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Dimensional psychopathology in preschool offspring of parents with bipolar disorder

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Abstract

Background—The purpose of this study is to compare the dimensional psychopathology, as ascertained by parental report, in preschool offspring of parents with bipolar disorder (BP) and offspring of community control parents.

Methods—122 preschool offspring (mean age 3.3 years) of 84 parents with BP, with 102 offspring of 65 control parents (36 healthy, 29 with non-BP psychopathology), were evaluated using the Child Behavior Checklist (CBCL), the CBCL-Dysregulation Profile (CBCL-DP), the Early Childhood Inventory (ECI-4), and the Emotionality Activity Sociability (EAS) survey. Teachers' Report Forms (TRF) were available for 51 preschoolers.

Results—After adjusting for confounders, offspring of parents with BP showed higher scores in the CBCL total, externalizing, somatic, sleep, aggressive, and CBCL-DP subscales; the ECI-4 sleep problem scale; and the EAS total and emotionality scale. The proportion of offspring with CBCL T-scores ≥ 2 SD above the norm was significantly higher on most CBCL subscales and the CBCL-DP in offspring of parents with BP compared to offspring of controls even after excluding offspring with attention deficit hyperactivity disorder and/or oppositional defiant disorder. Compared to offspring of parents with BP-I, offspring of parents with BP-II showed significantly higher scores in total and most CBCL subscales, the ECI-4 anxiety and sleep scales and the EAS emotionality scale. For both groups of parents, there were significant correlations between CBCL and TRF scores ($r = .32-.38$, p -values $\leq .02$).

Conclusions—Independent of categorical axis-I psychopathology and other demographic or clinical factors in both biological parents, preschool offspring of parents with BP have significantly greater aggression, mood dysregulation, sleep disturbances, and somatic complaints compared to offspring of control parents. Interventions to target these symptoms are warranted.

Keywords

BP; offspring; dimensional psychopathology

Introduction

Onset of bipolar disorder (BP) usually occurs during the adolescent years, but initial symptoms may appear earlier (Birmaher & Axelson, 2006; Leibenluft & Rich, 2008; Merikangas et al., 2012). BP significantly disrupts the normative developmental trajectory and is associated with serious psychosocial difficulties in youth that continue into adulthood. Therefore, there is a need to promptly identify and treat and/or prevent the early manifestations of this illness (Birmaher & Axelson, 2006).

As the single most significant risk factor for developing BP is a positive family history (Luby & Navsaria, 2010; Pavuluri, Henry, Nadimpalli, O'Connor, & Sweeney, 2006), research aiming to identify early BP phenotypes has focused on offspring of individuals with BP. School-aged offspring of parents with BP are specifically at risk for developing BP, but they also are at high risk for other psychiatric disorders, especially anxiety and disruptive disorders (Birmaher et al., 2009; Delbello & Geller, 2001). Studies focusing on dimensional psychopathology (as opposed to categorical diagnoses) show that relative to offspring of healthy or non-BP parents, school-aged offspring of parents with BP exhibit more internalizing problems, aggression, irritability, depressed mood, rapid mood fluctuations, affective dysregulation, anxiety symptoms, and attention and sleep difficulties (Dienes, Chang, Blasey, Adleman, & Steiner, 2002; Diler et al., 2011; Duffy, Alda, Crawford, Milin, & Grof, 2007; Giles, Delbello, Stanford, & Strakowski, 2007).

The scanty literature regarding preschool-aged offspring of parents with BP suggest that similar to the school-aged offspring, preschool offspring also have significantly higher rates of attention deficit and hyperactive disorder (ADHD), disruptive behavior disorders (DBDs), and anxiety disorders relative to offspring of control parents (Hirshfeld-Becker et al., 2006; Radke-Yarrow, Nottelmann, Martinez, Fox, & Belmont, 1992). For example, in the largest preschool age high-risk study published to date, we demonstrated higher rates of ADHD among preschool offspring of parents with BP as compared with preschool offspring of parents with non-BP psychopathology and preschool offspring of healthy controls after adjusting for confounding factors (e.g., demographic factors and both biological parents' non-BP comorbid disorders) (Birmaher et al., 2010).

