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Chapter 5: Prediction of change in level of problem behavior among children of bipolar parents

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Abstract

Objective. To determine the effects of familial loading, birth weight, and family problems on the change in parent reported problems across a 14-month period among children of bipolar parents. **Methods**. A sample of 140 offspring aged 12-21 years at initial assessment of bipolar parents was followed up across a mean interval of 14 months. Emotional and behavioral problems in the offspring were assessed at both measurements. Familial loading (FL) of unipolar mood disorders in the offspring's first- and second-degree relatives was determined with the FH-RDC. Parents reported the birth weight of their offspring and completed a questionnaire on family problems. Multiple linear regression analyses were performed to assess associations of familial loading, birth weight, and family problems, adjusted for problem scores at initial assessment, age, gender and socio-economic status (SES), with problem scores at follow-up. **Results**. Behavioral and emotional problems that parents reported in their offspring persisted across the 14-month follow-up. Familial loading of unipolar disorder was a strong and unique predictor for an increase in problem scores from the first to the second measurement with ß-coefficients ranging from .17 to .24. Birth weight and family problems were not associated with change in problem scores across the two measurements. **Conclusion**. Familial loading of unipolar disorder was a strong predictor of increase in behavioral and emotional problems across a 14-month follow-up interval among children of bipolar parents. Birth weight and perceived family environment did not predict change in the level of psychopathology across a 14-month follow-up in children of bipolar parents. **Key words.** bipolar offspring, familial loading, birth weight, family problems, problem behavior

Introduction

Children of bipolar parents are at increased risk to develop mood disorders. A number of studies have stressed the importance of genetic factors in the etiology of unipolar and bipolar mood disorders (Craddock and Jones, 1999). We found familial loading of unipolar mood disorder in first- and second-degree relatives of the bipolar offspring to be positively associated with increased risk of meeting DSM-IV criteria for lifetime mood disorders (both unipolar and bipolar) in these offspring (Wals et al., 2004, 2003).

Genetic factors alone are not a sufficient explanation for the etiology of depression, environmental factors seem to play a role as well (Goodwin and Jamison, 1990; Harrington, 2002). Among environmental factors increasing the risk of developing mood disorders low birth weight can be viewed as a marker of prenatal environmental influences. The relevance of prenatal factors that may influence birth weight has been stressed by Barker (1988) who studied the relationship between prenatal influences, especially fetal malnutrition resulting in low birth weight, and increased risk of adult physical diseases including

cardiovascular diseases and diabetes. Birth weight has been reported to increase the risk of various types of psychopathology in childhood and adulthood (e.g. McCormick et al., 1990; Verdoux et al., 1993; Sommerfelt et al., 1996; Horwood et al., 1998; Van Os et al., 2001; Wichers et al., 2002), although the exact mechanisms by which these associations work are not known yet. Other studies reported on the association between birth weight and cognitive functioning (e.g. Eaton et al., 2001). In accordance with these findings, we found in our sample of bipolar offspring that birth weight was associated with an increased risk of DSM-IV mood as well as non-mood disorders. This association was independent of the association between genetic liability as measured by familial loading of unipolar, bipolar and substance use disorder and psychopathology (Wals et al., 2003).

Another environmental contributor to the risk of increasing behavioral and emotional problems in offspring of unipolar or bipolar parents seems to be poor family functioning. For instance, Billings and Moos (1983) found variations in family stressors and resources to be strongly related to the probability of disturbance among 133 children of depressed parents as compared to 135 children of non-depressed parents. Chang et al. (2001) found families with a bipolar parent to report significant differences in their family environment compared to population means. Families with a bipolar parent differed from the average family in having less cohesion and organization, and more conflict. However, Family Environment Scale (FES Moos & Moos, 1986) scores did not differ significantly for 6-18 year-old children with or without an Axis I disorder in these families. A drawback of these studies is that because of their cross-sectional nature it is not possible to determine the temporal relationship between family problems and child/adolescent psychopathology. Therefore, longitudinal research is needed.

