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Mental disorders in offspring of parents with bipolar and major depressive disorders

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Abstract

Objectives—There is limited information on the specificity of associations between parental bipolar disorder (BPD) and major depressive disorder (MDD) and the risk of psychopathology in offspring. The chief aim of the present study was to investigate the association between mood disorder subtypes in the two parents and mental disorders in the offspring.

Methods—A total of 376 offspring (aged 6.0–17.9 years; mean = 11.5 years) of 72 patients with BPD (139 offspring), 56 patients with MDD (110 offspring), and 66 controls (127 offspring) participated in a family study conducted in two university hospital centers in Switzerland. Proband, offspring, and biological co-parents were interviewed by psychologists blind to proband diagnoses, using a semi-structured diagnostic interview.

Results—Rates of mood and anxiety disorders were elevated among offspring of BPD probands (34.5% any mood; 42.5% any anxiety) and MDD probands (25.5% any mood; 44.6% any anxiety) as compared to those of controls (12.6% any mood; 22.8% any anxiety). Moreover, recurrent MDD was more frequent among offspring of BPD probands (7.9%) than those of controls (1.6%). Parental concordance for bipolar spectrum disorders was associated with a further elevation in the rates of mood disorders in offspring (64.3% both parents versus 27.2% one parent).

Conclusions—These findings provide unique information on the broad manifestations of parental mood disorders in their offspring. The earlier onset and increased risk of recurrent MDD

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Disclosures

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in the offspring of parents with BPD compared to those of controls suggests that the episodicity characterizing BPD may emerge in childhood and adolescence.

Keywords

bipolar disorder; co-parents; DSM–IV mental disorders in offspring; high-risk offspring; major depressive disorder

There is a growing convergence of evidence from retrospective community samples of adults and prospective studies of community samples of youth (1) that the majority of mood disorders emerge in childhood and adolescence (2). In light of the serious consequences and impact of bipolar disorder (BPD) (3), there is a critical need for identification of the early manifestations of this significant public health problem. The high-risk study design that utilizes the well-established familial aggregation of mood disorders is a powerful tool to facilitate identification of prognostic risk factors and early clinical manifestations of mood disorders (4).

The growing body of high-risk studies of the offspring of parents with mood disorders, particularly BPD, has provided insight into the specificity of familial aggregation of specific subtypes of mood disorders, and their association with other behavioral and affective conditions (5, 6). Table 1 provides a summary of the ten controlled studies of the offspring (in the age range between six and 18 years on recruitment into the study) of parents with both major subtypes of mood disorders [BPD and major depressive disorder (MDD)], with adequate sample sizes for meaningful analysis. These studies demonstrate an elevation of mood disorders and a range of other conditions, including disruptive behavioral disorders (DBD), attention-deficit hyperactivity disorder (ADHD), and substance misuse irrespective of parental MDD or BPD subtype, and increased rates of anxiety disorders, among the offspring of parents with BPD (Table 1). However, aggregation of estimates across studies is impeded by methodological differences, including: differences in incorporating parental comorbid disorders, failure to account for co-parent disorders, lack of or non-comparable control groups, or differences in methods for assessing disorders in youth. Only one study (7) examined the specificity of the familial transmission of the subtypes of mood disorders based on inclusion of independent proband groups with BPD and MDD; however, the small size of this sample may have led to unreliable estimates. Similarly, only two studies controlled for the potential effect of co-parental disorders, one by excluding co-parents with major psychiatric disorders from the study (8) and the other by adjusting for the effects of co-parent disorders in the analyses (9). However, no previous study has provided data on the effect of co-parental disorders on psychopathology in the offspring.

The major goal of the present study was to investigate the associations between mood disorder subtypes and concordance for mood disorders in probands and co-parents with mood and other Axis-I mental disorders in their offspring. Based on emerging evidence for the spectrum concept of BPD (10), we also examined the associations between parental mood disorders and subthreshold manifestations of mood disorders in offspring.

Methods

Sample

The data in the present study are based on a controlled family study of adults with unipolar or bipolar mood disorders. Probands with BPD and MDD were consecutively recruited from the inpatient and outpatient facilities of the psychiatric departments of Lausanne and Geneva, Switzerland. Inclusion criteria for mood disorder probands were: (i) lifetime DSM–IV bipolar I disorder (BPD-I), bipolar II disorder (BPD-II), schizoaffective BPD, or MDD and (ii) permission to enroll at least one child in the age range 6.0 to 17.9 years. Comparison probands were recruited from orthopedic departments in the same inpatient and outpatient clinical settings in Lausanne and Geneva. Inclusion criteria for the comparison probands required: (i) the absence of a lifetime DSM–IV mood or psychotic disorder and (ii) the same criterion for inclusion of offspring as that in the mood disorder cases. A positive family history of mood disorders or BPD was not an exclusion criterion for either comparison or MDD probands.