The above preschool offspring studies mainly focused on the presence of DSM categorical psychopathology. However, preschool-aged children often present psychiatric symptomatology that does not fulfill full criteria for categorical diagnoses. Furthermore, only evaluating categorical diagnoses may obscure the detection of subthreshold symptoms that may predate the onset of syndromal disorders. In fact, in our prior study, not a single child met DSM-IV criteria for BP, but preschool offspring of parents with BP had significantly higher rates of subthreshold manic and depressive symptoms compared to offspring of controls (Birmaher et al., 2010). The few available preschool studies using dimensional methods also show that compared to offspring of controls, preschool offspring

of parents with BP have higher rates of behavioral disinhibition, disruptive and depressive symptoms, fidgetiness, hyperactivity, aggression, and difficulty managing anger and hostile impulses (Hirshfeld-Becker et al., 2006; Radke-Yarrow et al., 1992; Zahn-Waxler et al., 1988). Thus, even though these preschoolers have not yet developed BP or other axis-I psychopathology, they exhibit a variety of psychopathological symptoms that may precede the onset of full threshold disorders. However, the existing preschool studies examining dimensional psychopathology are limited by small sample sizes and by only using offspring of healthy parents as a comparison group. The latter limitation is important, as we do not know whether the increased rates of dimensional psychopathology in preschool offspring of parents with BP is specifically related to parental diagnosis of BP, comorbid non-BP psychopathology, or environmental factors associated with parental psychopathology.

The main purpose of this study is to examine the presence of dimensional psychopathology in preschool offspring of parents with BP as compared with offspring of control parents with and without non-BP psychopathology. To our knowledge, this is the first comprehensive study to examine dimensional psychopathology in a large sample of preschoolers at high risk to develop BP. On the basis of existing literature, we hypothesized that after adjusting for any between-group significant demographic and clinical difference, offspring of parents with BP would show higher levels of dimensional psychopathology, particularly aggressive behavior, attention problems, and emotional reactivity.

Methods

Participants

Subjects included in this study were recruited through the Pittsburgh Bipolar Offspring Study (BIOS). The methods employed in BIOS are described in detail in prior publications (Birmaher et al., 2010). Briefly, 122 preschool offspring of 84 parents (82.1% females) with BP-I ($n = 51$) or BP-II ($n = 33$) and 102 offspring of 65 control parents (36 healthy and 29 with non-BP psychopathology, 75.3% females) were recruited. The parents with BP were recruited through advertisement (53%), adult BP studies (31%), and outpatient clinics (16%). There were no differences between recruitment sources in BP subtype, age at onset of BP, or rates of comorbidity. Exclusion criteria for parents were current or lifetime diagnoses of schizophrenia, mental retardation, and mood disorders secondary to substance abuse, medical conditions, or medications. Control parents were group matched by age, sex, and neighborhood and recruited from the community via telephone using random dialing by the University Center for Social and Urban Research of the University of Pittsburgh (Birmaher et al., 2010). The exclusion criteria for the control parents were the same, with the additional requirements that neither biological parent had BP, nor a first-degree relative with BP. However, control parents could have other psychiatric disorders. Except for children with a condition that impeded their participation in the study (e.g., mental retardation), all offspring aged 2–5 from each family were included.

Procedures

The study was approved by the University of Pittsburgh Institutional Review Board. Informed consent was obtained from all parents. As described in detail elsewhere (Birmaher

et al., 2010), parents were evaluated using the Structured Clinical Interview for DSM-IV (SCID). The psychiatric history of the child's first- and second-degree relatives was ascertained using the Family History–Research Diagnostic Criteria method (FH-RDC) (Andreasen, Endicott, Spitzer, & Winokur, 1977) plus ADHD, separation anxiety disorder (SAD), and DBD items from the schedule for affective disorders and schizophrenia for School-Age Children–Present and Lifetime version [K-SADS-PL] (Kaufman et al., 1997). The kappas for all disorders were .0.8. Forty-six percent of the biological coparents were evaluated directly using the SCID; the rest were evaluated indirectly using the FH-RDC. There was no difference in rates of direct assessments used to obtain the biological coparent's psychiatric disorders between BP parents and controls. Socioeconomic status (SES) was ascertained using the Hollingshead scale (Hollingshead, 1975). Parents were interviewed about their offspring's axis-I disorders using a modified version of the KSADS-PL. Details regarding the use and the psychometrics of KSADS-PL for preschoolers are described in detail elsewhere (Birmaher et al., 2010).