It is thus likely that offspring of bipolar parents are at increased risk of showing psychopathology through both genetic and environmental influences. The next question is whether or not vulnerability or risk factors, such as familial loading, birth weight and family functioning, can also be held responsible for changes in the level of psychopathology across time. In order to capture changes in the level of problems in this high risk sample, we have decided to assess our sample at short time intervals. Few studies have focused on the course of psychopathology in bipolar offspring (e.g. Lee and Gotlib, 1989; Hammen et al., 1990; Radke-Yarrow et al., 1992). In a 3-year follow-up, Hammen et al. (1990) found a chronic or intermittent course of both mood and non-mood disorders in 18 children of bipolar mothers, 22 children of unipolar mothers and 14 children of medically ill mothers after initial evaluation. Radke-Yarrow et al. (1992) followed 22 children of bipolar parents (as well as offspring of unipolar and normal control parents) for up to 3 years. They found significantly more children of affectively ill than well mothers to show depressive and disruptive problems by middle and late childhood and that their problems increased over time. None of the above-mentioned studies have focused on factors influencing change in psychopathology over time.

In the present study, we expected our sample of bipolar offspring, which was aged 12-21 years at initial assessment, to be in a developmental period with

elevated risk of showing the first signs of psychopathology given their genetic vulnerability, and environmental risks. To enable a close examination of changes in the level of psychopathology, we have chosen to study this sample at relatively short time intervals; 14 months. Increases in the level of emotional and behavioral problems, even when occurring at a sub clinical level, may signal increasing vulnerabilities in offspring who may eventually develop more serious psychopathology, including bipolar and other mood disorders.

We aimed to study the course of individual levels of problem behavior in adolescent and young-adult offspring of bipolar parents, as well as factors that are associated with possible changes in the level of problem behavior in these offspring. Based on the previous findings that were discussed above, the most obvious candidate determinants of change were familial loading of unipolar disorder and birth weight. In addition, we chose the amount of family problems reported at initial assessment as environmental factor that, in addition to familial loading and birth weight, may influence the risk of developing psychopathology in adolescent and young adult bipolar offspring.

More specifically, we aimed to determine whether familial loading of unipolar and disorder, birth weight, and family problems are predictive of changes in the level of parent reported emotional and behavioral problems across time.

Methods

Sample

The sample consisted initially of 140 children aged 12-21 years of a parent with bipolar disorder. Children with a severe physical disease or handicap or with an IQ below 70 were excluded. A family was excluded if one or more family members aged 12 to 21 years refused to participate.

All subjects were enrolled into the study between November 1997-March 1998. Sixty-four bipolar I and 22 bipolar II patients and their offspring (72 boys and 68 girls) participated in the study. Fifty-two out of 86 proband parents were mothers (60%). The mean age of the bipolar parents was 45.4 years. The mean age of the participating offspring at time 1 was 16.1 years (SD = 2.7; range 12-21). Fourteen months after the first measurement (time 1), 132 subjects, aged 13 to 23 years, were reassessed.

The Medical Ethical Review Committee of the University Medical Center Utrecht approved the study. After a complete description of the study was given to all participating parents, their spouses and their offspring, written informed consent of all participants was obtained.

For a more detailed description of the recruitment and demographic characteristics of the sample we refer to Wals et al. (2001).

Instruments

Assessment of bipolar disorder in the parents

None of the affected parents was depressed or manic at the moment of completing the questionnaires and of administering the interviews.

DSM-IV bipolar I or II diagnoses were confirmed by administering the mood disorders section of the International Diagnostic Check List (IDCL) (Hiller et al., 1993) in the interview with the bipolar parent. We compared the IDCL-based diagnoses with the DSM-IV diagnoses made by the treating psychiatrist and did not find any discrepancies. The spouses of the bipolar parents did not have bipolar disorder but some of them were diagnosed with unipolar disorder (see the FH-RDC section below).

Assessment of familial loading

Lifetime prevalence of psychopathology in the parents (n = 177) and their non-offspring first-degree relatives (n = 932) was assessed with the Family History-Research Diagnostic Criteria (FH-RDC; Andreasen et al., 1977) interview which was administered to both parents. We only applied sections of the FH-RDC yielding the following diagnoses: unipolar disorder, bipolar disorder, and substance use disorder. A previously described method of calculating a familial loading score was used, considering family history as an attribute of the individual cases themselves, which might be related to their psychopathological outcome (Verdoux et al., 1996). This index of familial loading for the bipolar offspring is based on the number and age of the affected first-degree relatives, excluding the siblings of the participating bipolar offspring and the affected second-degree relatives of the adolescent. Every relative examined with the FH-RDC contributed to the index depending on whether the person was affected and on the age at which the person was affected. We decided to limit the analyses for this paper to the familial loading score for unipolar because the variance of familial loading of bipolar disorder ranged from individuals with high familial loading to individuals with extremely high familial loading (the variance was always positive) thereby making differentiation between subjects more difficult. For a more detailed description of the familial loading score we refer to Wals et al. (2004, 2003).