A total of 72 BPD (58.5%), 56 MDD (57.7%), and 66 (71.0%) orthopedic patients agreed to enroll at least one of their children in the required age range in the present study. Participants did not differ from non-participants (patients with minor children but not one child enrolled in the study) with respect to professional level, lifetime history of anxiety or alcohol use disorders, ADHD, or DBD. However, participants in the control group were more likely than non-participating controls to be female; participants in the MDD group were more likely to be younger than non-participating patients with MDD; and non-participants in the bipolar group were more likely to exhibit illicit drug use disorders than participating patients with BPD. Among the 72 bipolar probands, 48 met the criteria for BPD-I, ten for BPD-II, and 14 for schizoaffective BPD; and among the 56 probands with MDD, 18 had had a single episode and 38 had a history of recurrent episodes.

The offspring sample ($n = 376$) included all of the children of the probands between the ages of six and 18 years [mean age: 11.5 years, standard deviation (SD) = 3.41 years; 50.8% girls]. There were 139 offspring of probands with BPD (88 BPD-I, 19 BPD-II, and 32 schizoaffective BPD probands), 110 of probands with MDD (72 of recurrent MDD, 38 of single episode MDD probands) and 127 of comparison probands. The majority of families included one ($n = 67$) or two ($n = 83$) children, whereas 44 families included three or more children. None of the offspring needed to be excluded because of mental retardation, autistic disorder, or any organic disorder. Diagnostic information was also collected on 200 of the 215 biological co-parents.

Procedures

Diagnostic information on probands and biological co-parents was obtained using the Diagnostic Interview for Genetic Studies (DIGS) (11). The French translation of the DIGS (12) revealed high kappa coefficients for inter-rater reliability and slightly lower coefficients for test–retest reliability for major Axis-I diagnoses including mood (13) and substance use disorders (SUD) (14). Offspring were directly interviewed using a French translation of the modified version of the Schedule for Affective Disorders and Schizophrenia for School-Age

Children–Epidemiologic version (K-SADS-E) (15) used in the previous high-risk Yale Family Study (16). The K-SADS-E has been found to be a reliable and valid instrument for obtaining lifetime diagnoses in prepubertal children (15) and adolescents (17, 18). Inter-rater reliability analyses of the French translation in a clinically referred sample revealed high kappa coefficients for major psychiatric diagnoses, ranging from 0.84 for depression and 0.86 for separation anxiety disorder to 1.0 for social phobia and psychosis.

Family history information on children and co-parents was systematically collected from all participants (if they were 15 years of age or older) using the Family History-Research Diagnostic Criteria (FH-RDC) (19). This also allowed us to obtain diagnostic information on non-interviewed co-parents and offspring. The validity of the French version of the FH-RDC has previously been established through the assessment of agreement between diagnoses relying on direct interviews and family history reports for a series of diagnoses in adults (20, 21) and children (22).

Participants were interviewed by Masters degree-level psychologists or psychiatrists who had completed intensive training over a three-month period. Training included supervision of videotaped interviews by clinically experienced senior psychologists. In a given family, each member was interviewed by a different interviewer and each interviewer was blind to the disease status of the other family members.

Diagnoses were assigned for lifetime according to a best-estimate procedure (23), which relied on the combining of information from direct interviews, family history reports, and medical records where available. In addition to the diagnoses based on DSM–IV criteria, diagnoses of mood syndromes below the threshold of DSM–IV in offspring were assigned using the algorithmically defined classification postulated by Angst and colleagues (10, 24). Accordingly, subthreshold depression was defined as either (recurrent) brief depression (5 DSM–IV depressive symptoms for 2–13 days) or minor depression (3–4 depressive symptoms for 2 weeks). Subthreshold BPD was defined as the occurrence of hypomanic episodes without major depressive episodes, brief mania (euphoria or irritability and at least three or four manic symptoms, respectively, for 2–3 days), or minor mania (euphoria or irritability and 1–2 or 2–3 manic symptoms, respectively, for 4 days).

This research project was approved by the local institutional review board. All participants gave written informed consent for their own participation prior to the assessments. In addition, parents gave written consent for the participation of their children.

Data analysis

Between-group analyses of demographic or clinical characteristics were performed using analysis of variance, chi-square, and Fishers exact tests (FETs) as appropriate. In order to simultaneously assess the effects of the probands and the spouses BPD or MDD on the risk of psychopathology in their children, generalized linear mixed models (25) were applied for those child disorders that revealed a significant association with the proband BPD or MDD in the univariate analysis of the whole sample. These generalized linear mixed models accounted for the lack of independence of the observations (varying number of children across families). In a first step, models which included the mood disorders of probands as

independent variables were entered, with an adjustment for the probands non-mood disorders (anxiety disorders, SUD, DBD, and ADHD) and the demographic characteristics of offspring. In a second step, the spouses diagnostic variables (mood and anxiety disorders, SUD, DBD, and ADHD) were added. This stepwise approach facilitates comparison with the results of previous studies, which generally focused on variables in probands only. Additional complementary models considered the subtype of the probands mood disorder and the familial situation (the child living with both biological parents versus not). In addition, the cumulative rates by age of onset of any mood and any anxiety disorders across the groups of children were established using the Kaplan–Meier procedure. Statistical analyses were performed using the Statistical Analysis System, version 9.2 (SAS Institute, Inc., Cary, NC, USA).

