ORIGINAL ARTICLES

Latent Class Analysis Shows Strong Heritability of the Child Behavior Checklist–Juvenile Bipolar Phenotype

Robert R. Althoff, David C. Rettew, Stephen V. Faraone, Dorret I. Boomsma, and James J. Hudziak

Background: *The Child Behavior Checklist (CBCL) has been used to provide a quantitative description of childhood bipolar disorder (BPAD). Many have reported that children in the clinical range on the Attention Problems (AP), Aggressive Behavior (AGG), and Anxious-Depressed (A/D) syndromes simultaneously are more likely to meet the criteria for childhood BPAD. The purpose of this study was to determine if Latent Class Analysis (LCA) could identify heritable phenotypes representing the CBCL-Juvenile Bipolar (CBCL-JBD) profile and whether this phenotype demonstrates increased frequency of suicidal endorsement.*

Methods: *The CBCL data were received by survey of mothers of twins in two large twin samples, the Netherlands Twin Registry. The setting for the study was the general community twin sample. Participants included 6246 10-year-old Dutch twins from the Netherlands Twin Registry. The main outcome measure consisted of the LCA on the items comprising the AP, AGG, and A/D subscales and means from the suicidal items #18 and #91 within classes.*

Results: *A 7 class model fit best for girls and an 8 class fit best for boys. The most common class for boys or girls was one with no symptoms. The CBCL-JBD phenotype was the least common—about 4%–5% of the boys and girls. This class was the only one that had significant elevations on the suicidal items of the CBCL. Gender differences were present across latent classes with girls showing no aggression without the CBCL-JBD phenotype and rarely showing attention problems in isolation. Evidence of high heritability of these latent classes was found with odds ratios.*

Conclusions: *In a general population sample, LCA identifies a CBCL-JBD phenotype latent class that is associated with high rates of suicidality, is highly heritable, and speaks to the comorbidity between attention problems, aggressive behavior, and anxious/depression in children.*

Key Words: ADHD, bipolar disorder, Latent Class Analysis

The phenotype of children with attention-deficit/hyperactivity disorder (ADHD) comorbid with juvenile bipolar disorder (JBD) has been a source of considerable study and debate over the past decade (Leibenluft et al 2003). The general description of this group of children includes prominent ADHD symptoms coupled with aggression, out of control behavior, and affective instability. Beginning with Biederman et al (1995), many groups have described a profile on the Child Behavior Checklist (CBCL) (Achenbach 1991) that occurs in children with JBD that is discrete from children with ADHD alone (Biederman et al 1995; Carlson and Kelly 1998; Dienes et al 2002; Geller et al 1998; Hazell et al 1999; Wals et al 2001). The CBCL profile includes elevation on the Attention Problems (AP), Aggressive Behavior (AGG), and Anxious/Depressed (A/D) syndromes. In contrast, ADHD children without bipolar disorder show elevations on the AP syndrome alone. The CBCL-JBD phenotype has shown consistent associations with the diagnosis of bipolar disorder across samples, across countries, and across methodologies. Mick et al's 2003 meta-analysis of the CBCL studies found considerable agreement between research sites indicating that bipolar children are characterized by problems with aggression, mixed mania with depression, and ADHD symptomatology (Mick et al 2003).

Building on these findings, we have demonstrated that this phenotype is highly heritable (Hudziak et al 2005). With CBCL data for 5418, 3562, and 1971 Dutch mono- and dizygotic twin pairs at ages 7, 10, and 12 years, we investigated the prevalence of and the genetic and environmental contributions to the CBCL-JBD phenotype and compared these results with those for CBCL-Attention Problems (CBCL-AP). With a cutpoint of T-scores on AP, AGG, and A/D all > 70, we found that the CBCL-JBD phenotype occurs in approximately 1% of children at all ages sampled. Among the children who met criteria for the CBCL-AP phenotype, 13%–20% also met criteria for the CBCL-JBD phenotype. With structural equation models, the variance in the CBCL-JBD phenotype was explained by a model that includes additive genetic, and shared and unique environmental factors: a profile different from the model for CBCL-AP, which showed dominant genetic, additive genetic, and unique environmental factors. These findings suggest that the CBCL-JBD phenotype is different genetically from the CBCL-AP phenotype and that further refinement of this phenotype might improve gene-finding explorations. Using a cutpoint approach, however, has the disadvantage of not including children who might have a score that is subthreshold on one of these subscales but generally have an item response profile that is very close to the CBCL-JBD phenotype. Here, we investigate a strategy for phenotypic refinement with Latent Class Analysis (LCA).

Latent Class Analysis allows the investigator to test empirically for the existence of discrete groups who endorse similar patterns of symptoms (Hudziak et al 1998). Using this strategy, distinct classes of responding with regard to ADHD symptoms (Hudziak et al 1998; Neuman et al 1999, 2001; Rasmussen et al 2002a, 2002b, 2004; Rohde et al 2001; Todd et al 2001), the CBCL subscales of anxious/depression (Wadsworth et al 2001), AP (Hudziak et al 1999), Aggression (van Lier et al 2003), as well as ADHD with the Conners' Parent and Teacher forms (Althoff et al, submitted) have been identified. Furthermore, our group and

From the Department of Psychiatry (RRA), Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts; Department of Psychiatry (DCR, JJH), University of Vermont, Burlington, Vermont; Medical Genetics Research Program and Department of Psychiatry and Behavioral Sciences (SVF), State University of New York Upstate Medical University, Syracuse, New York; and The Free University (DIB), Amsterdam, The Netherlands.

Address reprint requests to James J. Hudziak, M.D., University of Vermont, Division of Behavioral Genetics, Department of Psychiatry, Given Building, B229, 1 South Prospect Street, Burlington, VT 05405; E-mail: james.hudziak@uvm.edu.

Received May 16, 2005; revised February 8; accepted February 10, 2006.