Family Problems Questionnaire

The Family Problems Questionnaire (Koot, 1997) aims to assess family problems as perceived by the parents. All offspring lived with their parents at time 1.The questionnaire contains 130 items that can be scored 0 = not applicable, 1 = a little or sometimes applicable, 3 = clearly or often applicable. Items can be scored on the following scales: 1. Support and communication; 2. Education; 3. Hostility; 4. Openness, 5; Execution of tasks, 6; Involvement, 7; Security, 8; Partner relationship; and 9. Problems with children. In addition to these scales a screen score and a total score can be derived. This instrument enables us to get a description of the experience of parents of strengths and weaknesses of family functioning. Good reliability (α's ranging from 0.72 to 0.97) of the Family Problems Questionnaire was found and all scales, except the Partner relationship and

Involvement scale discriminated well between a referred and non-referred sample selected from a general population cohort of 488 families. The non-referred sample consisted of families of 368 children who did not use mental health services during the 12 months preceding completion of the questionnaire whereas the referred group consisted of families with 156 children who were referred for mental health service (Koot, 1997). On 125 of the 130 items of the questionnaire the referred group scored significantly higher than the non-referred group. The 5 items that did not discriminate between the two groups were excluded from the total score.

For the purpose of this study, both mothers and fathers were requested to complete the questionnaire. Total scores of mothers and fathers were averaged. The questionnaire was completed at both time 1 and time 2. However, since we were interested in whether family problems preceded changes in levels of psychopathology, we decided to use only the family problems scores of time 1.

Assessment of problem behavior in bipolar offspring

Both affected and non-affected mothers completed the Child Behavior Checklist for ages 4 to 18 (CBCL; Achenbach, 1991a, 1991b). The CBCL is a questionnaire containing 120 problem items that can be scored 0 if the behavior is not true of the child, 1 if the behavior is sometimes or somewhat true, and 2 if the behavior is very true or often true. The problem items can be scored on eight syndrome scales and two broad-band groupings of syndromes: Internalizing (consisting of the Withdrawn, Somatic Complaints, and Anxious/Depressed scales) and Externalizing (consisting of the Delinquent Behavior and Aggressive Behavior scales). The sum of the 120 individual item scores is the total problems score. The good reliability and validity of the CBCL have been replicated for the Dutch translation (Verhulst et al., 1996). The Young Adult Behavior Checklist (YABCL; (Achenbach, 1997) is an upward extension of the CBCL for ages 18 years and older, and contains problem items that are completed by parents. The YABCL can be scored on syndrome scales similar to those of the CBCL, except for the Social Problems scale, which is replaced by the Intrusive Behavior scale. The syndrome scales can be scored on two broad-band groupings of syndromes: Internalizing (consisting of the Anxious/Depressed and Withdrawn scales) and Externalizing (consisting of the Intrusive Behavior, Delinquent Behavior, and Aggressive Behavior scales). For the present study, we computed a total problems score, and Internalizing and Externalizing scores from the items that were common to the CBCL and YABCL.

Socio-economic status (SES)

Socio-economic status (SES) was scored on a 9-point scale of parental occupational level with 1 = lowest and 9 = highest. If both parents worked, the highest score was used.

Statistical analysis

In order to assess the stability of problem behavior between time 1 and time 2, Pearson correlations were calculated. Paired sample t-tests were used to calculate differences in the means of problem behavior at time 1 and time 2.

Simple linear regression analyses were performed for each predictor with each problem score as outcome, yielding regression coefficients (ß) as a measure of effect size.

Next, stepwise multiple linear regression analysis was used to identify which set of variables were the strongest predictors of increase in problem behavior at follow-up, while controlling for possible confounding effects from other predictors. To determine their independent effects, familial loading, family problems and birth weight were entered stepwise into the regression equation. In order to assess the effect of the predictors on problem behavior at time 2 over and above the effect of time 1 problem behavior, we entered time 1 (total problems, Internalizing, and Externalizing) problem scores as independent variables. For each of the three CBCL/YABCL problem scales we did a separate analysis. All analyses were adjusted for age of the offspring at time 2, gender and SES. These confounders were chosen a priori.