Results

Demographic comparisons and Axis-I disorders in probands

The characteristics of probands are presented in Table 2. With respect to demographic differences, there was a lower proportion of married subjects among mood disorder probands compared to controls. Moreover, the families of MDD probands had a lower mean socioeconomic status than those of BPD and control probands. Regarding comorbid disorders, the proportion of probands with lifetime anxiety disorders and alcohol dependence was greater among MDD probands than among BPD probands and comparison probands, who had the lowest proportion of comorbid conditions. Moreover, both BPD and MDD probands were found to have alcohol abuse more frequently than comparison probands.

Demographics and Axis-I disorders in the biological co-parent

Diagnostic information was collected on 94.1% of the biological co-parents of BPD probands, 97.1% of those of the MDD probands, and 99.9% of those of the comparison probands. The proportion of directly interviewed co-parents was higher in the spouses of BPD (55.0%) and comparison probands (69.1%) than those of MDD probands (36.5%; $\chi^2 = 12.64$, $p = 0.002$). Co-parents had a mean age of 42.6 years ($SD = 8.16$ years), 46.0% were women, and 27.3% held professional specialty positions. There were no differences in spouse demographic characteristics by proband diagnostic groups.

Regarding psychopathology, 11.3% of spouses of BPD probands, 11.5% of those of MDD probands, and 2.9% of those of comparison probands met the criteria for disorders of the bipolar spectrum (threshold and subthreshold BPD) (FET; $p = 0.11$). In addition, 26.3% of spouses of BPD probands, 25.0% of those of MDD probands, and 27.9% of those of comparison probands exhibited MDD ($\chi^2 = 0.14$, $p = \text{n.s.}$). Similarly, the rates of anxiety disorders, alcohol abuse, illicit SUD, DBD, and ADHD in co-parents did not vary significantly as a function of the probands diagnosis. However, the spouses of MDD probands had higher rates of alcohol dependence (17.3%) than those of BPD probands (10.0%) and those of comparison probands (1.5%; FET; $p < 0.01$).

Demographic comparisons and Axis-I disorders in offspring

More than 90% of offspring accepted the direct diagnostic interview. There were no significant differences in the age, sex, or proportion of interviews among offspring by parental diagnostic status (Table 2). However, the offspring of probands with BPD and MDD were less likely to be living with both biological parents than those of control probands.

Table 3 presents the gender-specific lifetime prevalence rates of psychiatric disorders across the three groups of offspring. The offspring of probands with mood disorders were found to be at an increased risk of any Axis-I psychiatric disorder and any mood disorder in the overall sample and among male children compared to offspring of controls (Table 3). Although the female children of probands with MDD did not evidence an increased risk of any Axis-I or mood disorder, the daughters of bipolar probands were at increased risk for these conditions compared to daughters of controls. Significantly higher rates of any depression, any MDD, and recurrent MDD were only found among the offspring of probands with BPD compared to offspring of controls. Only eight children exhibited syndromes of the bipolar spectrum (four BPD-I, one BPD-II, and three subthreshold BPD). Five of them were children of probands with either schizoaffective BPD or BPD-I and three of them were children of probands with recurrent MDD.

Regarding non-mood disorders, the children of probands with BPD and MDD met the diagnostic criteria for any anxiety disorder and separation anxiety disorder more frequently than those of comparison probands. When analyses were stratified by child age, the increased risk of any anxiety disorders ($\chi^2 = 6.9$, $p = 0.033$) and separation anxiety disorder ($\chi^2 = 6.4$, $p = 0.042$) in the offspring of probands with BPD and MDD was present in offspring aged between six and 11 years. Finally, alcohol use disorders were more common in female children of probands with MDD compared to female children of controls, whereas male children of BPD probands revealed a higher rate of cannabis abuse or dependence relative to male children of the other probands.

As illustrated in Figure 1, the cumulative morbid risk (26) of any anxiety disorder increased more steeply in the offspring of MDD and BPD probands as compared to the offspring of controls. Similarly, the cumulative morbid risk of any mood disorder increased more sharply in the offspring of affected probands than in those of comparison probands, although this difference reached statistical significance only in the offspring of BPD probands. The respective cumulative risk rates for any anxiety disorder developing by the age of 12 in the offspring of MDD, BPD, and comparison probands were 47%, 46%, and 27%, respectively. However, the respective cumulative risk rates for any mood disorder developing in the offspring by the age of 12 were 26%, 28%, and 15%, respectively. The respective rates for any anxiety disorder developing by the age of 18 were very similar to those for the age of 12: 47%, 48%, and 27%, whereas they increased for any mood disorders developing by that age to 45%, 64%, and 20%, respectively.

Children from families in which both parents were affected with bipolar spectrum disorders ($n = 14$) exhibited any mood disorder (64.3% versus 27.2%, FET $p = 0.01$) and any depressive disorder (57.1% versus 23.5%, FET $p = 0.02$) more frequently than the offspring of families in which only the proband parent was affected with a bipolar spectrum disorder.

However, a depressive disorder in the co-parent contributed no increased risk of disorder in the offspring of BPD probands. However, parental concordance for MDD increased the risk of DBD among offspring (22.2% versus 3.5%, FET $p = 0.01$).