0006-3223/06/$32.00
doi:10.1016/j.biopsych.2006.02.025

others have shown that heritability within latent classes are higher than across latent classes, suggesting their utility for phenotypic refinement in ADHD (Neuman et al 1999; Rasmussen et al 2004). Todd et al (2003) extended this work, showing that they could use LCA to uncover an association between a single nucleotide polymorphism in the nicotinic acetylcholine receptor α subunit gene and the inattentive latent class of ADHD. We hope to begin a similar enterprise by first identifying a CBCL-JBD phenotype with LCA and show that heritability within a latent class is stronger than across latent classes.

One argument against the use of proxies such as the CBCL-JBD phenotype has been the lack of impairment information that is necessary for a diagnosis in the current DSM-oriented nosology (American Psychiatric Association 1994). Given that JBD has been shown to be a risk factor for suicidality (Brent et al 1988) and that suicidality is one of the most extreme examples of impairment in childhood psychopathology, we also investigated the prevalence of suicidal ideation as indicated on the CBCL.

Methods and Materials

Participants and Procedure

The data of the present study are derived from a large ongoing longitudinal study that examines the genetic and environmental influences on the development of problem behavior in families with 3–12-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 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 mother report for 10-year-old twin pairs. Mothers of twins were asked to fill out questionnaires about problem behavior for the eldest and youngest twin at age 10 years. After 2 months a reminder was sent to the non-responders, and after 4 months those who still did not respond were telephoned. The continued participation rate for the Netherlands Twin Registry is 80%. This study was approved by the institutional review boards of both the Free University, Amsterdam, and the University of Vermont.

For 822 same gender 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 completed 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 on the basis of blood/DNA typing in a group of same-gender 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 participants, broken down by zygosity. An earlier comparison of the parental socioeconomic status distribution with those obtained for the general Dutch population showed a slightly higher frequency of the middle and higher socioeconomic status groups (for details see Rietveld et al 2003). Attrition rates as well as a detailed discussion on the representativeness of the sample at each age are discussed in detail elsewhere (van Beijsterveldt et al 2003).

Table 1. Sample Composition and Breakdown by Zygosity

Twin Type	Number of Participants (Number Missing)
MZ Boys	1214 (176)
DZ Boys	1096 (138)
MZ Girls	1476 (162)
DZ Girls	1090 (136)
DOS M_F	1184 (132)
DOS F_M	1064 (134)
TOTAL	7124 (878)

MZ, monozygotic; DZ, dizygotic; DOS M_F, dizygotic opposite gender male eldest; DOS F_M, dizygotic opposite gender female eldest.

Measures

Problem behavior was measured with the CBCL/4–18 (Achenbach 1991), a questionnaire of 118 items developed to measure problem behavior in 4–18-year-old children. Parents were asked to rate the behavior of the child for the preceding 6 months on a three-point scale.

For the CBCL/4–18, eight syndrome scales were composed according to the 1991 profile (Achenbach 1991) that has been normed specifically for the Dutch (Achenbach et al 1987; Verhulst et al 1988). We specifically used the 44 items from the AP, AGG, and A/D subscales. Because items on the CBCL are listed on a Likert scale from 0 to 2, items from the AP, AGG, and A/D subscales were first truncated to create dichotomous variables with either 1 ("somewhat true") or 2 ("often true") considered as positive responses and 0 ("not true") considered as a negative response.

Twin pairs where one twin had missing items on one or more of these subscales were not included in the analysis. The numbers of excluded participants by zygosity is listed in Table 1.

LCA

Latent Class Analysis is a form of categorical data analysis that hypothesizes that it is possible to account for the observed symptom (or item) endorsement profiles of respondents in terms of some small number of mutually exclusive respondent classes (M), with each class having its own set of symptom endorsement probabilities. Latent Class Analysis presupposes the existence of discrete latent categories or classes, distinguishing it from factor analysis, which assumes continuous latent variables are present. Local independence is assumed (i.e., under an M-class solution, the conditional probabilities of endorsing a set of items are statistically independent for a given class) (Goodman 1974). If the underlying latent variable is continuous rather than categorical, then the LCA-derived classes will reflect differences in severity, whereas discrete classes of responding will emerge from the analysis if the underlying latent structure is categorical. The parameter estimates that result from LCA are: 1) probabilities of class membership assignment for individuals, and (2) symptom endorsement probabilities for each class.

Latent class models were fitted by means of an Expectation Maximization (EM) algorithm (Dempster et al 1977), with the program Latent Gold (Vermunt and Magidson 2000). Models estimating 1-class through 10-class solutions were compared. To calculate the best fitting model, we first ensured goodness of fit with the bootstrapping algorithm built into Latent Gold—a step that is essential when dealing with sparse data matrices such as these—and then compared the change in the Bayesian Information Criterion (BIC) when moving from an M to an M + 1 class solution. The BIC is a goodness-of-fit index that considers the rule of parsimony, because other log-likelihood–based estimates are biased in an analytic environment with large samples and sparse data matrices, although other indices such as the Consistent Akaike Information Criterion (CAIC) were also examined.

Because we and others have shown differences in latent class structure by gender for ADHD (Hudziak et al 1998; Rasmussen et al 2002a) and because we showed a gender effect in the genetic model for the CBCL-JBD phenotype, LCA was performed separately for boys and girls. Once the most parsimonious class solution was determined, these classes were named on the basis of their response profiles. It is important to note that these names are subjective and, although we believe them to represent the information contained in the classes, we present the classes of items and their graphs in the results for the interpretation of the reader. Once each individual had been assigned to a unique latent class, we computed odds ratios by gender and zygosity for all comparisons between classes by looking at the probability of being in a particular class for one twin given that the co-twin was in the class (versus the probability of being placed into any of the other classes). We also computed intraclass correlations (ICCs) with the Reliability module of SPSS (Chicago, Illinois). We entered into this analysis the probability of class membership for each twin pair. The ICCs allow for the rough estimation of heritability with the formula 2(rMZ−rDZ), where rMZ is the ICC between monozygotic (MZ) twins and rDZ is the ICC between dizygotic (DZ) twins.

