a goodness-of-fit index that takes parsimony (i.e., number of parameters) into account. The AIC is the χ^2 minus two times the degrees of freedom.

Results

Means

The means and standard deviations for the separate subscales and the combined CBCL-JBD phenotype are provided in Table 2. Looking only that the CBCL-AP and CBCL-JBD measures, there were differences between males and females across all ages with males showing significantly higher scores on both measures. Additionally, there was a main effect of age with both measures showing an overall decrease in scores with older age. There was no interaction of sex by age.

Prevalence

The prevalence of the AP only phenotype at all ages was approximately 5% at all ages (see Table 3A and 3B). The prevalence of the CBCL-JBD (AP/AGG/AD) phenotype was approximately 1% in those same twins at all ages. This is consistent with the reports of the prevalence of bipolar disorder in adulthood, where it is also estimated that the lifetime prevalence is 1% (Lewinsohn et al 1995). A second use of prevalence data is to determine what percentages of the children who are deviant on AP (and thus at risk for ADHD) also exceed the cutpoints for the CBCL-JBD phenotype. Approximately 20% of those who are deviant on AP also met criteria for the CBCL-JBD phenotype. These data help explain why rates of the complex phenotype are reported to be so much higher in ADHD clinics than in general pediatric settings.

Table 3B. Prevalence of the CBCL-JBD Phenotype Among Those with the CBCL-AP Phenotype

Age	Male	Female
7	16.7%	14.2%
10	23.0%	17.3%
12	25.8%	13.5%

CBCL, Child Behavior Checklist; AP, attention problems; JBD, juvenile bipolar disorder.

Table 4A. Twin-Twin Correlations for CBCL-AP Phenotype by Gender and Zygosity

Age	Twin Type	Male	Female
7	MZ	.729	.720
	DZ	.233	.275
	DOS	.261 (M_F)	.333 (F_M)
10	MZ	.716	.731
	DZ	.217	.218
	DOS	.282 (M_F)	.293 (F_M)
12	MZ	.688	.711
	DZ	.203	.288
	DOS	.246 (M_F)	.195 (F_M)

MZ, monozygotic; DZ, dizygotic; DOS, dizygotic opposite sex; M_F, first born male, second born female; F_M, first born female, second born male; CBCL, Child Behavior Checklist; AP, attention problems.

Correlations

Twin correlations for AP and for JBD are presented in Tables 4A and 4B. When additive genetic effects are present, MZ correlations will be higher than DZ correlations. If genetic dominance, or social competition effects are present, however, the MZ correlation will be more than twice the DZ correlation (Neale and Cardon, 1992). In the case of the CBCL-AP phenotype (Table 4A) it can been seen that for both male and female twins at all ages, the MZ correlations are more than twice the DZ correlations, suggesting that genetic dominance, or social interaction factors as well as additive genetic factors are playing a role. In cases where interaction is playing a role rather than dominance, the variance between MZ and DZ twins will be different (Rietveld et al 2003b). A model that tested for differences in variance between MZ and DZ twins showed that variances for the CBCL-AP phenotype were not different in MZ and DZ pairs for any age group (Table 5A), allowing us to conclude that that the most probable explanation of the differences in MZ and DZ correlations for the CBCL-AP phenotype is the presence of dominance genetic effects in addition to the additive genetic effects.

In the case of the CBCL-JBD phenotype, the correlations between MZ twins were greater than those for the DZ twins, but less than a two fold difference. This demonstrates the presence of additive genetic and shared environmental effects. The fact that we again observed no differences in variances suggests that social interaction (of the cooperative type) does not play a role for JBD.

Table 4B. Twin-Twin Correlations for CBCL-JBD Phenotype by Gender and Zygosity

Age	Twin Type	Male	Female
7	MZ	.852	.827
	DZ	.490	.530
	DOS	.487 (M_F)	.516 (F_M)
10	MZ	.821	.793
	DZ	.470	.493
	DOS	.458 (M_F)	.496 (F_M)
12	MZ	.822	.813
	DZ	.418	.505
	DOS	.463 (M_F)	.471 (F_M)

MZ, monozygotic; DZ, dizygotic; DOS, dizygotic opposite sex; M_F, first born male, second born female; F_M, first born female, second born male; CBCL, Child Behavior Checklist; JBD, juvenile bipolar disorder.

