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Original Article

Aggression, hostility, and irritability in children at risk for bipolar disorder

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Objectives: To assess aggression, irritability and hostility in children at risk for bipolar disorder (BP).

Methods: Using the parent and the child versions of the Children's Hostility Inventory (CHI), we assessed aggression, hostility, and irritability in 300 offspring aged 6–18 years old of BP parents and 169 children of community controls.

Results: Children of BP parents have significantly higher scores on the total CHI and its subscales than do children of control parents. After adjusting for demographic variables, both parents' non-BP psychopathology, child psychopathology, and within-family correlations, three factors remain significant: total CHI by parent rating, irritability subscale by parent rating, and irritability by child self-report. The hostility subscale by parent rating became a trend.

Conclusions: Children of BP parents score higher on ratings of hostility and irritability than children of community control parents, independent of child psychopathology and non-BP parental psychopathology. Follow-up of these children to evaluate whether these symptoms are markers for the development of BP or mood disorders is warranted.

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Bipolar disorder (BP) is a severe, persistent mental illness associated with significant morbidity and mortality. It is also well-established as a familial disorder, with a 5–10% prevalence in first-degree relatives of adults and children with BP, compared to 0.5–1.5% prevalence in community samples [1–4, (Birmaher B, Axelson D, Monk K et al. Psychiatric disorders in children of bipolar parents. Manuscript in preparation.)]. In addition, the concordance for BP I in monozygotic twins is significantly higher (43–67%) than in dizygotic twins (7–20%) (3, 5–8). In recent years, researchers have begun to focus on high-risk populations, such as children of bipolar parents. Of the studies thus far, many have focused on the risk of developing BP or other psychiatric disorders (9–13). Some studies have also looked at temperament (14, 15) and family environment (16). Nonetheless, a well-defined premorbid phenotype remains elusive.

The ability to identify populations at risk for developing BP has important public health implications. Early recognition and treatment of BP may decrease the morbidity and mortality associated with the disorder. Given the high risk of suicide in BP patients, this is no small consideration.

There is reason to suspect that aggression is a potential marker for early-onset BP, with anger and irritability as possible prodromal symptoms (17, 18). Juvenile mania may be particularly disorganized and explosive (19, 20). Also, aggression is a frequent reason for hospitalization in manic youths (21). The considerable overlap with disruptive behavior and attention-deficit hyperactivity

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disorders (ADHD) supports the idea that children with BP tend to be aggressive (though one must differentiate between planned disruptive behaviors and the behavioral disinhibition of BP) (2, 22).

While Leibenluft and colleagues (23) suggested that the development of sensitive and specific measures of irritability in children with psychopathology would be an important advance in our field, to date there is no universally accepted rating scale with which to assess irritability or aggression. For this study, one of the instruments we chose to evaluate these symptoms was the Children's Hostility Inventory (CHI) (24), a measure which can be used to examine aggression, hostility, and irritability as separate symptoms.

Given the heritability of BP, and the suspicion that irritability, aggression, and/or hostility may precede other symptoms in early-onset BP, it is reasonable to examine the extent and nature of these symptoms in offspring of BP parents. We hypothesized that children of BP parents would have higher CHI scores (total and each subscale) than children of non-BP parents.

Methods

Subjects

Subjects were recruited as part of the National Institute of Mental Health (NIMH) Bipolar Offspring Study (BIOS) (principal investigator Boris Birmaher MD, RO1 MH060952-06), a project which aims to cross-sectionally and longitudinally examine the clinical and psychosocial characteristics of offspring of BP parents. For this study we included the first 300 children of 183 parents with BP recruited from the Western Psychiatric Institute and Clinic inpatient units, adult bipolar clinics, and through local advertising. Control parents were recruited from the community through the University Center for Social and Urban Research (UCSUR) at a ratio of one control parent to two BP parents. The control parents were frequency matched by age, sex, and neighborhood using the area code and first three digits of the telephone number of the BP parents. For this study we included 169 children of 100 community control parents. To obtain this sample, UCSUR made numerous calls, of which only 3,600 parents were available to take the call. After a general explanation of the study, 230 agreed to be screened. The BIOS coordinator called these subjects and explained the study in more detail and eligible subjects were enrolled as controls.