To comprehensively assess dimensional symptoms of psychopathology in preschool offspring, we utilized three parent-report questionnaires: the Child Behavior Checklist for ages 1½–5 (CBCL 1½–5) (Achenbach, 2001), The Early Child Inventory-4 (ECI-4) (Sprafkin, Volpe, Gadow, Nolan, & Kelly, 2002) and the Emotionality Activity Sociability survey (EAS) (Buss, 1984).

The CBCL 1½–5 contains 99 items and has seven syndrome subscales, including emotionally reactive, anxious/depressed, somatic complaints, withdrawn, sleep problems, attention problems, and aggressive behavior. In addition, it yields scores for two broad groupings of syndromes: the *internalizing*, consisting of the first four subscales mentioned above, and the *externalizing*, consisting of the last two. T-scores ≥ 2 standard deviations (*SD*) above normal have been recommended as a clinically meaningful threshold for deviation from age- and sex-matched healthy children (Achenbach, 2001). We also calculated the CBCL-Dysregulation Profile (CBCL-DP) that includes the sum of T-scores of anxious/depressed, attention problems, and aggressive behavior subscales (Kim et al., 2012; Mick, Biederman, Pandina, & Faraone, 2003). The CBCL-DP has been shown to run in families and to be associated with severe psychopathology (Althoff, Verhulst, Rettew, Hudziak, & van der Ende, 2010; Diler et al., 2011). Collateral information was obtained using the Caregiver-Teacher Report Form (TRF) (Achenbach, 2001) for a subsample of preschoolers who attended preschool programs. The TRF contains six subscales that, with the exception of the sleep problems subscale, are identical to the CBCL.

The ECI-4 includes 108 symptoms scored 0 ('never') to 3 ('very often') for the following DSM-IV preschool psychiatric disorders: ADHD, ODD, conduct disorder, SAD, MDD, dysthymia, pervasive developmental disorder, posttraumatic stress disorder, sleep problems, feeding problems, reactive attachment disorder, and elimination disorders (Gadow, Sprafkin, & Nolan, 2001; Sprafkin et al., 2002). In addition, it contains individual screening items for other disorders (e.g., selective mutism, simple phobia). The ECI-4 has adequate psychometrics in community and clinical preschool samples.

The Emotionality Activity Sociability survey (EAS) evaluates four temperamental dimensions (emotionality, activity, sociability and shyness) that appear early in life and are stable throughout development (Buss, 1984). The EAS contains 20 items, each rated from 1 ('not characteristic or typical for the child') to 5 ('very characteristic or typical').

Statistical analyses

We analyzed the CBCL raw and T-scores as per the manual instructions. Cutoff scores for each CBCL subscale and the CBCL-DP were set at T-score 70 and 210, respectively. The sum of the total scores was used for the ECI and the EAS.

We conducted analyses in several stages. First, we employed univariate analyses using *t*-tests, chi-square tests, and Fisher exact tests as appropriate to compare between-group demographic and clinical variables for both parents and offspring. As it is important to evaluate whether dimensional psychopathology is present in offspring over and above the effects of categorical diagnoses, we also compared the rates of categorical psychiatric disorders between the two offspring groups. Second, we conducted multivariate analysis using generalized linear modeling in which we entered parental variables with *p*-values <.2 in the univariate comparisons (i.e., parental race, general functioning, comorbid anxiety disorders, ADHD, disruptive behavior disorders and SUD, coparents any axis-I disorder). Also, as some families included more than one child, within-family correlations were adjusted using family unit as a random effect in the mixed model. Third, we repeated the multivariate analysis above, controlling for between-group differences in rates of offspring DSM-IV categorical disorders. As expected, given the age of the sample, few preschoolers had TRFs. Thus, the TRF data were used to compare parent report (i.e., CBCL) with teacher report using Pearson's correlations. All tests were two-sided with a significance level set at 0.05.