Table 5A. Model Fitting, CBCL-AP

Model Type	−2 log Likelihood	Number of Estimated Parameters	Compared to Model	Δ *df*	Δ chi^2	Δ AIC	*p*
7 Year Old							
1. Fully saturated	27631.225	30	—	—	—	—	—
2. Equal variance MZ-DZ	27639.053	26	1	4	7.828	−.172	.098
3. ADE	27640.308	18	1	12	9.083	−14.917	.6958
4. AE	27680.094	16	3	2	39.785	35.786	.000
5. ADE no sex	27644.131	15	3	3	3.823	−2.177	.281
6. AE no sex	27682.302	14	5	1	38.171	36.171	.000
10 Year Old							
1. Fully saturated	18291.960	30	—	—	—	—	—
2. Equal variance MZ-DZ	18296.966	26	1	4	5.006	−2.994	.287
3. ADE	18310.098	18	1	12	18.138	−5.862	.447
4. AE	18331.659	16	3	2	21.561	17.561	.000
5. ADE no sex	18317.877	15	3	3	7.779	1.779	.051
12 Year Old							
1. Fully saturated	10117.935	30	—	—	—	—	—
2. Equal variance MZ-DZ	10120.058	26	1	4	2.123	−5.877	.7131
3. ADE	10126.333	18	1	12	8.398	−15.602	.7533
4. AE	10140.390	16	3	2	14.057	10.057	.001
5. ADE no sex	10152.120	15	3	3	25.787	19.787	.000

AIC, Akaike Information Criterion = −2 log likelihood + 2*number of estimated parameters. Fully saturated = model has all parameters estimated. Equal variance MZ-DZ = variance between MZ and DZ is constrained to be equal. ADE = model contains (A)dditive genetic, (D)ominance genetic and unique (E)nvironmental parameters with male and female estimates allowed to differ. ADE no sex = model contains ADE but male and female estimates are constrained to be equal. AE = model contains only A and E. AE no sex = model contains only AE but male and female estimates are constrained to be equal. Boldface type indicates best fitting model. Δ *df*, Δchi^2, and Δ AIC are calculated as the difference between the model being examined and the model to which it is being compared.

CBCL, Child Behavior Checklist; AD, attention problems; MZ, monozygotic; DZ, dizygotic.

Model Fitting

Table 5A summarizes the model fitting results for the CBCL-AP phenotype. An ADE model (either with or without sex differences, depending on the age at which the sample was taken) fits these data best as has been seen elsewhere (Rietveld et al 2003a). Model fitting results for CBCL-JBD are presented in

Table 5B. Model Fitting, CBCL-JBD

Model Type	−2 log Likelihood	Number of Estimated Parameters	Compared to Model	Δ *df*	Δ chi^2	Δ AIC	*p*
7 Year Old							
1. Fully saturated	34700.602	30	—	—	—		—
2. Equal variance MZ-DZ	34705.902	26	1	4	5.3	−2.7	.2578
3. ACE	34716.559	18	1	12	15.957	−8.043	.1932
4. ACE no sex	34722.680	15	3	3	6.290	.121	.179
5. AE, no sex	34836.271	14	4	1	113.591	111.591	.000
6. CE, no sex	35406.479	14	4	1	683.799	681.799	.000
10 Year Old							
1. Fully saturated	23294.670	30	—	—	—		—
2. Equal variance MZ-DZ	23297.182	26	1	4	2.512	−5.488	.642
3. ACE	23305.530	18	1	12	10.86	−13.14	.541
4. ACE no sex	23313.664	15	3	3	8.134	2.134	.043
5. AE	23352.530	16	3	2	47	43	.000
6. CE	23753.595	16	3	2	448.065	444.065	.000
12 Year Old							
1. Fully saturated	12969.670	30	—	—	—	—	—
2. Equal variance MZ-DZ	12970.644	26	1	4	.974	−7.026	.9137
3. ACE	12978.831	18	1	12	9.161	−14.839	.6891
4. ACE no sex	12995.812	15	3	3	16.981	10.981	.0007
5. AE	13010.405	16	3	2	31.574	27.574	.000
6. CE	13231.688	16	3	2	252.857	248.857	.000

AIC, Akaike Information Criterion = −2 log likelihood + 2*number of estimated parameters. Fully saturated = model has all parameters estimated. Equal variance MZ-DZ = variance between MZ and DZ is constrained to be equal. ADE = model contains (A)dditive genetic, (C)ommon environmental and unique (E)nvironmental parameters with male and female estimates allowed to differ. ACE no sex = model contains ACE but male and female estimates are constrained to be equal. AE = model contains only A and E. AE no sex = model contains only AE but male and female estimates are constrained to be equal. Boldface type indicates best fitting model. Δ *df*, Δ chi^2, and Δ AIC are calculated as the difference between the model being examined and the model to which it is being compared.

