LONGITUDINAL GENETIC STABILITY OF THE CBCL JUVENILE BIPOLAR PHENOTYPE

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Introduction

Many prior investigations of children with Juvenile Bipolar Disorder (JBD) 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) subscales of the CBCL. This profile has been shown to predict DSM bipolar disorder in children (Faraone et al, in press). The developmental stability of JBD is currently unknown and available studies have reported conflicting outcomes for subjects who are diagnosed as having JBD as a child. This study uses the CBCL-JBD as a quantitative phenotype of JBD based on parental ratings of the behavior of the child.

We have shown previously that this profile shows evidence of heritability of this phenotype using cross-sectional analyses of Dutch twin data (Hudziak et al, in press). This phenotype has been shown to be sensitive and specific, stable across informants and influenced by genetic and environmental factors in a way that is different from children who have inattention, aggression, or anxious/depressed syndromes only.

Objective

To assess the developmental stability and change of the CBCL-JBD across ages 7, 10, and 12 years in a large population based twin sample and to estimate the genetic architecture of the CBCL-JBD phenotype across childhood.

Sample

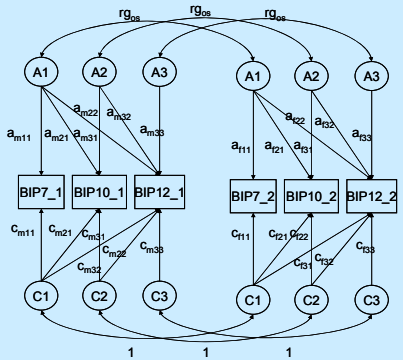
	Number of Participants		
Twin Type	Age 7	Age 10	Age 12
Monozygotic (MZ) males	1215	746	424
Dizygotic (DZ) males	1230	681	379
Monozygotic (MZ) females	1396	910	494
Dizygotic (DZ) females	1157	657	353
Dizygotic Opposite Sex male eldest (DOS M_F)	1186	732	369
Dizygotic Opposite Sex female eldest (DOS F_M)	1103	674	330
TOTAL	7287	4400	2349

Measures

- The CBCL (Achenbach, 1991) was used to measure eight behavioral and emotional syndromes.
- Three syndrome scores known to distinguish between problems with attention only and Bipolar-ADHD were selected - Attention Problems (AP), Aggressive Behavior (AGG), and Anxious/Depressed (A-D)
- A "CBCL-Bipolar" score was created using the sum of scores on AP, AGG, and A-D.

Data Analyses

- Means, variances, and twin correlations were calculated using the statistical software program Mx. Differences in mean scores were tested by likelihood-ratio χ^2-tests. Because the CBCL-JBD score was not normally distributed, the data were square-root transformed to approximate normal distribution before analysis. Transformed scores were used in the correlation and structural equation modelling.
- All model fitting was performed on transformed data with Mx. The basic model was a Cholesky decomposition of longitudinal data. The basic model is shown below.
- The significance of the A and C factors or sibling interaction was tested by dropping these variance components, using the χ^2- difference test. We also computed likelihood-based 95% confidence intervals.



Cholesky Decomposition Model: Analysis of longitudinal data on Juvenile Bipolar Disorder (JBD) at ages 7, 10 and 12 years (Non-shared environment is omitted in the figure for simplicity, but is modeled in a similar way). The rectangles represent the phenotypic measures at ages 7, 10 and 12 for first-born twins (male) and for second-born twins (female). In parameter subscripts m stands for males and f for females. Resemblance in JBD phenotype is explained by additive genetic effects (A) and environmental factors shared by the members of the same family (C). These are represented as latent, unmeasured factors within circles. Genes (A) and environment (C) across time are represented by three latent factors so that the first factors are the stable sources of variance present at 7, 10 and 12 years old; the second factors represent the sources of variance common to 10 and 12 years old that were not present at 7; and the third factors represent the sources of variance specific to 12 years of age.