Multilevel mixed models assessing the risk of disorders in offspring

Table 4 presents the adjusted odds ratios (ORs) derived from hierarchical multilevel mixed models, which progressively included an increasing number of variables. Except for separation anxiety disorder, the models that adjusted for proband non-mood disorders and socio-demographic characteristics in the offspring (Model 1) supported all associations found in the previous univariate analyses between BPD in probands and psychiatric disorders in the offspring. By contrast, the probands MDD was no longer associated with offspring mood disorders, but remained associated with any anxiety disorder and separation anxiety disorder in the children. Although the probands MDD was not associated with any of the mood disorders in the offspring, the ORs for these parent–child associations lay within the 95% confidence intervals (CIs) of the respective associations for parental BPD and offspring mood disorders, indicating no significant difference in the risk of mood disorders between the two groups of offspring.

Models that further adjusted for the co-parents disorders (Model 2) yielded similar findings to the previous models regarding the effect of the probands mood disorders (Table 4). These models also revealed that the co-parents bipolar spectrum disorder increased the risk of any mood disorder and any depression in the offspring, whereas the co-parents MDD was associated with the risk of any mood disorder and any depression in the offspring. Additional analyses, excluding co-parents with MDD from control probands (See Supplementary Tables 1 and 2) as well as co-parents with BPD from MDD probands (See Supplementary Tables 3 and 4), yielded similar results.

Complementary models, including the subtypes of proband mood disorders as independent variables, revealed that proband BPD-I disorder (OR = 2.5, 95% CI: 1.3–4.9) was significantly associated with an increased risk for any psychiatric disorder in the offspring. In addition, both the probands BPD-I and BPD-II disorders showed associations with any mood disorder (BPD-I: OR = 3.0, 95% CI: 1.3–6.8; BPD-II: OR = 5.1, 95% CI: 1.7–15.4) and any depression (BPD-I: OR = 3.0, 95% CI: 1.3–6.7; BPD-II: OR = 4.6, 95% CI: 1.5–14.6) in the offspring, whereas only the probands BPD-II disorder was associated with an increased risk of any MDD (OR = 5.2, 95% CI: 1.2–22.1) in the offspring. Furthermore, the probands BPD-II (OR = 8.8, 95% CI: 1.8–43.6) and the probands bipolar schizoaffective disorder (OR = 7.7, 95% CI: 1.4–43.3) were associated with recurrent MDD in offspring. However, the ORs for these associations did not differ significantly between the subtypes of the probands BPD. Regarding the subtype of MDD in probands (recurrent versus single-episode MDD), the risk of morbidity in children did not differ for any disorder in function of the probands depression subtype.

When the familial situation (living with both biological parents versus not) was introduced into the models, the strength of the associations between mood disorder in the proband and in the offspring diminished. Indeed, the probands BPD was no longer associated with any MDD (OR = 2.2, 95% CI: 0.9–5.1) or recurrent MDD (OR = 3.4, 95% CI: 1.0–11.9), and

co-parent BPD remained associated only with any mood disorder in the offspring (OR = 3.0, 95% CI: 1.1–8.2). Similarly, the probands MDD remained associated only with an increased risk of any anxiety disorder in the offspring (OR = 2.0, 95% CI: 1.1–3.8). However, the introduction of the familial situation into the models did not affect the associations between the co-parents MDD and mood disorders in offspring. The variable living with both biological parents was found to be negatively associated with any mood disorder (OR = 0.3, 95% CI: 0.2–0.7) and any depressive disorder (OR = 0.4, 95% CI: 0.2–0.7) in offspring.

Discussion

This study was the first to provide information on the rates of mental disorders in the offspring of probands with BPD, MDD, and controls, while also including a systematic evaluation of the coparent. The findings provide unique information on the initial manifestations of mood disorders in the offspring, and suggest that there may be some specificity with respect to the episodicity of depression in the offspring of parents with BPD, but also a lack of specificity between parental and co-parental mood disorders and a range of other disorders in childhood and adolescence. The strong impact of both parental concordance for mood disorders and parental marital status also highlights the need for inclusion of co-parent disorders and the familial context in providing a comprehensive picture of risk.

Mood disorders in the offspring of BPD and MDD probands

Our findings of risk rates of more than 50% for any disorder in general and more than 20% for mood disorders in the offspring of parents with mood disorders corroborate the findings of previous high-risk studies demonstrating the magnitude of risk attributable to familial factors (7–9, 27–29). Similarly, the further increase in the risk for mood psychopathology in the offspring of parents concordant for BPD is in line with that found in a previous study (9). The association between the non-intact marital status of parents and mental disorders in the offspring could either be a marker of the severity of the probands mood disorder or an intermediate factor through which the probands disorder is associated with an increased risk for mood disorders in the offspring.