Parents with BP were considered for inclusion in the study provided they had at least one child between the ages of 6 and 18 years and at least one of the biological parents had custody of their children. Parents with current or lifetime diagnoses of schizophrenia, mental retardation (IQ $\leq$ 70), mood disorder secondary to substance abuse, a medical condition or use of medications (e.g., corticosteroids), or who lived more than 200 miles away from Pittsburgh were excluded from the study. Additionally, in parents whose current psychiatric condition impeded cooperation with the interview (e.g., acute mania, psychosis, severe depression), recruitment was deferred until after remission of their acute episode. Similar inclusion and exclusion criteria were used for community controls, with the additional exclusion criterion of any lifetime or current bipolar spectrum diagnosis and history of BP in first-degree relatives. As shown in Table 1, the parents varied demographically in sex, race, and marital status, with more female parents ($p = 0.02$), fewer Caucasian parents ($p = 0.02$), and more married parents ($p = 0.01$) in the community control group than the BP group.

Offspring of parents with BP and community controls between 6 and 18 years old were included in the study. Except for mental retardation and autism, no psychiatric diagnoses were considered exclusionary in the offspring; however, if a child's acute psychiatric condition precluded cooperation with the interview (e.g., acute mania, psychosis, severe depression), the interview was deferred until after remission of the acute episode. As depicted in Table 2, children of BP parents were less likely to live with both biological parents than offspring of community controls ($p = 0.006$).

As shown in Table 2, children of BP parents were more likely than children of control parents to have had any psychiatric diagnosis at the time of assessment ($p < 0.001$). Children of BP parents were more likely to be diagnosed with mood and anxiety disorders, as well as ADHD, oppositional defiant disorder (ODD), and conduct disorder (CD) (all p-values $\leq$0.01). Birmaher et al. [4, (Birmaher B, Axelson D, Monk K et al. Psychiatric disorders in children of bipolar parents. Manuscript in preparation.)] provide further discussion of the lifetime rates of psychiatric disorders in this sample.

Assessment

After Institutional Review Board approval and consent was obtained, parents were assessed for psychiatric and personality disorders, family history of psychiatric disorders and other variables such as dimensional psychopathology, psychosocial functioning, family environment, and exposure

Table 1. Demographics and lifetime psychiatric disorders of bipolar disorder and control probands

	Parents with BP (n = 183)	Controls (n = 100)	Statistic	p-value
Mean age (SD)	40.1 (7.5)	40.6 (6.7)	$t = 0.51$	0.61
Sex (% female)	79.2	90.0	$\chi^2 = 5.32$	0.02
Race (% Caucasian)	89.1	79.0	$\chi^2 = 5.29$	0.02
Mean SES (SD)	35.4 (14.3)	37.1 (13.2)	$t = 0.96$	0.34
Married proband (% yes)	49.7	65.0	$\chi^2 = 6.10$	0.01
Any Axis I disorder	100.0	57.0	$\chi^2 = 92.8$	<0.001
Bipolar disorder I	60.7	–	–	–
Bipolar disorder II	33.3	–	–	–
Other BP (NOS, cyclothymia)	7.1	–	–	–
Unipolar MDD	–	30.0	–	–
Dysthymic disorder	3.3	8.0	FET	0.09
Any anxiety	72.7	29.0	$\chi^2 = 50.4$	<0.001
Panic disorder	39.3	5.0	$\chi^2 = 38.5$	<0.001
ODD or CD	33.3	7.0	$\chi^2 = 24.6$	<0.001
ADHD	25.1	1.0	$\chi^2 = 27.2$	<0.001
Any substance abuse (alcohol, marijuana, cocaine)	63.4	26.0	$\chi^2 = 36.2$	<0.001

SD = standard deviation; SES = socioeconomic status; BP = bipolar disorder; NOS = not otherwise specified; MDD = major depressive disorder; ODD = oppositional defiant disorder; CD = conduct disorder; ADHD = attention-deficit hyperactivity disorder; FET = Fisher's exact test.

to negative life events. Only instruments relevant to this paper will be discussed.

