LATENT CLASS ANALYSIS OF THE CBCL-BIPOLAR PHENOTYPE

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Introduction

The existence, prevalence and proper taxonomic designation of the comorbid condition, ADHD with bipolar disorder, has been the source of considerable attention 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 behavior and affective instability.

Many prior investigations of these children (Biederman et al., 1995) and children of bipolar mothers (Wals et al., 2001) yield a profile on the Child Behavior Checklist (CBCL) that includes elevation about a T score of 70 on the Attention Problems (AP), Aggressive Behavior (AGG) and Anxious/Depressed (A/D) syndromes of the CBCL.

Rationale

We have shown that the CBCL-Juvenile Bipolar Disorder (CBCL-JBD) phenotype is distinguishable from severe ADHD and is heritable (Hudziak et al., *in review*). Todd and his colleagues have demonstrated that different genotypes are associated with different discrete latent classes in ADHD (Todd et al., 2003).

We questioned whether use of LCA with items from the subscales that define the CBCL-JBD phenotype (AP, A/D, and AGG) would yield an endophenotype that could be identified as the CBCL-JBD phenotype and further questioned whether use of this endophenotype would show evidence of heritability using a twin study design.

Objective

To examine the latent structure of the CBCL AP, A/D, and AGG subscales in combination to determine if a CBCL-JBD endophenotype emerges and to examine the heritability of that endophenotype.

Questions

1) Does the latent class structure of the CBCL include a CBCL-JBD endophenotype.?
2) Is there evidence of heritability within endophenotypes?
3) What other endophenotypes emerge and what are their implications for childhood psychopathology?

Sample

Mother report CBCL data for Dutch twin at age 10

Twin Type	Number of Participants (missing)
Monozygotic (MZ) males	1214 (176)
Dizygotic (DZ) males	1096 (138)
Monozygotic (MZ) females	1476 (162)
Dizygotic (DZ) females	1090 (136)
Dizygotic Opposite Sex male eldest (DOS M_F)	1184 (132)
Dizygotic Opposite Sex female eldest (DOS F_M)	1064 (134)
TOTAL	7124 (878)

Measures

The CBCL (Achenbach, 1991) was used to measure eight behavioral and emotional syndromes.

Three syndrome scores known to distinguish CBCL-JBD were selected - Attention Problems (AP), Aggressive Behavior (AGG), and Anxious/Depressed (A/D)

The items from the AP, AGG, and AD 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.

Data Analyses

Latent class analysis was performed using Latent Gold. Participant response profiles on the 44 items were placed into the analysis separately for boys and girls.

Latent class models were fitted by means of an EM algorithm. Models estimating 1-class through 10-class solutions were compared. To calculate the best fitting model, we compared an M class solution to an M+1 class solution using the change in the Bayesian Information Criterion (BIC), a goodness-of-fit index that considers the rule of parsimony.

Odds ratios between classes were then computed and examined for differences between MZ and DZ twins both within and across latent classes.

Results

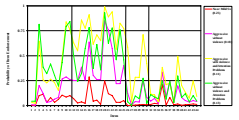
A 7 class model fit the females best while an 8 class model fit the males. The most common classes for boys or girls was one with no symptoms. The CBCL-Bipolar phenotype was the least common - about 4% of the boys and 5% of the girls.

Differences between the sexes were a primarily anxious-depressed class in the girls that did not show up in boys. In boys there was a class that showed increased item endorsement probabilities on AP and AGG with and without the violent items (fights, attacks people, etc.). These violent items were only endorsed with increased probabilities in the girls who had the CBCL-Bipolar phenotype.

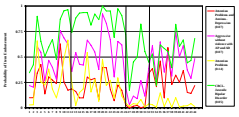
Class Membership Results

Class	Class Designation	Probability of Class Membership
Girls		
1	No Symptoms	0.32
2	Aggressive without violence	0.19
3	Aggressive with Attention Problems	0.14
4	Attention Problems and Aggressive with Mild Anxious/Depression	0.12
5	Anxious/Depressed	0.10
6	Attention Problems and Aggressive with Moderate Anxious/Depression	0.09
7	CBCL-Bipolar	0.04
Boys		
1	No Symptoms	0.25
2	Aggressive without violence	0.18
3	Attention Problems	0.14
4	Aggressive without violence with Attention Problems	0.13
5	Aggressive with violence with Attention Problems	0.11
6	Aggressive without violence with Attention Problems and Anxious/Depression	0.07
7	Attention Problems and Anxious/Depression	0.07
8	CBCL-Bipolar	0.05

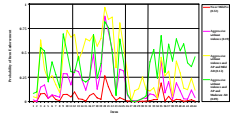
Boys – 8 Class Solution (Classes 1-4)



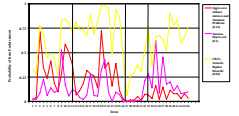
Boys – 8 Class Solution (Classes 5-8)



Girls – 7 Class Solution (Classes 1-4)



Girls – 7 Class Solution (Classes 5-7)



Heritability Results

Odds ratios for across class comparisons were calculated and showed very high ratios for within class comparisons and markedly lower ORs across classes. Comparing MZ to DZ twins showed a markedly higher odds ratio for within class comparisons for the MZ twins, especially for the extreme CBCL-JBP endophenotype. Much higher MZ as opposed to DZ odds ratios suggest the presence of within endophenotype heritability.