Finally, we computed the average scores and proportion of children endorsing CBCL items #18 (“deliberately harms self or attempts suicide”) and #91 (“talks about killing self”) as an indication of the amount of suicidal thought or behavior present in each of the classes. These items do not appear in any of the subscales being examined in the LCA but are coded on the “Other Problems” section of the CBCL. Average score on the suicidal items alone and in combination was compared between classes with the General Linear Modeling subroutine of SPSS. A univariate model was computed with the score on the suicidal items as the dependent variable and latent class assignment as the fixed variable. Analyses were run separately for boys and girls, owing to their different class structure (see Results). Difference contrasts were performed to compare the mean score on this item across all pairings of the classes, and the p value was corrected for multiple comparisons with a Bonferroni correction with corrected significance level set at $p = .05$.

Results

LCA Results

As the number of classes increased, improvements were made in the goodness of fit, as evidenced by a decrease in the BIC. Additional classes failed to result in meaningful, more parsimonious solutions at the point of an 8 class solution for boys and a 7 class solution for girls.

The class solution information, including prevalence of assignment of individuals to each class, are presented in Table 2 and are presented graphically in Figures 1A–1H. Table 2 gives the number of the latent class, the name of the latent class that we assigned on the basis of the profile (see following), the proportion of the sample that falls into each latent class, the proportion of the members in each class who answered positively on the suicidal items, and the overall average score on that item within each class. Figure 1 shows the probability of item endorsement plotted versus item number. Figure 1 is divided into AP items (far left), AGG items without violence next, AGG items with violence (e.g., fights, attacks people) as the third section, and A/D item in the rightmost column.

Table 2. Latent Class Membership and Suicidality Probabilities

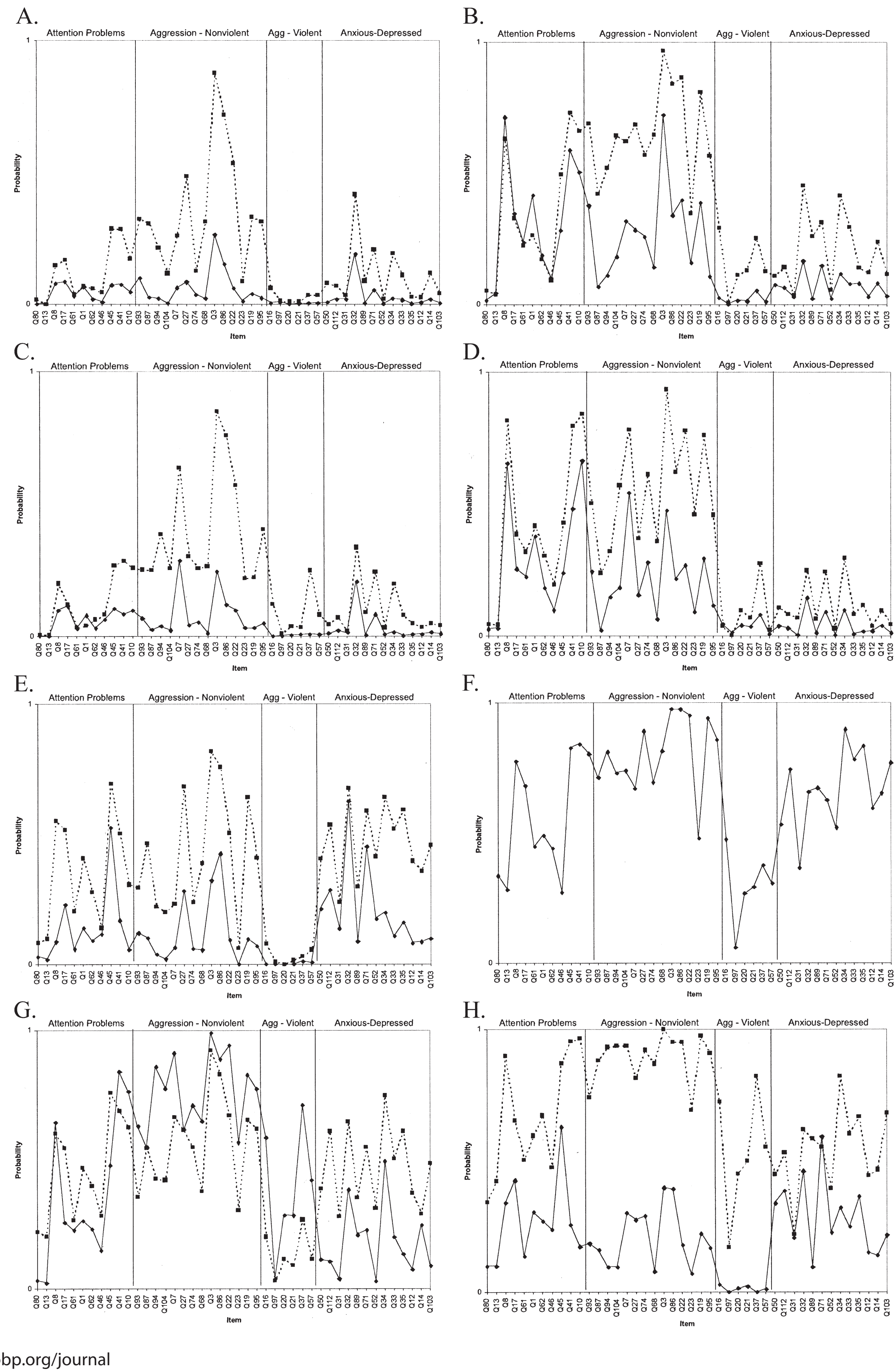
Class	Class Name	Probability of Class Membership	Probability Suicidal[a]
Female			
1	No Symptoms	.32	.01
2	Aggressive Without Violence	.19	.02
3	Aggressive With Attention Problems	.14	.02
4	Attention Problems and Aggressive With Mild Anxious/Depression	.12	.03
5	Anxious/Depressed	.10	.02
6	Attention Problems and Aggressive With Moderate Anxious/Depression	.09	.03
7	CBCL-Bipolar	.04	.17
Male			
1	No Symptoms	.25	.01
2	Aggressive Without Violence	.18	.03
3	Attention Problems	.14	.01
4	Aggressive Without Violence With Attention Problems	.13	.02
5	Aggressive With Violence With Attention Problems	.11	.05
6	Aggressive Without Violence With Attention Problems and Anxious/Depression	.07	.10
7	Attention Problems and Anxious/Depression	.07	.03
8	CBCL-Bipolar	.05	.22

CBCL, Child Behavior Checklist.
[a]Probability suicidal = score of 1 or 2 on Item #18 or Item #91.