All available parents were interviewed using the DSM-IV Structured Clinical Interview (SCID) to assess presence of psychopathology (25). For 31% of children in the study, both biological parents were interviewed directly. In all other cases, one parent was interviewed directly, and the non-participating parent's diagnostic information was obtained through family history. Once parental diagnosis was confirmed by a psychiatrist, children were recruited. After children signed consent/assent, parents and their children completed the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version (K-SADS-PL) (26), including the Mania Rating Scale (K-SADS MRS) (27) and the Depression section of the KSADS (KSADS-Dep) (28). Children were interviewed by raters blind to parental diagnoses. Children also completed the self-report version of the CHI, and parents were asked to complete the parent version of the CHI. If children had difficulty reading the instrument, their parents were allowed to help them read the form. Parent ratings were completed by mothers in 91% of cases. There were no significant differences between mother and father reports.

Table 2. Demographics and lifetime psychiatric disorders of offspring of bipolar disorder and control parents

	Offspring of bipolar parents (n = 300)	Offspring of control parents (n = 169)	Statistic	p-value
Mean age (SD)	12.1 (3.6)	11.6 (3.5)	$t = 1.30$	0.19
Sex (% female)	48.3	55.6	$\chi^2 = 2.30$	0.13
Race (% Caucasian)	82.0	76.9	$\chi^2 = 1.75$	0.19
Mean SES (SD)	35.7 (14.3)	37.4 (13.1)	$t = 1.30$	0.19
Lives with both biological parents (%)	46.7	59.8	$\chi^2 = 7.42$	0.006
BP spectrum (%)	8.3	0.6	$\chi^2 = 12.37$	<0.001
Unipolar MDD/dysthymia (%)	10.7	2.4	$\chi^2 = 10.51$	0.001
Any mood (BP, MDD, dysthymia) (%)	20.0	3.6	$\chi^2 = 24.19$	<0.001
Any anxiety (%)	24.3	10.1	$\chi^2 = 14.20$	<0.001
SAD, GAD, social phobia (%)	21.0	8.3	$\chi^2 = 12.74$	<0.001
ODD or CD (%)	17.3	8.9	$\chi^2 = 6.32$	0.01
ADHD (%)	23.7	14.2	$\chi^2 = 6.00$	0.01
Any psychiatric disorder (%)	50.3	27.2	$\chi^2 = 23.71$	<0.001

SD = standard deviation; SES = socioeconomic status; BP = bipolar disorder; MDD = major depressive disorder; SAD = separation anxiety disorder; GAD = general anxiety disorder; ODD = oppositional defiant disorder; CD = conduct disorder; ADHD = attention-deficit hyperactivity disorder.

The CHI was derived from the Buss–Durkee Hostility Inventory for adults (29), which has been widely used to ascertain aggressive and irritable behavior in subjects with psychiatric disorders and the general population (see Table 3 for sample items). The CHI has been validated against the Interview for Antisocial Behavior (30) and the Child Behavior Checklist (31, 32). Two versions of the scale – self-report and parent-rated – are available, each with 38 true/false items. In addition to an overall measurement, subscores for Aggression (overt acts), Hostility (attitudinal, perceptual, affective), and Irritability (which has elements of both) can be generated.

With the exception of an operationalized definition of BP not otherwise specified (BP-NOS), NOS disorders for both adults and children were not included. BP-NOS was defined as clinically relevant BP symptoms that did not fulfill DSM-IV criteria for BP I or BP II. Subjects were also required to have a *minimum* of elated mood plus two associated DSM symptoms or irritable mood plus three associated DSM symptoms and change in functioning. These symptoms were required to last a minimum of 4 hours within a 24-hour period, and at least four cumulative lifetime days meeting the criteria.