Odds Ratios -- Boys

MONOZYGOTIC MALES

Twin 1 Class \ Twin 2 Class	1	2	3	4	5	6	7	8
1	**37.39**	0.21	0.39	0.00	0.00	0.09	1.27	0.00
2	0.37	**10.83**	0.24	0.68	0.49	0.40	1.16	0.00
3	0.84	0.51	**18.03**	0.61	0.08	0.58	0.21	0.29
4	0.00	0.97	0.53	**14.35**	0.41	2.70	0.49	0.00
5	0.00	0.46	0.00	0.52	**37.20**	0.87	0.22	2.69
6	0.09	0.32	0.31	2.05	0.83	**13.59**	1.33	0.84
7	0.79	0.83	1.77	0.74	0.22	0.45	**7.89**	0.00
8	0.00	0.00	0.00	0.00	1.97	0.80	0.00	**148.85**

DIZYGOTIC MALES

Twin 1 Class \ Twin 2 Class	1	2	3	4	5	6	7	8
1	**4.66**	0.71	1.83	0.43	0.18	0.28	0.43	0.15
2	0.58	**2.29**	0.57	1.49	0.70	0.94	1.28	0.72
3	1.40	0.93	**1.99**	0.60	0.23	0.57	1.86	0.63
4	0.46	0.93	1.08	**2.63**	1.08	0.73	1.94	0.37
5	0.11	0.42	0.00	0.95	**9.63**	2.67	0.29	3.18
6	0.36	1.52	0.43	1.80	1.17	**1.74**	0.41	2.31
7	1.06	0.72	1.51	0.26	0.97	2.65	**1.02**	0.00
8	0.15	0.53	0.38	0.90	1.62	1.80	1.66	**9.71**

Odds Ratios -- Girls

MONOZYGOTIC FEMALES

Twin 1 Class \ Twin 2 Class	1	2	3	4	5	6	7
1	**33.60**	0.17	0.41	0.00	0.20	0.10	0.00
2	0.44	**15.48**	0.39	0.37	0.30	1.91	0.11
3	0.41	0.95	**58.52**	0.21	0.45	0.62	0.00
4	0.02	0.83	1.16	**47.05**	0.18	0.55	1.41
5	1.33	0.58	0.29	0.23	**6.31**	1.08	0.00
6	0.12	0.94	1.61	0.21	1.21	**18.49**	1.58
7	0.00	0.00	0.73	2.27	0.00	1.20	**51.46**

DIZYGOTIC FEMALES

Twin 1 Class \ Twin 2 Class	1	2	3	4	5	6	7
1	**12.47**	0.36	0.78	0.04	0.34	0.34	0.09
2	0.36	**2.10**	2.59	1.39	0.36	2.47	0.34
3	1.23	0.91	**1.12**	0.57	1.37	1.60	0.82
4	0.21	1.42	2.46	**2.84**	0.13	1.24	2.04
5	0.62	1.99	1.93	0.82	**1.00**	0.60	0.72
6	0.36	0.71	1.85	1.21	0.82	**4.74**	1.81
7	0.00	0.64	0.00	1.74	1.03	2.17	**13.55**

Discussion

The CBCL-JBP endophenotype emerges from LCA of the component items of the AP, AGG, and A/D subscales of the CBCL using a large population-based twin sample.

There is evidence of heritability within endophenotypes, as evidenced by higher odds ratios for MZ twins than DZ twins within the latent classes.

Other classes that emerge support the idea that attention problems, anxious-depressive symptoms, and aggressive symptoms rarely occur in isolation in children, but appear in combinations that have not had the benefit of receiving their own name.

There are reasons to consider the use of LCA in genotyping studies as a way to further refine phenotypes when searching for genetic relationships and gene x environment interactions in JBD.

1) Achenbach TM (1991), Manual for the Child Behavior Checklist/4-18 and 1991 Profile. Burlington, VT: University of Vermont Department of Psychiatry
2) Biederman J, Wozniak J, Kiely K, Ablon S, Faraone S, Mick E, Mundy E, Kraus I (1995), CBCL clinical scales discriminate prepubertal children with structured interview-derived diagnosis of mania from those with ADHD. J Am Acad Child Adolesc Psychiatry 34:464-71
3) Carlson GA, Kelly KL (1998), Manic symptoms in psychiatrically hospitalized children--what do they mean? J Affect Disord 51:123-35
4) Hudziak JJ, Althoff RR, Derks, EM, Rettew DC, Faraone SV, Boomsma DI (2004), The prevalence and genetic and environmental contributions to the CBCL-JBD phenotype. Biol Psychiatry. In Review.
5) Leibenluft E, Charney DS, Towbin KE, Bhangoo RK, Pine DS (2003), Defining clinical phenotypes of juvenile mania. Am J Psychiatry 160:430-7
6) 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 8:103-8
7) 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 40:1094-102

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