We chose names for these classes on the basis of the pattern of symptom endorsement within the response profile and the apparent “strength” of the symptom endorsement. As would be predicted, the majority of 10-year-old children, both boys and girls, were assigned to a class in which very few items were endorsed. Additionally, a profile that resembles the CBCL-JBD phenotype emerged in both boys (Class 8) and girls (Class 7), was remarkably similar in its appearance, and was the least common in either boys (5%) or girls (4%). The other classes, which have not had the benefit of being given discrete names in the past, represent a combination of elevations on the three subscales.

For girls, there was an aggressive (without violence) class and an anxious-depressed class, but a specific attention problems class without elevations on AGG or A/D items did not emerge from the analysis. Next, there were three classes that seemed to be a continuum of AP and AGG with no (Class 3), mild (Class 4), or moderate (Class 6) endorsement of the anxious-depressed items. This would suggest that there is a continuum in the distribution of the CBCL-JBD phenotype in girls; however, neither of these classes showed high endorsement for the violence items. Thus, for girls there were no classes with the exception of the CBCL-JBD class that showed high item endorsement probabilities on the AGG with violence items.

The class solutions were different in the boys. Here, there was an isolated attention problems class (Class 3) that emerged with relatively little endorsement of aggression items. Aggression was more prominently endorsed, consistent with the norms for the


A.
B.
C.
D.
E.
F.
G.
H.
Attention Problems
Aggression - Nonviolent
Agg - Violent
Anxious-Depressed
Probability
1
0
Item
Q80 Q13 Q8 Q17 Q61 Q1 Q62 Q46 Q45 Q41 Q10 Q93 Q87 Q94 Q104 Q7 Q27 Q74 Q68 Q3 Q86 Q22 Q23 Q19 Q95 Q16 Q97 Q20 Q21 Q37 Q57 Q50 Q112 Q31 Q32 Q89 Q71 Q52 Q34 Q33 Q35 Q12 Q14 Q103

CBCL showing that boys have a higher "base-rate" of aggression than girls. Anxious/Depressed items did not appear in isolation for boys, instead only being endorsed in children who had either endorsement of AP items (Class 7) or AP and AGG items (Class 6 and the CBCL-JBD phenotype, Class 8). Also, AGG with violence was not only present in the CBCL-JBD phenotype but appeared with attention problems in the relative absence of A/D item endorsement (Class 5), and the violent "gets into fights" item #37 is elevated more frequently than in girls.

Comparing Class Assignment Across Twins

The odds ratios of class assignment across gender and zygosity are presented in Table 3. Here, the within-class agreement is represented on the diagonal, whereas the across-class agreement is on the off-diagonal. What can be seen generally is the much higher likelihood of having a co-twin placed into the same latent class than into a different latent class for all of the individual classes for MZ twins and all but one for DZ twins. Comparing monozygotic with dizygotic odd ratios, it is evident that there is a much higher likelihood of twins being placed into the same CBCL-JBD class for monozygotic than dizygotic twins, most prominently in boys. In fact, for boys, the odds ratio of agreement between being in the CBCL-JBD class was more than 15 times higher for MZ twins than for DZ twins. The ICCs are shown in Table 4. What can be seen is that across all classes, there are higher correlations for MZ than DZ twins—often more than twice the difference—suggesting that genetic dominance might play a role in the expression of these subscales, as we have shown in attention problems (Rietveld et al 2004). Specifically, estimating heritability for the CBCL-JBD class showed that for girls the estimate is approximately .53 and for boys approximately .87 in these age-10 twins. This is lower for girls and higher for boys than we have seen with the CBCL-JBD measure as a continuous variable. Such findings argue strongly that the CBCL-JBD class is highly heritable and independent of the other latent classes that emerged in these analyses.

Comparing Suicidal Behavior Across Latent Classes

The proportion of mother's endorsing either of the suicidal items for her children and the comparison between groups is shown in Table 2. As is readily seen, the most frequent and strongest endorsement of this item occurred in the CBCL-JBD classes for both boys and girls—occurring 25–36 times more commonly in the CBCL-JBD class than in the No Symptoms class. In fact, although the CBCL-JBD item accounts for only 4%–5% of the total sample, these children account for 20%–25% of the endorsement of suicidal behavior in the population. Looking at the Bonferroni-corrected contrasts between classes on the average score on these items, it is only the CBCL-JBD class that is significantly different from any other at the $p = .05$ level for girls, and only the CBCL-JBD class, the Aggressive without violence with AP, and Anxious/Depression class were significantly different from the others in boys. The score on the suicidal items was significantly higher between the CBCL-JBD class and all other classes in boys and girls.

Discussion

The data presented here support the idea that the CBCL-JBD phenotype is a consistent, replicable, and heritable phenotype that might have been under-represented in studies using a T-score cutpoint approach to identifying the phenotype. With an LCA approach, 4% of girls and 5% of boys were consistent with this phenotype, whereas a previous report from the same sample using a T-score approach identified only about 1% of boys or girls with the phenotype (Hudziak et al 2005). The T-score–identified percentages are more in-line with the general-population epidemiological estimates of youth bipolar disorder that have been performed in America (Lewinsohn et al 2000). All of the individuals identified with this T-score approach were placed into the CBCL-JBD latent class. Further investigation showed that those participants who fell into the CBCL-JBD latent class who did not meet the T-score criteria were only subtly sub-syndromal on one or more of the subscales. Thus LCA was able to identify individuals who would not have been captured with a cutpoint approach, likely because it is sensitive to the overall pattern of the responses rather than depending on a categorical T-score cutoff for placing an individual into a class.