All assessments were completed by bachelor's level or master's prepared interviewers with at least 2 years of experience. Most assessments were carried out at the subjects' homes. All adult, child, and family psychiatric information was presented to a child psychiatrist for diagnostic consensus. When necessary, subjects' medical records were obtained and reviewed. To ensure blindness to parental diagnoses, the parents and their offspring were assessed by different interviewers. The child psychiatrists were also blind to the psychiatric status of the parents. The overall SCID and KSADS kappas for psychiatric disorders were ≥0.8. The intraclass correlation coefficients (ICC) for the KSADS-MRS and the KSADS-Dep were ≥0.95.

Socioeconomic status (SES) was ascertained using the 4-factor Hollingshead scale (33, 34).

Statistical analyses

The demographic and clinical characteristics between the groups were compared using *t*- and χ^2-tests as appropriate. Total CHI scores and scores on subscales (Aggression, Hostility, and Irritability) were examined, both by parent rating and child self-report. Mean scores between the two groups were compared using *t*-tests. We further controlled for demographic differences (age, race, sex, SES, proband parent sex, living with a single parent, both biological parents' non-BP psychopathology, and child psychopathology status) using hierarchical linear regression. Interaction effects were tested and included in the models if significant. Because a number of our families had more than one child in the study, we performed a mixed effects regression analysis, covarying for any intrafamilial correlations. Only one family had more than one parent with BP.

To further clarify the contribution of child psychopathology, we performed additional analyses. First, we used correlations to determine which diagnoses were most related to the CHI score, looking specifically at BP, ADHD, disruptive behavior disorders (ODD and CD), anxiety disorders, any mood disorder, and unipolar mood disorders (major depressive disorder and dysthymia), as well as presence of any disorder. Based on these results, we performed hierarchical regression analyses, stratifying subjects by presence or absence of disruptive behavior disorders, presence

Table 3. Selected items from the Children's Hostility Inventory

Aggression
Once in a while he cannot control his wanting to harm others.
He would feel that anyone making fun of him or his family is asking for a fight.
He sometimes says bad things about people he doesn't like.
He can remember being so mad that he picked up the nearest thing and broke it.
He can't help getting into arguments when others don't agree with him.
Hostility
He thinks other people always seem to have good things happening to them.
Almost every week he sees someone he dislikes.
He often thinks about what reasons another person may have for doing something nice for him.
He used to think that most people told the truth, but he doesn't anymore.
Irritability
Sometimes people bug him just by being around.
He is usually madder than most people realize.
He often feels like a bomb ready to explode inside.

or absence of mood disorders, or presence or absence of BP. Each stratified sample was analyzed separately, again controlling for demographic differences, both parents' non-BP psychopathology, and intrafamilial correlations.

For all analyses reported below, the results remained consistent after controlling for within-family correlations.

All values are reported as means ± standard deviations. Unless otherwise noted, all p-values are based on two-tailed tests with α_2 levels of 0.05.

Results

As illustrated in Table 4, with the exception of a trend for the child-rated Hostility, children of BP parents scored significantly higher on the total CHI and each of its subscales than children of community control parents, both by parent rating and by self-report. Adjusting for biological parents' non-BP psychopathology, child's age, and significant demographic variables (age, race, sex, SES, proband parent sex, and single-parent status) yielded similar results.

Given that children of BP parents had significantly more psychiatric disorders than children of control parents (Table 2), we also controlled for the presence of child psychopathology. When child psychopathology was added to the regression model (Table 5) for the parent report, with the exception of a trend in the Aggression scores (0.07), the results were similar to those reported in Table 4. With respect to the child reports, children of BP parents continued to show significantly higher Irritability scores with a trend for higher total CHI and Aggression scores.