CBCL, Child Behavior Checklist; JBD, juvenile bipolar disorder; MZ, monozygotic; DZ, dizygetic.

Table 5B. An ACE model (either with or without sex differences , depending on the age at which the sample was taken) fit these data best. There were sex differences at ages 10 and 12, but these were not seen at age 7, nor were they extreme at the older ages. Model estimates are given in Tables 6A and 6B. The magnitude of the C contribution in the CBCL-JBD phenotype ranges from 18 to 30%, with the higher estimates in girls, especially at age 12.

Conclusions

Although this study did not diagnostically evaluate children for JBD, our use of the CBCL-JBD phenotype sheds light on the prevalence and genetic architecture of JBD given the replicated statistical association between it and JBD (Mick et al 2003). Our results show that this complex phenotype is relatively common in the general population (1%) and quite common among children with ADHD (20%), with the latter risk being consistent with what others have reported regarding the risk for JBD among ADHD children (Biederman et al 1996). Further, these data provide evidence for different genetic and environmental contributions to the manifestation of each condition.

The findings that 20% of the children with CBCL-AP also meet the criteria for CBCL-JBD may help explain why rates of the complex phenotype are reported to be so much higher in ADHD clinics than in general pediatric settings. We found that CBCL-AP is influenced by genetic factors that are both dominant and additive, while the CBCL-JBD phenotype is influenced by additive genetic and shared environmental factors. The different genetic architecture suggests CBCL-JBD is not an extreme version of CBCL-AP, although the difference between the two models may be a difference of degree. In the classical twin study of MZ and DZ twins either the effects of genetic dominance or the effects of common family environment may be estimated. To test if both effects are present additional data from other groups, e.g. unrelated siblings, are required. Our finding is consistent with reports by Faraone et al (1997; 1998; 2001; 2003) suggesting that the DSM-defined phenotypes of ADHD and bipolar disorder with comorbid ADHD are genetically distinct disorders.

Our finding of a shared environmental contribution to the expression of the CBCL-JBD phenotype is novel and has both clinical and research implications. Prior work has shown the transmission of bipolar disorder to be accounted for by genes or unique environment. Although a significant genetic component is seen in our data, the finding of a shared environmental component, especially in the young, suggests a possibility of a moderating factor in the expression of this extreme phenotype. More research into characterizing this component is warranted to better understand its nature and to determine if modifications of the shared environment could one day help prevent or treat JBD.

Table 6A. Model Estimates, CBCL-AP

		Male		Female	
Age	Source of Variance	Standardized Estimate	95 % CI	Standardized Estimate	95 % CI
7	A	.60	.55–.64	.60	.55–.64
	D	.14	.09–.17	.14	.09–.17
	E	.27	.25–.29	.27	.25–.29
10	A	.60	.52–.68	.60	.52–.68
	D	.12	.06–.21	.12	.06–.20
	E	.27	.24–.31	.28	.25–.31
12	A	.61	.50–.70	.54	.42–.66
	D	.09	.02–.19	.18	.07–.30
	E	.30	.26–.35	.28	.24–.32

CBCL, Child Behavior Checklist; AP, attention problems.

Table 6B. Model Estimates, CBCL-JBD

		Male		Female	
Age	Source of Variance	Standardized Estimate	95 % CI	Standardized Estimate	95 % CI
7	A	.59	.56–.64	.59	.56–.64
	C	.27	.22–.31	.27	.22–.31
	E	.15	.14–.16	.15	.14–.16
10	A	.68	.58–.75	.57	.47–.68
	C	.18	.11–.27	.26	.16–.36
	E	.14	.13–.16	.17	.15–.19
12	A	.66	.55–.75	.54	.42–.67
	C	.18	.10–.29	.30	.17–.42
	E	.15	.13–.18	.15	.13–.18

CBCL, Child Behavior Checklist; JBD, juvenile bipolar disorder.

Limitations

We did not directly interview the parents or children in this study and therefore cannot present data on the number of children who would meet criteria for DSM-IV bipolar affective disorder.

Data in this report are limited to children up to the age of 12. Since the expression of bipolar affective disorder is often in late adolescence or early adulthood, these data and the estimates of heritability resulting would apply best to childhood bipolar disorder. We aim to assess these samples at ages 14-16.

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