Regarding the psychopathology of BPD, our rate of 2.3% for BPD in the offspring of BPD probands was low compared to those documented in most North American samples (8, 28, 30). Nevertheless, our rate was higher than the 1% observed in a Romanian sample (31) and comparable to the 3% observed in a non-controlled Dutch study (32). As a recent meta-analysis has provided similar rates of pediatric BPD in the USA and other countries, including in Europe (33), the lower rates of BPD in European high-risk studies are likely to be attributable to methodological differences across studies, including the definition of BPD in the offspring, the type of diagnostic interview (K-SADS-E or Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime version), and the selection of subjects. Indeed, studies assessing the whole bipolar spectrum, including BPD not otherwise specified [e.g., (8)] unsurprisingly found higher rates of BPD than those restricted to BPD-I and BPD-II (e.g., both European studies) (31, 32). Moreover, the comparison between the proband samples in the study by Birmaher et al. (9) and those in the

present study revealed considerable differences regarding comorbid disorders in the BPD probands, suggesting less severe forms of BPD in our probands which could partially explain the lower rates of BPD in the offspring. Indeed, Birmaher et al. reported rates of ADHD (2.8%) and DBD (8.4%) in their control probands that were similar to those in the present study (3.0% and 6.1%, respectively), whereas their rates in BPD probands were more than the double those in the present study for both ADHD (27.5% versus 12.5%) and DBD (36.9% versus 12.5%).

The earlier onset of mood disorders and the increased risk of recurrent depressive episodes in the offspring of parents with BPD compared to those of controls suggest that the episodicity that characterizes BPD may emerge in childhood and adolescence. However, the rates of depression did not differ between the offspring of BPD and those of MDD probands. In addition, the low base rates of BPD in the offspring precluded our distinguishing specificity for BPD between the unipolar and BPD proband groups. Future follow-up studies may elucidate the extent to which these findings persist as these children progress to adulthood.

Non-mood disorders and SUD

The elevation in rates of anxiety disorders among the offspring of probands with both mood disorder subtypes demonstrates a lack of specificity of parental mood and anxiety disorders, as reported in previous studies (8, 9, 28, 30, 31, 34). Likewise, the probands MDD independently predicted SUD (alcohol) among older offspring in this research, extending the range of disorders associated with parental mood disorders (9, 27). In contrast to the majority of previous high-risk studies of school-age (Table 1) and pre-school-age offspring of probands with BPD (35), the present research did not provide evidence of increased rates of DBD and ADHD in these children. However, it corroborates the recent findings of Birmaher et al. (9), who showed that increased rates of DBD and ADHD in the children of parents with BPD are attributable to general parental psychopathology or other related factors rather than to parental mood disorders. Moreover, comparison with the study by Birmaher et al. (9), which included probands with BPD with much higher rates of comorbid ADHD and DBD than in our research, suggests that the large variance in the crude rates of both ADHD and DBD in the offspring of probands with BPD across studies is likely to be attributable to differences in the prevalence of these disorders in the probands.

Strengths and limitations

In contrast to previous high-risk research on mood disorders, which rarely included probands with both BPD and MDD (7), the design of the present study allowed us to simultaneously compare the risk of specific DSM–IV disorders and algorithmically defined subthreshold mood syndromes in the offspring of probands with both major subtypes of mood disorders to that of children in a medical comparison group. In addition, the collection of diagnostic information on the biological co-parent enabled us to examine the association between parental concordance for mood disorders and the risk of mood disorders in the offspring.

The results of the present study should also be considered in the context of several limitations. First, our sample may have been too small to accurately estimate the prevalence of relatively rare disorders in childhood and adolescence, such as BPD or SUD. Moreover, even though this was one of the largest high-risk studies of BPD to date, the sample size limited the ability to test the effects of more refined subtypes of parental mood disorders. Second, our sample may have been biased because of the refusal to participate by a substantial proportion of eligible probands, particularly those with comorbid illicit drug use disorders. Third, diagnoses of approximately 10% of the offspring were based on family history reports rather than direct interviews. However, it is unlikely that the results were subject to differential bias because of the equal distribution of non-interviewed children across the three offspring groups. Fourth, although a lifetime history of mental disorders was collected for almost all biological co-parents, we had to rely on informant reports for almost half of them. Fifth, given the young mean age of the sample, the results of the present study only partially reflect the psychopathology that typically occurs during adolescence, such as manic episodes or SUD.

Implications

The findings of the present study have several potential clinical implications. First, the high rates of early mood and anxiety disorders in the offspring of patients with both BPD and MDD emphasize the need to pay particular attention to the offspring of these patients. The prompt identification and treatment of mood and anxiety disorders in these children may be critical for the prevention of complications such as poor school performance, difficulties in social relationships, and the development of SUD. The follow-up of this sample will provide further evidence on the extent to which offspring with recurrent depression develop manic symptoms and disorders, and the links between early anxiety disorders and the later onset of BPD, as suggested in prior retrospective studies of adults with BPD (36–38) and in a recent high-risk study of BPD with a follow-up of up to 15 years (39). Indeed, Duffy et al. (39) reported the offspring of subjects with BPD to manifest higher rates of anxiety and sleep disorders, followed by major mood disorders and SUD and, subsequently, by an index (hypo)manic episode compared to controls.

Second, similar to the children of BPD-I probands, those of BPD-II probands revealed a high risk of mood disorders, demonstrating the importance of including the full range of BPD in such studies. Third, as the children of patients with BPD exhibited early manifestations of anxiety and depressive symptoms, the establishment of a thorough history of parental manic symptoms may be critical to alert the clinician of the possibility of antidepressant-induced *switching* to BPD in these offspring. Fourth, the significant role of the familial situation regarding the risk of mood disorders in the offspring demonstrates the importance of family-based treatments designed specifically for people with BPD (40).