Within the regression model, child psychopathology was the strongest predictor of CHI scores, both total and subscales, regardless of informant. Therefore, analyses were performed to evaluate the relative contribution of different psychiatric disorders. For nearly all CHI variables, scores were most highly correlated to disruptive behavior disorders, but correlations with mood disorders and BP were also noted (Table 6). Using presence or absence of disruptive behavior disorders in the regression model, results are similar to those above. Further analyses examining the role of child mood disorders and child BP also yielded similar results.

Discussion

Overall, this study showed that having a BP parent seems to confer a specific risk for higher CHI scores, particularly for parent-reported Irritability, above and beyond the contribution of child psychopathology and both parents' non-BP psychopathology.

Before discussing in detail the findings noted above, we must stress that these results should be viewed in light of certain study limitations. Most notably, this is a cross-sectional design. Though we know which children are ostensibly at risk for BP, we do not yet know which children will go on to develop BP, so it will be worthwhile to follow these children over time. We plan to follow this cohort longitudinally, and will re-evaluate these data based on eventual psychopathology. Finally, in this study we did not adjust for multiple comparisons. However, it is customary not to control for multiple comparisons for *a priori* hypotheses. Moreover, since it is important to explore for early phenotypes that may predict the development of BP in children, we feel that the results should be presented without being overly conservative. That said, the results presented in this paper require replication by other groups.

The finding of selective high levels of irritability is not entirely surprising. 'Irritability' is a nearly universal feature of pediatric BP, though it tends to be poorly defined. In fact, there is an ongoing

Table 4. Children's Hostility Inventory (CHI) scores: parent-rated and child self-report

CHI scores	Offspring of bipolar parents (n = 300)	Offspring of control parents (n = 169)	Statistic	p-value	Effect size (*d*)
CHI-P total	18.6 ± 7.5	14.7 ± 6.8	$t = 5.58$	<0.001	0.54
Aggression-P	9.7 ± 3.7	8.2 ± 3.4	$t = 4.11$	<0.001	0.41
Hostility-P	2.6 ± 2.2	1.7 ± 1.9	$t = 4.50$	<0.001	0.44
Irritability-P	3.4 ± 1.6	2.6 ± 1.5	$t = 5.22$	<0.001	0.50
CHI-C total	19.4 ± 7.2	16.7 ± 6.6	$t = 3.97$	<0.001	0.38
Aggression-C	9.1 ± 3.3	7.9 ± 3.2	$t = 3.68$	<0.001	0.36
Hostility-C	3.8 ± 2.1	3.4 ± 2.2	$t = 1.90$	0.06	0.19
Irritability-C	3.2 ± 1.7	2.6 ± 1.4	$t = 4.05$	<0.001	0.37

Values indicated as mean ± standard deviation.
P = parent-rated; C = child self-report.

Table 5. Hierarchical linear regression controlling for (i) parent and child demographics, (ii) non-bipolar disorder parental psychopathology, (iii) child psychopathology

	Statistic			
CHI scores	B	SE	*t*	p-value
CHI-P total	2.01	0.70	2.86	0.005
Aggression-P	0.66	0.36	1.82	0.07
Hostility-P	0.50	0.21	2.35	0.02
Irritability-P	0.51	0.16	3.14	0.002
CHI-C total	1.33	0.71	1.88	0.06
Aggression-C	0.59	0.34	1.76	0.08
Hostility-C	0.06	0.23	0.25	0.80
Irritability-C	0.37	0.16	2.25	0.03

CHI = Children's Hostility Inventory; B = coefficient for offspring of bipolar parents; SE = standard error; P = parent-rated; C = child self-report.