The high prevalence of children showing symptoms of violent aggression with mood dysregulation highlights the differential diagnostic problem faced by clinicians. Although many of these children might have bipolar disorder, the majority will not, despite showing some psychopathology consistent with the disorder. The existence of a broad spectrum of mood-dysregulated aggression emphasizes the need for clinicians to attend carefully to all bipolar diagnostic criteria when considering this diagnosis for aggressive, mood-dysregulated children.

We found different patterns of latent classes in boys and girls. In girls, at least at age 10, there is almost no aggression with violence that occurs in the absence of the CBCL-JBD phenotype. This suggests that there might be some discriminating power in looking at these particular items in the CBCL, but this remains to be seen empirically. This might change as the girls age, as aggression becomes more common in both genders postpubertally. In girls, there also seems to be a continuum of the expression of anxious/depression in its association with high attention problems and aggression. Of note, there is no isolated attention problems latent class that emerges in the analysis, suggesting that the distribution of attention problems in the general population, if not in the clinical population, is most often in co-occurrence with other dimensions of psychopathology (Spencer et al 1999).

In boys, the story changes slightly. Anxious/depression items here seem to be less of a continuum and never occur in isolation. The CBCL-JBD phenotype seems to be slightly more continuously represented in boys, with classes 5, 6, and 8 all seeming to represent elevations on similar symptom domains. These differences in the latent structure of these symptoms might in part explain why genetic modeling of the phenotype shows some gender-specific genetic effects (Hudziak et al 2005). The identification of aggression with violence in boys outside of the

Figure 1. (A) Girl: No Symptoms (solid) and Aggressive without violence (dashed) classes. **(B)** Girl: Aggressive with Attention Problems (solid) and Attention Problems and Aggressive with Mild Anxious/Depression (dashed) classes. **(C)** Boy: No Symptoms (solid) and Aggressive without violence (dashed) classes. **(D)** Boy: Attention Problems (solid) and Aggressive without violence with Attention Problems (dashed) classes. **(E)** Girl: Anxious/Depressed (solid) and Attention Problems and Aggressive with Moderate Anxious/Depression (dashed) classes. **(F)** Girl: CBCL-Bipolar class. **(G)** Boy: Aggressive with violence with Attention Problems (solid) and Aggressive without violence with Attention Problems and Anxious/Depression (dashed) classes. **(H)** Boy: Attention Problems and Anxious/Depression (solid) and CBCL-Bipolar (dashed) classes.

Table 3. Odds Ratios Across Latent Classes Between MZ and DZ Twins With 95% Confidence Intervals

Class Twin 1	Class Twin 2: 1	2	3	4	5	6	7	8
MZ Boys								
1	37.39 (21.09–66.28)	.21 (.09–.46)	.39 (.16–.93)			.09 (.01–.67)		
2	.37 (.2–.69)	10.83 (6.43–18.24)	.24 (.07–.78)					
3			18.03 (9.32–34.88)		.08 (.01–.61)			
4				14.35 (7.73–26.64)		2.7 (1.19–6.11)		
5					37.2 (18.91–73.2)			
6						13.59 (5.64–32.74)		
7							7.89 (3.13–19.9)	
8								148.85 (42.82–517.44)
DZ Boys								
1	4.66 (2.93–7.42)		1.83 (1.01–3.33)	.43 (.19–.99)	.18 (.05–.59)	.28 (.1–.79)		
2		2.29 (1.32–3.97)						
3			1.99 (1–3.96)		.23 (.06–.99)			
4				2.63 (1.27–5.41)				
5	.11 (.03–.48)				9.63 (4.76–19.5)	2.67 (1.19–6)		3.18 (1.1–9.22)
6								
7						2.65 (1.02–6.92)		
8								9.71 (3.1–30.49)
MZ Girls								
1	33.6 (20.88–54.08)	.18 (.09–.34)	.31 (.16–.6)		.39 (.18–.83)	.09 (.02–.38)		
2	.33 (.2–.56)	9.26 (5.88–14.57)	.29 (.12–.69)	.43 (.19–.97)				
3	.31 (.17–.58)		12.6 (7.42–21.39)	.24 (.07–.79)				
4	.02 (0–.12)			31.32 (17.12–57.31)				
5			.22 (.05–.92)		11.1 (5.82–21.2)			
6	.09 (.03–.3)					10.23 (5.33–19.65)		
7							67.15 (25.44–177.28)	
DZ Girls								
1	12.47 (7.73–20.12)	.35 (.19–.66)	.5 (.26–.98)	.04 (.01–.3)		.24 (.08–.68)	.09 (.01–.71)	
2	.27 (.14–.51)	2.12 (1.24–3.63)						
3					2.5 (1.15–5.45)			
4	.16 (.06–.45)			3.62 (1.76–7.45)				
5	.47 (.22–1)	1.99 (1.01–3.93)						
6	.27 (.12–.62)					3.2 (1.49–6.87)		
7							15.3 (4.91–47.62)	

Empty cells indicate that the confidence interval crossed 1 and thus was not significant. There are no odds ratios (ORs) for class 6 for dizygotic (DZ) boys, because all confidence intervals crossed 1. Odds ratios here were calculated with the equation $(a \times d)/(b \times c)$ where a = number of twins where both in class, b = number of where twin 1 in class but co-twin not in class, c = number where twin 2 in class, but co-twin not in class, and d = number where neither twin in class. These ORs are not symmetrical for twin 1→ twin 2 and twin 2 → twin 1 because there are slightly different proportions of the sample placed into a given class. Odds ratios of 1 demonstrate no association between two classes. MZ, monozygotic.