Results

Stability and change of problems across the 14-months follow-up interval

Table 1 shows the CBCL/YABCL mean total problems, Internalizing and Externalizing scores at time 1 and time 2 and the Pearson correlations between time 1 and time 2 scores.

Table 1: Means, standard deviations and Pearson Correlations of CBCL/YABCL Total problems, Internalizing and Externalizing scores between time 1 (T1) and time 2 (T2)

	CBCL/YABCL[a]						
	T1		T2		Diff[b] T1-T2		
	Mean	SD	Mean	SD	p	r[c]	p
Total Problem score	20.91	17.3	18.74	16.4	n.s.	.70	< 0.01
Internalizing	8.39	8.7	7.26	7.5	n.s.	.69	< 0.01
Externalizing	6.50	5.9	6.23	6.3	n.s.	.71	< 0.01

Note: [a] CBCL = Child Behavior Checklist and YABCL = Young Adult Behavior Checklist; [b] Mean difference between CBCL scores at T1 and T2; [c] r = Pearson Correlations time 1 vs. time 2

Differences between time 1 and time 2 scores were computed by paired sample t-tests. Mean total problems, Internalizing and Externalizing scores were somewhat lower at time 2 than at time 1. However, none of the differences were significant. Pearson correlations between time 1 and time 2 scores were

significant and could be regarded as large ($r > 0.5$) according to Cohen's (1988) criteria to evaluate the magnitude of stability coefficients.

Prediction of change in problem scores: univariate analyses

Table 2 shows the results of the univariate linear regression analyses in which familial loading, birth weight, and family problems are associated with change in total problems, Internalizing and Externalizing scores between time 1 and time 2, thus, adjusted for time 1 total problems, Internalizing and Externalizing scores respectively, and adjusted for age at time 2, gender and SES at time 1.

Table 2: Simple linear regression analyses of familial loading, birth weight, family problems at time 1, age at time 2, gender, SES predicting change in CBCL/YABCL total problems, Internalizing and Externalizing behavior at 14 months-follow-up

Predictor variables[a]	Dependent variables		
	CBCL/YABCL time 2		
	total problems	Internalizing	Externalizing
	β	β	β
FL unipolar depression	0.18**	0.17**	0.15*
Birth weight	0.06	0.07	0.07
Family problems time 1	0.03	0.05	-0.02
Gender	0.02	0.01	0.00
Age	-0.06	-0.02	-0.08
SES	-0.03	-0.04	-0.02

Note: [a] All variables were adjusted for time 1 total problems, Internalizing and Externalizing scores; *p* < 0.05, ** *p* < 0.01,

Familial loading of unipolar disorders was positively associated with change in CBCL/YABCL total problems, Internalizing, and Externalizing scores between time 1 and time 2 (ß = .18, *p* < .01, ß = .17, *p* < .01, ß = .15, *p* < .05 respectively) indicating that familial loading of unipolar disorder is associated with an increase of problem behavior. There were no significant associations between family problems and change in problem behavior and between birth weight and change in problem behavior. However, offspring of bipolar parents received significantly higher scores on the family problems questionnaire than offspring in the general population (total score on the Family Problems Questionnaire by mothers was 50.9 in our sample versus 28.6 in the general population, t = 8.0, *p* < 0.01, and for fathers 45.7 in our sample versus 27.8 in the general population, t = 6.0, *p* < 0.01). The (a priori chosen) confounders: age, gender and SES, were not significantly associated with total problems, Internalizing and Externalizing scores.

Prediction of change in problem scores: multivariate analyses

Table 3 shows the results of the multiple linear regression analysis. As can be seen from this table, familial loading of unipolar disorders significantly predicted an increase in total problems, Internalizing, and Externalizing problems (ß = .24, *p* < .01, ß = .25, *p* < .01, ß = .17, *p* < .05 respectively). All other candidate variables did not predict change of problem behavior between time 1 and time 2.

We reanalyzed the data with the total family problems for mothers and fathers separately and did not find any significant differences in results.