Longitudinal studies that follow high-risk young people through adolescence and early adulthood are necessary to determine the extent to which early manifestations of mood and anxiety disorders are indeed predictors of adult BPD and MDD and to identify genetic, biological, and environmental determinants of mood and non-mood disorders that persist into adulthood.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1. Cumulative rates by age of onset of any anxiety (**A**) and any mood disorders (**B**). BPD = bipolar disorder; MDD = major depressive disorder.

Table 1.

Controlled high-risk studies (> 40 subjects/group) of mood disorders with direct diagnostic interviews of offspring younger than 18 years

Parents										Offspring										Results									
Parents with mood disorders										Comparison parents										Lifetime Axis-I disorders in high-risk (H) and low-risk (L) offspring, %									
Study	N	Diagnosis (diagnostic system)	Source	N	Source	Assessments	High-risk		Low-risk		Assessments	Any		BPD		MDD		Anxiety		DBD		ADHD		Substance abuse					
							N	Mean age and range	N	Mean age and range		H	L	H	L	H	L	H	L	H	L	H	L	H	L	H	L	H	L
Weissman et al. 1987 (27)	56	MDD (RDC)	Out-patients	35	Community survey	SADS-L	125	17	95	17	K-SADS-E	73	65	—	—	38 ^a	24	37	27	22 ^b	17 ^b	5	7	17 ^a	7				
Orvaschel et al. 1982 (15)	34	MDD recurrent (DSM-III)	Treated subjects	29	Community or controls of other studies	SADS-L	61	10.7	46	11.1	K-SADS-E	41 ^a	15	—	—	—	—	20	9	—	—	20 ^a	7	—	—				
	47	BPD-I (DSM-III)	In-patients	61	Non-clinical subjects	Clinical interview	72	12.9	72	13.1	K-SADS-E	—	—	1 ^c	0 ^c	8 ^{a,c}	1 ^c	12 ^{a,c}	4 ^c	14 ^c	7 ^c	21 ^{a,c}	7 ^c	—	—				
Grigoriu-Serb nescu et al. 1989 (31)	54	MDD (DSM-III-R)	In-patients	70	Non-clinical subjects	SCID-I	96	13.1	96	13.0	K-SADS-E	—	—	—	—	12 ^d	5 ^d	8 ^d	6 ^d	12 ^d	7 ^d	18 ^{a,d}	7 ^d	—	—				
	22	BPD	Mothers recruited through clinicians or advertisement	37	Mothers recruited by advertisement	SADS-L	22	5-6	37	5-6	CAS CBCL (mother)	38	20	—	—	24 ^a	3	9	17	24	6	—	—	—	—				
Radke-Yarrow et al. 1992 (7)	41	Unipolar depression (RDC)					22	8-11	35	8-11		61	40	—	—	44 ^a	14	44	34	28 ^a	3	—	—	—	—				
	113	MDD and panic disorder	Treated subjects	61	Subjects recruited by advertisement	SCID	179	6.8	113	6.8	K-SADS-E	—	—	—	—	5.1 ^{a,e}	—	—	—	—	—	—	—	—	—				
Hirschfeld-Becker et al. 2008 (29)	39	MDD					59	6.7				—	—	—	—	9.0 ^{a,e}	—	—	—	—	—	—	—	—	—				
	30	MDD and DBD		47			50	11.0	106	10.0		—	—	10 ^a	1	28 ^a	3	—	—	44 ^a	6	40 ^a	12	—	—				
Henin et al. 2005 (28)	60	MDD (DSM-III-R)					119	10.3				—	—	3	1	14 ^a	3	—	—	25 ^a	6	26	12	—	—				
	88	BPD (DSM-IV)	In-patients	95	Subjects recruited by advertisement	SCID	117	8-12	171	8-12	K-SADS-E	—	—	12 ^a	1	34 ^a	8	21 ^{a,f}	5 ^f	34 ^a	5	22 ^a	8	3	1				

Parents				Comparison parents				Offspring		Results														
Parents with mood disorders								High-risk		Low-risk		Lifetime Axis-I disorders in high-risk (H) and low-risk (L) offspring, %												
Study	N	Diagnosis (diagnostic system)	Source	N	Source	Assessments	N	Mean age and range	Mean age and range	Assessments	Any		BPD		MDD		Anxiety		DBD		ADHD		Substance abuse	
											H	L	H	L	H	L	H	L	H	L	H	L	H	L
Duffy et al. 2007 (8)	36	BPD-I lithium responders	Out-patients	41	Parents of school children	SADS-L	67	16.8	13–18	K-SADS-PL	—	—	33 ^a	3	52 ^a	28	21 ^{a,f}	5 ^f	45 ^a	11	22 ^a	8	14	16
											—	—	21 ^a	0	19 ^a	2	19 ^a	5	0	0	5	2	10 ^a	0
Birmaher et al. 2009 (9)	27	BPD-I lithium non-responders (DSM-IV)					60	16.1	8–25		—	—	20 ^a	0	28 ^a	2	32 ^a	5	3	0	17*	2	22*	0
Birmaher et al. 2009 (9)	233	BPD (DSM-IV)	Advertisement, adult BP studies, out-patients	143	Matched parents from the community	SCID	388	11.9	8–25	K-SADS-PL	52 ^a	29	3 ^a	0	9 ^a	3	26 ^a	11	19 ^a	8	25 ^a	17	4	3
													7 ^{a,g}	0 ^g										
Nurnberger et al. 2011 (30)	88	BPD (DSM-IV)	5% in-patients, 95% out-patients	58	General medicine clinics, motor vehicle records, advertising	DIGS	141	16.7	6–18	K-SADS-PL	—	—	7 ^a	0	10 ^h	3 ^h	26 ^a	14	11	8	8	6	18 ^a	9
													1 ^g	0	6 ⁱ	1 ⁱ								