Results

Parents

As shown in Table 1, there were no between-group demographic differences except that parents with BP were significantly more likely to be Caucasian. Also, parents with BP had significantly greater rates of nearly all psychiatric disorders than the control parents (all *p*-values .04) except for history of separation anxiety disorder, dysthymia, and binge-eating disorders. Parents with BP had significantly lower ratings of past and current overall functioning as assessed by the Global Assessment of Functioning (GAF). There were no statistical differences in demographic and clinical factors between parents with BP-I and BP-II. The biological coparents of offspring of parents with BP had significantly higher rates of any axis-I disorder than the coparents of the controls (40.5% vs. 24.1%, $\chi^2 = 4.02$, *p* = .05). In only two families, both parents had BP. There were no other significant differences between the coparents.

Offspring

On average, 1.5 offspring per family were included in the study. As shown in Table 2, there were no demographic differences between offspring of parents with BP and offspring of

controls. Thirty-two (26.2%) offspring of parents with BP had an axis-I disorder compared to 10 (9.8%) offspring of the controls ($p = .002$). The most common disorders were ADHD, oppositional defiant disorder (ODD), and anxiety disorders (mainly SAD), but only the rate of ADHD was significantly different between the two groups of offspring. There were no differences in rates of psychiatric disorders between offspring of parents with BP-I and BP-II.

Child Behavior Checklist (CBCL)

CBCLs were available for 218 offspring (97.3%). As depicted in Table 3, univariate analysis showed that the CBCL total and all subscales scores were significantly higher in the offspring of parents with BP than in the offspring of control parents (all p -values $< .001$). Adjusting for within-family correlations and between-group differences in parental demographic and clinical variables (i.e., parental race, general functioning, comorbid anxiety disorders, ADHD, disruptive behavior disorders and SUD, coparents' any axis-I disorder), in comparison with offspring of the controls, offspring of parents with BP had significantly higher scores in the CBCL total, externalizing, somatic complaints, sleep problems, aggressive behavior and CBCL-DP. To evaluate whether the CBCL findings were accounted for by the higher prevalence of ADHD and a trend for more ODD in offspring of parents with BP, the multivariate analysis was repeated also adjusting for these disorders. This analysis yielded similar results.

Significantly more offspring of parents with BP had T-scores above the cutoff point (70) for all subscales of CBCL except the somatic complaints subscale. The total, externalizing, sleep problems, and aggressive subscales remained significantly different even after excluding subjects with ADHD and ODD from both groups (23 offspring of BP parents and 6 offspring of controls, Figure 1). Nineteen offspring of parents with BP (15.8%) compared to only 1 (1.0%) offspring of control parents had CBCL-DP ≥ 210 ($p < .001$).

Both offspring of parents with BP-I and BP-II showed significantly higher raw and T-scores in all CBCL subscales compared to offspring of the controls. However, offspring of parents with BP-II had higher scores in total and almost all CBCL scores (e.g., externalizing and emotionally reactive) and the CBCL-DP than the offspring of parents with BP-I (p -values $< .03$). These results were adjusted for multiple comparisons, yielding similar results.

Caregiver–Teacher Reports (TRF)

TRFs were available for 53.3% of the preschoolers (56/105). Five reports were incomplete, leaving a total of 51 TRFs (23 offspring of parents with BP and 28 offspring of control parents). There were no demographic or clinical differences between children whose caregivers did or did not complete the TRFs. Pearson's correlations for total, internalizing, and externalizing scores of the parent's CBCL and the TRF ranged from 0.32 to 0.38 (all p -values $< .02$). There were no significant differences in the CBCL correlations with the TRF between parents with BP and control parents.