Table 6. Selected correlations between Children's Hostility Inventory (CHI) scores and child psychopathology

CHI scores	Any diagnosis	Disruptive behavior disorder	Unipolar mood disorder
CHI-P total	0.44	0.42	0.18
Aggression-P	0.37	0.38	0.11[a]
Hostility-P	0.35	0.28	0.19
Irritability-P	0.38	0.39	0.17
CHI-C total	0.30	0.33	0.20
Aggression-C	0.28	0.34	0.15
Hostility-C	0.22	0.22	0.16
Irritability-C	0.24	0.29	0.22

P = parent-rated; C = child self-report.
[a]All correlations are significant at $p \leq 0.001$ except where indicated.

debate in the literature with regards to the nature of this irritability. While some suggest that the irritability in pediatric BP is, like in adults, episodic in nature and coincides with periods of illness, others describe children with chronic irritability and episodic 'affective storms' (prolonged, aggressive, often violent outbursts of temper) during periods of mania (19, 20).

Ratings of Irritability and Aggression were highly correlated in our sample (parent report $r = 0.64$, child report $r = 0.57$; $p < 0.001$ for both). Although, in general, children of BP parents had higher scores on the child- and parent-rated Aggression subscales than children of controls, it is not clear why this difference was not as consistent as for Irritability.

To explore this question we carried out a series of analyses (not included in the *Results* section), which showed that general child psychopathology was a significant predictor of both parent-reported Aggression and Irritability. However, whereas parental *BP* was a predictor of parent-reported Irritability, both parents' *non-BP psychopathology* was not a predictor. The reverse is true for parent-reported Aggression: both parents' non-BP psychopathology was a significant predictor; parental BP was not. Thus, it is possible that irritability is a specific early risk factor for BP and might be used in genetic and other biological studies as an early marker or phenotype for BP. In fact, a retrospective study by Fergus et al. (35) suggests that irritability may precede more classic BP symptoms. It is possible that irritability may precede aggression in children at risk for BP – that, perhaps, aggression may develop later, or may not present until children have developed full blown mood disorders. Since we are following all children included in the study, we will be able to probe the hypothesis that irritability may predict aggression. If this is, indeed, true, there may be a window of opportunity to treat these youth before they become aggressive. Thus, with early identification and treatment, the negative individual, family, and societal consequences of overt aggressive behaviors may be averted. With longitudinal follow-up, we hope that this relationship may be clarified.

Our data indicate that children of BP parents, regardless of their own diagnoses, are more likely to exhibit high CHI scores, especially parent-reported Irritability, than children of community controls. However, among the psychiatric disorders, the presence of disruptive behavior disorders

has the strongest relationship to parent- or child-reported Irritability, Hostility, or Aggression. If these symptoms do, indeed, precede mood symptoms in children who ultimately develop mood disorders, then the presence of disruptive disorders in children of BP parents may be a marker for increased risk for mood disorders. In opposition to this hypothesis, a number of studies have also linked general parental psychopathology to child aggression. Child aggression has been linked with parental major depressive disorder, general anxiety disorder and ADHD (36, 37), as well as maternal stress (38) and parental conflict (37). However, these studies did not specifically analyze irritability. Again, as we evaluate more subjects, and follow them over time, we hope to better understand the nature of aggression and irritability in children with and at risk for mental illness.

As expected, there was a disparity between parent ratings and child self-report (correlations = 0.3 to 0.5). Parent-rated CHI scores were more highly correlated with diagnosis. Parent ratings also remained more consistently significant, even after controlling for child psychopathology. There is some evidence in the literature to suggest that parent reports are more related to child diagnosis (39); however, other studies suggest that the extent of parent–child agreement on ratings may be related to the severity of parents' own psychiatric symptoms (40). Possible interpretations of our finding may be that children may under-report symptoms, making parent reports more reliable, or that parents' own psychopathology may color their view of their children's symptoms.

This study underscores the importance of considering any child psychopathology that may already be present in samples of high-risk children. The differences in our groups were not accounted for by any other clinical or demographic variable. Given that child psychopathology was the strongest predictor of CHI score in all our regression models, it is clear that this factor must be taken into account before any statements can be made about the effects of having a parent with BP.

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