BPD = bipolar disorder; BPD-I = bipolar I disorder; CAS = Child Assessment Scale; CBCL = Child Behavior Checklist; DIGS = Diagnostic Interview for Genetic Studies; K-SADS-E = Schedule for Affective Disorders and Schizophrenia for School-Age Children–Epidemiologic version; K-SADS-PL = Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime version; MDD = major depressive disorder; RDC = research diagnostic criteria; SADS-L = Schedule for Affective Disorders and Schizophrenia–Lifetime version; SCID-I = Structured Clinical Interview for DSM –IV.

^ap < 0.05.

^bConduct disorder.

^cPoint prevalence.

^d12-month prevalence.

^eAdjusted odds ratio.

^fSeparation anxiety disorder.

^gBPD not otherwise specified.

^hSingle-episode MDD.

ⁱRecurrent MDD.

Table 2.

Sample characteristics

	Proband with BPD (n = 72)	Proband with MDD (n = 56)	Comparison probands (n = 66)	Statistic	p-value	Pairwise comparison
Demographic						
Female, %	59.7	60.7	43.9	$\chi^2_2 = 4.63$	n.s.	—
Age, mean (SD)	40.7 (6.8)	41.0 (7.1)	41.4 (6.7)	$F_2 = 0.15$	n.s.	—
Married, %	61.1	53.6	78.8	$\chi^2_2 = 9.20$	0.01	AB
No. of offspring included, mean (SD)	1.93 (0.95)	1.96 (0.87)	1.92 (0.77)	$F_2 = 0.04$	n.s.	—
Non-mood disorders						
Any anxiety disorder, %	27.8	51.8	6.1	$\chi^2_2 = 31.91$	< 0.0001	ABC
Alcohol dependence, %	19.4	44.6	3.0	$\chi^2_2 = 31.67$	< 0.0001	ABC
Alcohol abuse, %	19.4	30.4	6.1	$\chi^2_2 = 12.25$	< 0.01	AB
Illicit substance abuse or dependence, %	18.1	17.9	7.6	$\chi^2_2 = 3.81$	n.s.	—
Disruptive behavioral disorders, %	12.5	16.4	6.1	$\chi^2_2 = 3.29$	n.s.	—
ADHD, %	12.5	7.1	3.0	$\chi^2_2 = 4.37$	n.s.	—
Offspring of BPD (n = 139)						
Offspring of MDD (n = 110)						
Offspring of controls (n = 127)						
Demographic						
Female, %	53.2	50.9	48.0	$\chi^2_2 = 0.72$	n.s.	—
Age, mean (SD)	11.80 (3.47)	11.3 (3.25)	11.3 (3.48)	$F_2 = 0.81$	n.s.	—
SES, mean (SD) ^a	3.5 (0.99)	2.9 (0.97)	3.5 (1.03)	$F_2 = 15.70$	< 0.0001	BC
Living with both parents, %	48.9	46.4	79.5	$\chi^2_2 = 35.06$	< 0.0001	AB
Directly interviewed, %	94.2	90.0	89.8	$\chi^2_2 = 2.15$	n.s.	—

A = BPD versus CTRL; ADHD = attention-deficit hyperactivity disorder; B = MDD versus CTRL; BPD = bipolar disorder; C = BPD versus MDD; CTRL = controls; MDD = major depressive disorder; ns = not significant; SES = socioeconomic status.

A value of 3 represents an SES of III (middle class) on the Hollingshead scale.

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Table 3.