Early Childhood Inventory – 4 (ECI-4)

The ECI-4 was available for 209 offspring (93.3% of the total sample). There was no difference in rate of ECI-4 completion between offspring of parents with BP and offspring of control parents. Also, there were no significant demographic and clinical differences between offspring with and without ECI-4. The mean ECI-4 unadjusted scores in all ECI-4 categories were significantly higher in offspring of parents with BP compared to offspring of control parents. After adjusting for between-group parental differences, offspring of parents with BP had significantly higher scores in ODD, generalized anxiety disorder, and sleep problems. However, after adjusting for the presence of offspring categorical ADHD and/or ODD diagnoses, the only between-group significant difference that remained significant was the sleep problems category (Table 3). Offspring of parents with BP-II had higher anxiety and sleep problems category scores compared to offspring of parents with BP-I (p -values = .04).

Emotionality Activity sociability (EAS) survey

The EAS was available for 96% of the sample. Offspring of parents with BP had significantly higher scores in total EAS and the emotionality scale compared to offspring of the controls (Table 3). These differences remained significant after adjusting for between-group parental demographic and clinical variables and offspring ADHD and/or ODD.

Offspring of parents with BP-II had higher scores in the emotionality scale compared to offspring of parents with BP-I (p -value = .05).

There was a significant positive correlation between the emotionality scale and total EAS and the CBCL-DP score ($R = .67$ and 0.59 respectively, p -values = .01).

Discussion

In a previous paper, we showed that preschool offspring of parents with BP were more likely to have ADHD and to have two or more psychiatric disorders, compared to offspring of control parents (Birmaher et al., 2010). However, only analyzing the prevalence of categorical disorders in preschool offspring does not give a complete picture of their psychopathology. In this study, preschool offspring of parents with BP showed significantly higher levels of dimensional psychopathology compared to preschool offspring of community controls, independent of between-group differences in parental demographic and clinical factors, as well as differential rates of categorical disorders in offspring. Specifically, they showed higher scores in the CBCL total, externalizing, somatic, sleep, aggressive, and CBCL-DP subscales, the ECI-4 sleep problems scale and the EAS total and emotionality scales. Further analysis showed that the proportion of offspring with CBCL T-scores ≥ 2 SD above the norm was significantly higher in most CBCL subscales in offspring of parents with BP compared to offspring of the controls after adjusting for confounding factors and even after excluding offspring with ADHD and/or ODD (Figure 1).

Unexpectedly, most of the CBCL scores, the ECI-4 anxiety and sleep scales, and EAS emotionality scores were significantly higher in offspring of parents with BP-II when compared with offspring of parents with BP-I.

Similar to our results, the limited available literature has reported more dimensional psychopathology in preschool offspring of parents with BP when compared to offspring of controls (Hirshfeld-Becker et al., 2006; Radke-Yarrow et al., 1992; Zahn-Waxler et al., 1988). These findings could have been attributed to higher prevalence of categorical psychopathology in the offspring (e.g., ADHD) and the parents, as well as to poor individual and family functioning found in parents with BP when compared with control parents (Fagiolini et al., 2005; Moreno et al., 2012).

High rates of psychopathology have also been reported in school-aged offspring of parents with other axis-I disorders, raising the possibility that the above-noted findings may not be specific for offspring of parents with BP (Goodman et al., 2011). However, in our study, even after adjusting for other non-BP parental axis-I disorders, the offspring of parents with BP continued to show more dimensional psychopathology than the offspring of the controls, suggesting that these symptoms indeed are specific for preschool offspring of parents with BP.