Table 4. Intraclass Correlations Between MZ and DZ Twins

Class Twin 1	Class Twin 2: 1	2	3	4	5	6	7	8
				MZ Boys				
1	.698	−.191	−.100	−.280	−.256	−.195	−.069	−.183
2	−.162	.496	−.090	−.044	−.106	−.094	−.057	−.161
3	−.047	−.060	.551	−.078	−.178	−.061	−.089	−.114
4	−.302	−.018	−.053	.552	−.059	.064	−.077	−.104
5	−.113	−.096	−.179	−.025	.666	−.021	−.110	.053
6	−.197	−.113	−.105	.068	−.040	.390	.011	.002
7	−.101	−.051	.035	−.071	−.094	−.039	.347	−.071
8	−.197	−.159	−.119	−.114	.045	−.005	−.061	.669
				DZ Boys				
1	.372	−.078	.078	−.147	−.193	−.146	−.143	−.181
2	−.109	.128	−.048	.084	−.058	−.054	−.005	−.078
3	.082	.017	.102	−.088	−.132	−.089	.032	−.089
4	−.142	.016	.010	.114	.037	−.018	.051	−.083
5	.007	−.108	−.148	.038	.353	.128	−.063	.118
6	−.161	.007	−.069	.069	.029	.052	−.034	.071
7	−.098	−.033	.024	−.054	−.028	.094	.031	−.039
8	−.177	−.096	−.110	−.055	.034	.056	.035	.236
				MZ Girls				
1	.742	−.274	−.209	−.293	−.145	−.237	−.228	
2	−.228	.527	−.072	−.106	−.066	−.024	−.149	
3	−.226	−.017	.545	−.100	−.070	−.040	−.133	
4	−.340	−.045	−.041	.615	−.115	−.036	.034	
5	−.023	−.098	−.124	−.121	.447	−.030	−.103	
6	−.269	−.023	−.013	−.074	.073	.359	.051	
7	−.245	−.173	−.101	.061	−.095	.000	.574	
				DZ Girls				
1	.559	−.165	−.132	−.273	−.119	−.211	−.217	
2	−.226	.140	.064	.078	−.079	.067	−.125	
3	−.067	−.011	.022	−.061	.092	−.007	−.039	
4	−.252	.026	.026	.224	−.060	.005	.070	
5	−.032	.046	.053	.020	.044	−.056	−.057	
6	−.217	−.032	.021	.032	.055	.139	.051	
7	−.233	−.105	−.124	.028	−.031	.011	.311	

MZ, monozygotic; DZ, dizygotic.

CBCL-JBD is consistent with findings of the higher incidence of elevated AGG scores and of DSM-IV conduct disorder in boys in the general population (Bartels et al 2003).

One argument that has been made concerning the use of the CBCL as a proxy for DSM and other clinical diagnoses has been that there is no evidence of impairment in the proxy scores. This certainly is the case in the proxy used here, although we have shown that this proxy score has a significantly higher likelihood of endorsement of self-harm or suicide attempts—much higher than aggression, anxious/depression, or attention problems in isolation. Given the recent concern about suicidal behavior in children (Whittington et al 2004) and concerns about an increased incidence in aggression and suicidal behavior in children with emergent mania or mixed states, this raises issues about how much of the apparent increase with selective serotonin reuptake inhibitors might be secondary to the presence of these children outside of clinical trials, because they might be sub-syndromal using DSM-IV Conduct Disorder, ADHD, oppositional defiance disorder, or bipolar disorder criteria but might fall into this latent class that has almost 3%–5% of children with some self-harm behavior. Even this number might be falsely low. When we dichotomized the item responses for use in the LCA, we included both "sometimes" and "often" responses as being positive. Thus, we include some children in this phenotype who do not meet the T-score criterion. When looking at only the children who meet the T-score cutpoint of 70, the percentage of these children that are positive on the suicidal items is even higher—about 38% of boys and 24% of girls. It is also useful to note that LCA clearly identifies more children than would be identified with purely a cutpoint approach. Of the twins identified with a cutpoint of either T-score > 65 or > 70, every one of them were classified into the CBCL-JBD latent class for either boys or girls. As a screening tool, the CBCL-JBD phenotype can likely be used with a cutpoint approach, and we have shown that it classifies children with JBD well (Faraone et al 2005).

The heritability within the latent class phenotype demonstrates the power of this approach. As discussed previously, Todd et al (2003) have been using a similar latent class approach for attentional problems and have been able to identify novel genotypic targets for the severe inattentive phenotype of ADHD. Because genotyping studies have shown a multitude of candidate genes for the phenotype and no single gene with large contributions (Althoff et al 2005), it is our hope that by using the CBCL we might be able to identify novel targets with a large genome scanning strategy. Moreover, we have shown that there are both unique and common (or shared) environmental factors in the expression of this phenotype (Althoff et al 2005). The shared environmental contribution is of particular interest, because there are relatively few psychiatric phenotypes that show a significant shared environmental component. Large epidemiological studies have the advantage of sampling a wide range of shared environments. Because much is known about the environments in which these twins were raised, it is possible to investigate the contributions of multiple combinations of environmental factors to examine how to explain this component, even taking into account issues such as population stratification (Boomsma et al 2002). Identification of more twins with this heritable phenotype allows for more opportunity to investigate the role of the environment and gene × environment interactions and correlations. This provides the tantalizing prospect of not only uncovering certain risks for the disorder but also identifying areas of intervention to decrease the later expression of the phenotype.

Molecular genetic studies of early-onset bipolarity are just beginning to yield results, and all findings require substantial replication. Early-onset forms of disease should produce stronger genetic "signals" in linkage and association studies, owing to reduced genetic heterogeneity, greater penetrance of risk alleles, or both. Such cases might also have a higher genetic loading of risk alleles (i.e., they possess a greater number of the critical alleles of risk genes), facilitating detection of one or more risk genes out of the many that might exist. The studies to date suggest that there is likely a similar or possibly lower heritability in the early-onset form of the bipolar illness, making this possibility less clear for bipolar disorder; however, by definition, these studies also demonstrate a higher shared and unique environmental component. If these components can be formally characterized, the search for gene × environment interactions might be more fruitful in the early-onset form of the disorder.

Finally, these data also suggest the presence of other potentially important classes of children that have yet to be studied as a group. Although the CBCL-JBD group might warrant particular attention given its association with suicidal behavior, further exploration into the other classes identified might similarly yield clearer results in future research than might be obtained by studying patterns of symptoms that do not seem to cluster together in the population.