Parental disorders (n)	All offspring (n = 376)					Daughters (n = 191)					Sons (n = 185)					Pairwise comparisons		
	BPD (139)	MDD (110)	CTRL (127)	χ^2_2	p-value	Pairwise comparisons	BPD (74)	MDD (56)	CTRL (61)	χ^2_2	p-value	Pairwise comparisons	BPD (65)	MDD (54)	CTRL (66)		χ^2_2	p-value
Offspring disorders																		
Any disorder	61.9	58.2	36.2	19.8	0.000	AB	64.9	57.1	41.0	7.9	0.020	A	58.5	59.3	31.8	12.4	0.002	AB
Any mood disorder	34.5	25.5	12.6	17.4	0.000	AB	35.1	26.8	14.8	7.2	0.027	A	33.9	24.1	10.6	10.2	0.006	AB
Any depression	30.9	22.7	12.6	12.9	0.002	A	31.1	25.0	14.8	4.9	n.s.	A	30.8	20.4	10.6	8.2	0.017	A
Any MDD	19.4	10.0	7.1	10.1	0.006	AC	20.3	12.5	8.2	4.2	n.s.	A	18.5	7.4	6.1	6.1	0.046	A
MDD recurrent	7.9	3.6	1.6	6.5	0.040	A	9.5	3.6	1.6	FET	n.s.	—	6.2	3.7	1.5	FET	n.s.	—
MDD single-episode	11.5	6.4	5.5	3.8	n.s.	—	10.8	8.9	6.6	0.8	n.s.	—	12.3	3.7	4.6	FET	n.s.	—
SAD	2.3	5.0	0.9	FET	n.s.	—	2.8	5.9	1.8	FET	n.s.	—	1.6	4.0	0.0	FET	n.s.	—
Dysthymia	2.2	1.8	1.6	FET	n.s.	—	1.4	1.8	1.6	FET	n.s.	—	3.1	1.9	1.5	FET	n.s.	—
Sub. depression	7.2	7.3	4.7	0.9	n.s.	—	6.8	5.4	4.9	FET	n.s.	—	7.7	9.3	4.6	FET	n.s.	—
Any BPD	3.6	2.7	0.0	FET	n.s.	—	4.1	1.8	0.0	FET	n.s.	—	3.1	3.7	0.0	FET	n.s.	—
BPD I or II	2.2	1.8	0.0	FET	n.s.	—	2.7	1.8	0.0	FET	n.s.	—	1.5	1.9	0.0	FET	n.s.	—
Sub. BPD	1.4	0.9	0.0	FET	n.s.	—	1.4	0.0	0.0	FET	n.s.	—	1.5	1.9	0.0	FET	n.s.	—
Any anxiety disorder	42.5	44.6	22.8	15.4	0.000	AB	50.0	44.6	29.5	6.0	0.049	A	33.9	44.4	16.7	11.2	0.004	AB
Separation anxiety	28.8	36.4	15.8	13.4	0.001	AB	37.8	37.5	19.7	6.2	0.045	AB	18.5	35.2	12.1	9.9	0.007	BC
GAD	2.2	2.7	0.0	FET	n.s.	—	4.1	1.8	0.0	FET	n.s.	—	0.0	3.7	0.0	FET	n.s.	—
Panic disorder	0.7	0.9	0.8	FET	n.s.	—	1.4	1.8	1.6	FET	n.s.	—	0.0	0.0	0.0	—	—	—

A = BPD versus CTRL.; ADHD = attention-deficit hyperactivity disorder; B = MDD versus CTRL.; BPD = bipolar disorder; C = BPD versus MDD; CTRL = controls; FET = Fisher's exact tests; GAD = generalized anxiety disorder; MDD = major depressive disorder; ns = not significant; PTSD = posttraumatic stress disorder; SAD = unipolar schizoaffective disorder; Sub. BPD = subthreshold bipolar disorder; Sub. depression = subthreshold depression.

Table 4.

Adjusted odds ratios and 95% confidence intervals for psychiatric disorders in the offspring of parents with mood disorders

	Model 1^a		Model 2^b		MDD of co-parent
	Offspring of BPD	Offspring of MDD	BPD of proband	MDD of proband	
Any disorder	2.3 (1.3–4.0) **	1.7 (0.9–3.1)	2.3 (1.3–4.0) **	1.6 (0.8–2.9)	1.4 (0.8–2.3)
Any mood disorder	3.3 (1.6–6.8) ***	1.7 (0.7–4.2)	3.1 (1.5–6.5) **	1.6 (0.7–3.7)	1.9 (1.0–3.6) *
Any depression	2.9 (1.4–6.0) **	1.6 (0.7–4.1)	2.9 (1.4–6.1) **	1.6 (0.7–4.0)	2.0 (1.0–3.9) *
Any MDD	2.6 (1.1–6.4) *	1.0 (0.3–3.3)	2.4 (1.0–5.9) *	1.0 (0.3–3.3)	2.0 (0.9–4.4)
<i>MDD recurrent</i>	5.8 (1.3–24.9) *	2.0 (0.3–15.0)	4.4 (1.2–16.0) *	1.5 (0.2–10.0)	1.0 (0.2–4.8)
Any anxiety disorder	2.1 (1.2–3.8) *	2.2 (1.1–4.1) *	2.2 (1.2–4.0) **	2.1 (1.1–4.0) *	1.1 (0.6–1.9)
Separation anxiety	1.7 (0.9–3.3)	2.1 (1.0–4.3) *	1.9 (1.0–3.6)	2.2 (1.0–4.5) *	1.0 (0.6–1.8)

BPD = bipolar disorder; MDD = major depressive disorder.

^a Adjusting for offspring's age, sex, and socioeconomic status, and proband's non-mood disorders.^b Adjusting for offspring's age, sex, and socioeconomic status, and proband's non-mood disorders as well as spouse's disorders

* p < 0.05

** p < 0.01

*** p < 0.001.