Using different instruments, higher rates of externalizing problems have been found in several high-risk studies of school-age and preschool children of parents with BP compared to offspring of controls (Duffy et al., 2007; Farchione et al., 2007; Giles et al., 2007; Radke-Yarrow et al., 1992; Shaw, Egeland, Endicott, Allen, & Hostetter, 2005; Zahn-Waxler et al., 1988). The externalizing subscale of the CBCL includes the aggressive behavior (e.g., behavioral problems, defiance, hostility, and temper outbursts) and the attention subscales. In our study, in the univariate analyses, both the attention and aggression subscales were significantly higher in the preschoolers of parents with BP. However, only the aggression subscale remained significant in the multivariate analysis. The presence of aggression in offspring at high risk for BP is a consistent finding in the literature (Conus et al., 2008; Diler et al., 2011; Farchione et al., 2007; Giles et al., 2007; Henin et al., 2005; Shaw et al., 2005). Studies in school-age children show that aggressive and other externalizing behaviors are associated with the development of disruptive, anxiety, depression, and substance use disorders during adolescence and adulthood in community samples (Reef, Diamantopoulou, van Meurs, Verhulst, & van der Ende, 2011; Stringaris & Goodman, 2009). However, in the context of family history for BP, aggression may be associated with increased risk for BP. In contrast to aggressive symptoms, perhaps due to methodological differences, studies evaluating the association between attention problems among youth and the risk for BP yield inconsistent results (Diler et al., 2011; Duffy, 2012; Farchione et al., 2007; Giles et al., 2007; Shaw et al., 2005).

The CBCL-DP, which is composed of the aggression, attention, and the anxious/depressed subscales of the CBCL, was also significantly higher in offspring of parents with BP when compared with offspring of the controls. This phenotype has been associated with emotional and behavioral dysregulation in preschoolers (Kim et al., 2012). Across ages, children with the CBCL-DP tend to exhibit mood dysregulation, poor overall functioning, marked psychosocial impairment and high risk for ADHD, anxiety, BP, and cluster B personality disorders (Althoff et al., 2010; Meyer et al., 2009). As with the externalizing findings noted above, aggression was the only subscale that remained significant after adjusting for several

confounding factors, suggesting again that aggression may be specifically related to familial loading for BP.

The EAS emotionality scores, which were significantly correlated with the CBCL-DP, were also significantly higher in offspring of parents with BP. The emotionality scale represents a global pattern of distress and a temperamental tendency to become easily and intensely aroused (Buss, 1984). Despite methodological differences in the literature, high emotional reactivity is one of the most consistent findings in preschool- and school-aged offspring of parents with BP (Conus et al., 2008; Luby & Navsaria, 2010; Shaw et al., 2005). These offspring have higher levels of irritability, are easily excited, and exhibit problems in emotional regulation compared to offspring of controls (Farchione et al., 2007; Shaw et al., 2005). High emotional reactivity has also been associated with future depression, disruptive, and anxiety disorders (Reef et al., 2011; Roza, Hofstra, van der Ende, & Verhulst, 2003; Stringaris, Maughan, & Goodman, 2010) and increased risk for BP in the context of family history of BP (Conus et al., 2008; Luby & Navsaria, 2010).

Some, but not all, studies report that offspring of parents with BP have high rates of anxiety and depressive symptoms (Duffy et al., 2007; Egeland et al., 2012; Shaw et al., 2005). In the univariate analyses of the CBCL and the ECI-4, we also found that anxiety and depressive symptoms were higher in offspring of parents with BP. However, these differences were no longer significant after adjusting for confounding factors, suggesting that these symptoms might be associated with general parental psychopathology and not specifically with BP.

One of the most significant findings in our study was the presence of sleep disturbances in offspring of parents with BP. The CBCL and ECI-4 sleep disturbances were not accounted for by parental psychopathology and presence of ADHD and ODD in the preschoolers. Moreover, it was the only finding that survived the multiple regressions in the ECI-4. Similar findings have been reported in school-age studies. These studies suggest that sleep disturbances may precede the onset of BP (Dienes et al., 2002; Duffy et al., 2007; Luby & Navsaria, 2010; Shaw et al., 2005). However, sleep problems are also associated with the development of other behavioral and emotional problems including aggression, anxiety, and depression (Gregory & Sadeh, 2012); As these are also more prevalent in offspring of parents with BP (Birmaher et al., 2009), there is a need for longitudinal studies to verify whether early-onset sleep disturbances are indeed a prodromal symptom for BP in offspring of parents with this disorder.