Table 3: Multiple linear regression analyses (stepwise backward), of familial loading, birth weight, and family problems at time 1 predicting change in CBCL/YABCL total problems, Internalizing and Externalizing behavior at 14 months-follow-up, adjusted for gender, SES and age at time 2

Predictor variables[a]	Dependent variable		
	CBCL/YABCL time 2		
	Total problems	Internalizing	Externalizing
FL unipolar depression	0.24**	0.25**	0.17*
Birth weight	Exc.	Exc.	Exc.
Family problems	Exc.	Exc.	Exc.
Gender	n.s.	n.s.	n.s.
Age	n.s.	n.s.	n.s.
SES	n.s.	n.s.	n.s.

Note: [a] All variables were adjusted for time 1 total problems, Internalizing and Externalizing scores;
**p* < 0.05, ** *p* < 0.01; ns = not significant (although factor included in overall significant model);
Exc. = factor, not significant, excluded from the model.

Interactions

There were no significant interactions between family problems, birth weight, SES on the one hand and familial loading of unipolar disorder on the other on change of problem behavior between time 1 and time 2; these are not shown in the table.

Discussion

As far as we know, this is the first study examining predictors of changes in the level of problems in bipolar offspring. Our findings indicate that the risk to offspring of bipolar parents to develop psychopathology is not transitory. Stability coefficients for total problems, Internalizing and Externalizing scores were large according to Cohen's (1988) criteria, indicating that behavioral and emotional problems of bipolar offspring aged 12-21 years at initial assessment were stable across this relatively short time interval. The mean problem scores did not change significantly across the 14-month follow-up indicating that there was no change in the overall level of problems in our sample.

The most salient finding of the present study was that familial loading of unipolar disorder in first- and second-degree relatives of children from bipolar parents was predictive of an increase in total, Internalizing and Externalizing CBCL/YABCL problem scores. Given the relatively short follow-up interval, it was striking to find familial loading to be associated with an increase in the level of problems.

In our previous study, in which we used K-SADS interviews to derive DSM-IV mood disorders in our sample, we found familial loading of unipolar disorder to be associated with mood disorders and not with non-mood disorders (Wals et al., 2004). In the present study familial loading of unipolar disorder predicted an increase of both Internalizing and Externalizing scores on the CBCL/YABCL. Externalizing behaviors have been found to precede the development of mood disorder in bipolar offspring. For instance, Carlson and Weintraub (1993) found a unique relationship between childhood behavioral and attention problems and the development of mood disorder in a sample of 134 bipolar offspring aged 7-16 years. Externalizing behavior may be an as yet undifferentiated early stage of the development of bipolar disorder. This might explain the significant association we found between familial loading of unipolar disorder and increase in Externalizing problem behavior. Of course, further research on this matter is necessary.

Another finding of the present study was that family problems and birth weight were not associated with an increase of problem behavior between the two measurements. The finding that family problems did not differentiate between offspring who showed an increase in problem behavior and those who did not does not mean that families in which one of the parents has a bipolar disorder do not experience more family problems. In line with Chang et al. (2001), we did find families of children of bipolar parents to experience more family problems than general population means. However, in the study by Chang et al. (2001) family problems did not differentiate children with or without psychopathology and in the present study family problems did not predict change in behavioral and emotional problems among children from bipolar parents.

The familial loading-score that we calculated largely concerned effects in relatives that are distant from the proband. Therefore, it is assumed that familial loading reflects genetic influences, although some environmental influences cannot be totally ruled out. In conclusion, the major finding of the present study is that familial loading of unipolar disorder was a strong predictor of increase in

behavioral and emotional problems in bipolar offspring across a 14-month follow-up interval. Birth weight and family problems did not predict change in psychopathology across a 14-month follow-up in children of bipolar parents. This does not preclude the possibility that other important environmental factors could predict developmental change in psychopathology among bipolar offspring.

Limitations

The sample is not population-based. Only patients with children who were willing to participate were included.

As the FH-RDC is relatively insensitive for the diagnosis of mood disorders when compared to the family study method (Andreasen et al., 1977), we may have missed diagnoses.

Implications

All subjects in our sample were similar in that they shared the risk that one of their parents had a bipolar disorder. In addition to this risk, the familial occurrence of unipolar disorder was positively associated with change of emotional and behavioral problems in our sample. This finding can make clinicians and researchers aware of the fact that familial loading of unipolar disorder increases the risk of developing emotional and behavioral problems in children of bipolar parents. If there is high familial loading of unipolar disorder in families with bipolar parents, it is important to inform parents and offspring of treatment possibilities whenever they show first signs of behavioral or emotional disturbance in order to prevent them from developing more problems.

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