Data in this report are limited to maternal reports of children at age 10. Because the expression of bipolar affective disorder is often in late adolescence or early adulthood, these data might not generalize to children at other ages. These data also might not generalize to youth self-reports; however, maternal reports tend to be correlated with youth report, are more accurate than paternal report, and tend to agree more on internalizing symptoms (Berg-Nielsen et al 2003; Seiffge-Krenke and Kollmar 1998). We aim to assess these samples at ages 3, 7, 12, 14, and 16 to examine the stability of the latent class structure and suicidal behavior. We were able to examine impairment by looking at suicidality in this sample, but unfortunately, a more direct test of impairment in these children with the competence subscales of the CBCL was not able to be performed, because the competence subscales were not collected in these twins. Additionally, CBCL queries for behavior over the last 6 months might make it more difficult to ascertain information about discrete episodes that might not have occurred over that time frame; although we have some evidence that the CBCL-JBD scale is adequate for determination of both lifetime and current episodes (Faraone et al 2005). Moreover, the early-onset of bipolar disorder is marked by a more chronic course with frequent cycles (Geller and Luby 1997; Wozniak et al 2004) making it less likely that symptoms would not have occurred in the last 6 months.

It is difficult to imagine a way in which LCA could be used at this time in the clinic. The identification of a heritable phenotype, however, as identified through LCA of the CBCL subscales, supports the use of the subscales as a possible screen for DSM bipolar disorder. The sensitivity and specificity of various cutpoints of these subscales is provided in Faraone et al (2005). At this point we can not present data on the number of children in each latent class who also met DSM-IV diagnostic criteria for bipolar affective disorder. Our group is currently interviewing a subset of this sample and analyzing these data to determine those relations. Importantly, despite using the name "CBCL-JBD," using the CBCL as a proxy for JBD does not include key components of bipolar disorder such as elation or grandiosity.

This research was supported by National Institute of Mental Health grants MH58799, NWO 904-57-94, and NWO 575-25-006 and the Centre for Neurogenomics and Cognition Research.

We would like to thank Jeri Ogle for her help in the preparation of this manuscript.

Achenbach TM (1991): *Manual for the Child Behavior Checklist/4–18 and 1991 Profile*. Burlington, Vermont: University of Vermont Department of Psychiatry.

Achenbach TM, Verhulst FC, Baron GD, Althaus M (1987): A comparison of syndromes derived from the Child Behavior Checklist for American and Dutch boys aged 6–11 and 12–16. *J Child Psychol Psychiatry* 28:437–453.

Althoff RR, Faraone SV, Rettew DC, Morley CP, Hudziak JJ (2005): Family, twin, adoption, and molecular genetic studies of juvenile bipolar disorder. *Bipolar Disord* 7:598–609.

American Psychiatric Association (1994): *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV*, 4th ed. Washington, DC: American Psychiatric Association.

Bartels M, Hudziak JJ, van den Oord EJ, van Beijsterveldt CE, Rietveld MJ, Boomsma DI (2003): Co-occurrence of aggressive behavior and rule-breaking behavior at age 12: Multi-rater analyses. *Behav Genet* 33:607–621.

Berg-Nielsen TS, Vika A, Dahl AA (2003): When adolescents disagree with their mothers: CBCL-YSR discrepancies related to maternal depression and adolescent self-esteem. *Child Care Health Dev* 29:207–213.

Biederman J, Wozniak J, Kiely K, Ablon S, Faraone S, Mick E, et al (1995): CBCL clinical scales discriminate prepubertal children with structured interview-derived diagnosis of mania from those with ADHD. *J Am Acad Child Adolesc Psychiatry* 34:464–471.

Boomsma DI (1998): Twin registers in Europe: An overview. *Twin Res* 1:34–51.

Boomsma DI, Vink JM, van Beijsterveldt TC, de Geus EJ, Beem AL, Mulder EJ, et al (2002): Netherlands Twin Register: A focus on longitudinal research. *Twin Res* 5:401–406.

Brent DA, Perper JA, Goldstein CE, Kolko DJ, Allan MJ, Allman CJ, et al (1988): Risk factors for adolescent suicide. A comparison of adolescent suicide victims with suicidal inpatients. *Arch Gen Psychiatry* 45:581–588.

Carlson GA, Kelly KL (1998): Manic symptoms in psychiatrically hospitalized children--what do they mean? *J Affect Disord* 51:123–135.

Dempster A, Laird N, Rubin D (1977): Maximum likelihood from incomplete data via the EM algorithm. *J R Statist Soc B* 39:1–38.

Dienes KA, Chang KD, Blasey CM, Adleman NE, Steiner H (2002): Characterization of children of bipolar parents by parent report CBCL. *J Psychiatr Res* 36:337–345.

Faraone SV, Althoff RR, Hudziak JJ, Monuteaux M, Biederman J (2005): The CBCL predicts DSM bipolar disorder in children: A receiver operating characteristic curve analysis. *Bipolar Disord* 7:518–524.

Geller B, Luby J (1997): Child and adolescent bipolar disorder: A review of the past 10 years. *J Am Acad Child Adolesc Psychiatry* 36:1168–1176.

Geller B, Warner K, Williams M, Zimerman B (1998): Prepubertal and young adolescent bipolarity versus ADHD: Assessment and validity using the WASH-U-KSADS, CBCL and TRF. *J Affect Disord* 51:93–100.

Goldsmith HH (1991): A zygosity questionnaire for young twins: A research note. *Behav Genet* 21:257–269.

Goodman L (1974): Exploratory latent structure analysis using both identifiable and unidentifiable models. *Biometrika* 61:215–231.

Hazell PL, Lewin TJ, Carr VJ (1999): Confirmation that Child Behavior Checklist clinical scales discriminate juvenile mania from attention deficit hyperactivity disorder. *J Paediatr Child Health* 35:199–203.

Hudziak JJ, Althoff RR, Derks EM, Faraone SV, Boomsma DI (2005): Prevalence and genetic architecture of Child Behavior Checklist-juvenile bipolar disorder. *Biol Psychiatry* 58:562–568.

Hudziak JJ, Heath AC, Madden PF, Reich W, Bucholz KK, Slutske W, et al (1998): Latent class and factor analysis of DSM-IV ADHD: A twin study of female adolescents. *J Am Acad Child Adolesc Psychiatry* 37:848–857.