Interestingly, after adjusting for confounding factors, the scores in the somatic complaints subscale of the CBCL, which includes items like headaches and gastrointestinal symptoms, were significantly higher in the offspring of parents with BP. A recent study in the Amish community also reported that somatic complaints in preschool offspring of parents with BP-I might represent a prodromal symptom for BP-I (Egeland et al., 2012). Moreover, the presence of somatic symptoms was found to be correlated with future depressive disorders in adolescents, while the number of somatic symptoms was associated with future development of mania in adolescents with depression (Bohman et al., 2012). It is yet to be established by longitudinal data whether increased somatic symptoms in preschool offspring of parents with BP predict future psychopathology, especially BP.

Unexpectedly, after adjusting for confounding factors and multiple comparisons, offspring of parents with BP-II had significantly higher dimensional psychopathology compared to offspring of parents with BP-I. To our knowledge, there is only one other study that showed that school-aged offspring of parents with BP-II have more ADHD, anxiety, and mood disorders compared to offspring of parents with BP-I (Garcia-Amador et al., 2013). The reasons for these findings are unclear as there were no demographic, clinical, and treatment differences between parents with BP-I and II. However, these analyses were cross-sectional; longitudinal studies of adults with BP show that individuals with BP-II exhibit a more chronic course with more frequent depressive episodes and more unstable interpersonal relationships and social maladjustment compared to patients with BP-I (Baek et al., 2011; Judd et al., 2003).

Similar to the literature (Achenbach, 2001; Berg-Nielsen, Solheim, Belsky, & Wichstrom, 2012), there were significant moderate correlations between the CBCLs and the TRFs and all parents. Moreover, there were no differences in the correlations between the parents and teachers for both groups of parents, suggesting that parents with BP were not over reporting symptoms in their offspring.

The results of this study need to be considered in the light of the following limitations. First, psychopathology was assessed using only parental reports, and we did not perform direct evaluations and observations of the preschoolers. Second, the parents with BP who agreed to participate in BIOS could have had more psychopathology than those who refused to participate. However, the rates of psychiatric comorbidity and level of functioning in parents with BP in our study are similar to those reported in the adult BP literature (Kessler, Merikangas, & Wang, 2007). Third, as expected, very few preschoolers had teachers' reports. Finally, as this is a cross-sectional study, we do not know whether the findings are stable over time. However, studies analyzing the continuity of psychopathology from preschool age through adolescence show high stability, especially for externalizing problems (Bufferd, Dougherty, Carlson, Rose, & Klein, 2012; Janson & Mathiesen, 2008).

In conclusion, the results of this study suggest that independent of categorical axis-I psychopathology and other demographic or clinical factors in both biological parents, preschool offspring of parents with BP, particularly offspring of parents with BP-II, have more dimensional psychopathology compared to offspring of control parents. Specifically, they showed more aggression, emotional dysregulation, sleep disturbances, and somatic complaints. Given the distress and impairment associated with this psychopathology and the risk to develop future mood and disruptive disorders, treating children with these problems and their families is clearly indicated (Furlong et al., 2012; Luby, Lenze, & Tillman, 2012). Furthermore, considering that more than 75% of these offspring have not manifested any categorical psychiatric illness at intake, there is an important opportunity for preventive interventions in this high-risk population (Garber et al., 2009; Miklowitz et al., 2011). In addition to targeting child's psychopathology, addressing the parental own psychopathology is important as several studies have shown that improvement of parental symptoms is associated with prevention and/or amelioration of psychopathology in their offspring (Wickramaratne et al., 2011).

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Key points

- School-aged offspring of parents with BP show more internalizing and externalizing psychopathology when compared to offspring of healthy parents or parents with non-BP psychopathology.
- However, studies regarding preschool offspring of parents with BP are scant and limited.
- This study shows that independent of categorical axis-I psychopathology (e.g., ADHD), and other demographic or clinical factors in both biological parents, preschool offspring of parents with BP have more aggression, emotional dysregulation, sleep disturbances, and somatic complaints compared to offspring of control parents (with and without other axis-I psychopathology).
- Longitudinal studies are warranted to assess whether the above-noted dimensional psychopathology in preschool age is associated with future BP or other axis-I psychopathology.