Results

The summary of twin correlations at each age and of the cross-twin-cross-age correlations is shown below. The twin correlations within age show that at each age, the DZ correlations appear somewhat larger than half the MZ correlations. This suggests that genes and shared family environment both explain familial resemblances in CBCL-JBD. The cross-twin-cross-age correlations represent JBD at one age (e.g. 7) in one twin with CBCL-JBD at another age (e.g. 10) in the other twin (correlations constrained to be equal for first- with second-born and second-born with first-born twin). As can be seen, the past behavior of the co-twin is more predictive for the current behavior of this or her twin in MZ pairs, than it is in DZ pairs. Based on this pattern of cross-twin-cross-age correlations for MZ and DZ twins, it may be expected that longitudinal stability in bipolar disorder is explained by genetic factors and by the shared environment.

Twin Type	Cross twin-within time correlation			Cross twin-cross time correlation		
	7	10	12	7-10	7-12	10-12
MZM	.84	.84	.81	.66	.60	.67
DZM	.55	.48	.44	.39	.33	.34
MZF	.82	.81	.83	.64	.59	.68
DZF	.52	.48	.47	.39	.39	.39
OS	.50	.47	.47	.37	.32	.36

Model Fitting

Model	-2LL	DF	C.T.*	$\Delta\chi^2$	Δdf	p
1/ Full ACE with rg OS=.5	187397.335	27850				
2/ No sex differences in variance components	187727.390	27868	1	330.05	18	.000
3/ Model 1 & Proportion of Variance explained by ACE equal for males and females	187418.059	27859	1	20.724	9	.014
4/ Model 3 & Proportion covariance explained by ACE equal for males and females	**187429.772**	**27868**	**3**	**11.713**	**9**	**.229**
5/ Proportion of variance explained by A equal at 7, 10 and 12 years	187441.126	27870	4	11.354	2	.003
6/ Proportion of variance explained by C equal at 7, 10 and 12 years	187445.505	27870	4	15.733	2	.000
7/ Proportion of variance explained by E equal at 7, 10 and 12 years	187431.511	27870	4	1.739	2	.419

*C.T. = the previous model to which the current model is being compared

Model Estimates

	Parameter estimates from reduced model without sex differences		
Age	7	10	12
	A: Additive genetic architecture (heritability on diagonal, genetic covariance above diagonal, genetic correlations below diagonal)		
7	**.63**	.75	.78
10	.81	**.71**	.84
12	.75	.89	**.75**
	C: Shared environment architecture (proportion of variance explained by C on diagonal, covariance above diagonal, correlations below diagonal)		
7	**.20**	.15	.11
10	.70	**.11**	.04
12	.62	.36	**.08**
	E: Unique environment architecture (proportion of variance explained by E on diagonal, covariance above diagonal, correlations below diagonal)		
7	**.17**	.10	.10
10	.42	**.18**	.12
12	.38	.54	**.18**

Discussion

- The CBCL-JBD measure is stable across ages and we have quantified the genetic and environmental contributions to its stability from ages 7 to 12.
- The influence of additive genetic effects on variation in JBD was found to be relatively high at each age, increasing from 63% at age 7 to 75% at age 12 years.
- The effects of the shared environment tend to decrease. At age 7, 20% of the variation in CBCL-JBD is explained by the influence of the common family environment and this percentage decreases to 8% at age 12 years.
- The small remaining part of the variance at each age was explained by unique, or individual-specific environmental influences.
- Similar genes may underlie the disorder in boys and girls
- About 80% of the stability on JBD in childhood is due to additive genetic effects, and about 10% of stability is explained by shared environmental effects.

Limitations

1. Data on maternal report may not generalize to other informants. Our group is currently collecting data on older twins by father and teacher report in order to test for these factors.
2. 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.
3. Data in this report are limited to children up to the age of 12. Because 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.

Conclusions

- Roughly 80% of the stability in childhood CBCL-JBD is due to additive genetic effects.
- The estimates for males and females are quite similar.

References

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