Hudziak JJ, Wadsworth ME, Heath AC, Achenbach TM (1999): Latent class analysis of Child Behavior Checklist attention problems. *J Am Acad Child Adolesc Psychiatry* 38:985–991.

Leibenluft E, Charney DS, Towbin KE, Bhangoo RK, Pine DS (2003): Defining clinical phenotypes of juvenile mania. *Am J Psychiatry* 160:430–437.

Lewinsohn PM, Klein DN, Seeley JR (2000): Bipolar disorder during adolescence and young adulthood in a community sample. *Bipolar Disord* 2:281–293.

Mick E, Biederman J, Pandina G, Faraone SV (2003): A preliminary meta-analysis of the child behavior checklist in pediatric bipolar disorder. *Biol Psychiatry* 53:1021–1027.

Neuman RJ, Heath A, Reich W, Bucholz KK, Madden PAF, Sun L, et al (2001): Latent class analysis of ADHD and comorbid symptoms in a population sample of adolescent female twins. *J Child Psychol Psychiatry* 42:933–942.

Neuman RJ, Todd RD, Heath AC, Reich W, Hudziak JJ, Bucholz KK, et al (1999): Evaluation of ADHD typology in three contrasting samples: A latent class approach. *J Am Acad Child Adolesc Psychiatry* 38:25–33.

Rasmussen ER, Neuman RJ, Heath AC, Levy F, Hay DA, Todd RD (2002a): Replication of the latent class structure of Attention-Deficit/Hyperactivity Disorder (ADHD) subtypes in a sample of Australian twins. *J Child Psychol Psychiatry* 43:1018–1028.

Rasmussen ER, Neuman RJ, Heath AC, Levy F, Hay DA, Todd RD (2004): Familial clustering of latent class and DSM-IV defined attention-deficit/hyperactivity disorder (ADHD) subtypes. *J Child Psychol Psychiatry* 45:589–598.

Rasmussen ER, Todd RD, Neuman RJ, Heath AC, Reich W, Rohde LA (2002b): Comparison of male adolescent-report of attention-deficit/hyperactivity disorder (ADHD) symptoms across two cultures using latent class and principal components analysis. *J Child Psychol Psychiatry* 43:797–805.

Rietveld MJ, Hudziak JJ, Bartels M, Van Beijsterveldt CE, Boomsma DI (2003): Heritability of attention problems in children: I. Cross-sectional results from a study of twins, age 3–12 years. *Am J Med Genet* 117B:102–113.

Rietveld MJ, Hudziak JJ, Bartels M, van Beijsterveldt CE, Boomsma DI (2004): Heritability of attention problems in children: Longitudinal results from a study of twins, age 3 to 12. *J Child Psychol Psychiatry* 45:577–588.

Rietveld MJ, van Der Valk JC, Bongers IL, Stroet TM, Slagboom PE, Boomsma DI (2000): Zygosity diagnosis in young twins by parental report. *Twin Res* 3:134–141.

Rohde LA, Barbosa G, Polanczyk G, Eizirik M, Rasmussen ER, Neuman RJ, et al (2001): Factor and latent class analysis of DSM-IVADHD symptoms in a school sample of Brazilian adolescents. *J Am Acad Child Adolesc Psychiatry* 40:711–718.

Seiffge-Krenke I, Kollmar F (1998): Discrepancies between mothers' and fathers' perceptions of sons' and daughters' problem behaviour: A longitudinal analysis of parent-adolescent agreement on internalising and externalising problem behaviour. *J Child Psychol Psychiatry* 39:687–697.

Spencer T, Biederman J, Wilens T (1999): Attention-deficit/hyperactivity disorder and comorbidity. *Pediatr Clin North Am* 46:915–927, vii.

Todd RD, Lobos EA, Sun LW, Neuman RJ (2003): Mutational analysis of the nicotinic acetylcholine receptor alpha 4 subunit gene in attention deficit/hyperactivity disorder: Evidence for association of an intronic polymorphism with attention problems. *Mol Psychiatry* 8:103–108.

Todd RD, Rasmussen ER, Neuman RJ, Reich W, Hudziak JJ, Bucholz KK, et al (2001): Familiality and heritability of subtypes of attention deficit hyperactivity disorder in a population sample of adolescent female twins. *Am J Psychiatry* 158:1891–1898.

van Beijsterveldt CE, Bartels M, Hudziak JJ, Boomsma DI (2003): Causes of stability of aggression from early childhood to adolescence: A longitudinal genetic analysis in Dutch twins. *Behav Genet* 33:591–605.

van Lier PA, Verhulst FC, van der Ende J, Crijnen AA (2003): Classes of disruptive behaviour in a sample of young elementary school children. *J Child Psychol Psychiatry* 44:377–387.

Verhulst FC, Achenbach TM, Althaus M, Akkerhuis GW (1988): A comparison of syndromes derived from the child behavior checklist for American and Dutch girls aged 6–11 and 12–16. *J Child Psychol Psychiatry* 29:879–895.

Vermunt JK, Magidson J (2000): *Latent GOLD User's Guide*. Belmont, Massachusetts: Statistical Innovations.

Wadsworth ME, Hudziak JJ, Heath AC, Achenbach TM (2001): Latent class analysis of child behavior checklist anxiety/depression in children and adolescents. *J Am Acad Child Adolesc Psychiatry* 40:106–114.

Wals M, Hillegers MH, Reichart CG, Ormel J, Nolen WA, Verhulst FC (2001): Prevalence of psychopathology in children of a bipolar parent. *J Am Acad Child Adolesc Psychiatry* 40:1094–1102.

Whittington CJ, Kendall T, Fonagy P, Cottrell D, Cotgrove A, Boddington E (2004): Selective serotonin reuptake inhibitors in childhood depression: Systematic review of published versus unpublished data. *Lancet* 363:1341–1345.

Wozniak J, Spencer T, Biederman J, Kwon A, Monuteaux M, Rettew J, et al (2004): The clinical characteristics of unipolar vs. bipolar major depression in ADHD youth. *J Affect Disord* 82(suppl 1):S59–S69.