Figure 1.

Percentage of preschool offspring with T-score >2SD above norm. * $p < .01$ (after excluding offspring with ADHD and/or ODD)

Table 1

Demographic and clinical characteristics of parents with bipolar disorder (BP) and control parents

	Parents with BP (<i>n</i> = 84)	Control parents (<i>n</i> = 65)	Statistics	Overall <i>p</i> -value
(Age, years), mean (<i>SD</i>)	32.3 (5.6)	33.8 (7.56)	<i>T</i> = 1.25	.22
Sex (female), <i>N</i> (%)	69 (82.1)	49 (75.3)	$\chi^2 = 0.22$	.64
Race (Caucasian), <i>N</i> (%)	75 (89.3)	48 (73.8)	$\chi^2 = 6.8$	.01
SES, mean (<i>SD</i>)	35.6 (14.6)	38.8 (15.2)	<i>T</i> = 1.27	.21
Number of offspring, mean (<i>SD</i>)	2.4 (1.1)	2.3 (1.0)	<i>T</i> = 0.17	.86
GAF Current, mean (<i>SD</i>)	63.94 (12.9)	82.12 (12.0)	<i>T</i> = 10.68	<.001
Highest in past	72.16 (10.6)	84.62 (10.1)	<i>T</i> = 8.80	<.001
Most severe in past	36.94 (15.4)	70.60 (16.2)	<i>T</i> = 15.67	<.001
Any axis-I disorder, <i>N</i> (%)	84 (100.0)	29 (44.6)	$\chi^2 = 61.3$	<.001
Bipolar I disorder	51 (60.7)	0 (0.0)	FET	<.001
Bipolar II disorder	33 (39.3)	0 (0.0)	FET	<.001
Depressive disorders ^a	0 (0.0)	16 (24.6)	FET	<.001
Anxiety Disorders ^b	58 (69.0)	13 (20.0)	$\chi^2 = 35.6$	<.001
ADHD	19 (22.6)	3 (4.6)	$\chi^2 = 9.46$	.003
DBD	26 (31.0)	7 (10.8)	$\chi^2 = 11.7$	<.001
SUD	50 (59.5)	19 (29.2)	$\chi^2 = 13.9$	<.001

Values are bolded in order to denote statistical significance.

SES, socioeconomic status; ADHD, attention deficit hyperactivity disorder; DBDs, disruptive behavior disorder; SUDs, substance use disorders; GAF, Global Assessment of Functioning; FET, Fisher's exact test.

^aMajor depression and dysthymic disorder.

^bGeneralized anxiety, separation anxiety, panic disorder, obsessive-compulsive disorder and posttraumatic stress disorder.

Table 2

Demographic and clinical characteristics of offspring of parents with bipolar disorder (BP) and offspring of control parents

	Offspring of parents with BP (<i>n</i> = 122)	Offspring of control parents (<i>n</i> = 102)	Statistics	Overall <i>p</i> -value
Age, years, mean (<i>SD</i>)	3.28 (1.23)	3.24 (1.18)	$F = 0.03$	.85
Sex (female), <i>N</i> (%)	63 (51.6)	45 (44.1)	$\chi^2 = 1.61$	.21
Race (Caucasian), <i>N</i> (%)	97 (79.5)	79 (77.5)	$\chi^2 = 0.35$	.55
Living with both biological parents, <i>N</i> (%)	81 (66.4)	77 (75.5)	$\chi^2 = 2.16$	.14
Any axis-I disorder, <i>N</i> (%)	32 (26.2)	10 (9.8)	$\chi^2 = 9.97$	.002
Any mood disorder ^a	3 (2.5)	0 (0.0)	FET	.25
Any anxiety disorder ^b	13 (10.7)	5 (4.9)	$\chi^2 = 2.47$	.1
ADHD	19 (15.6)	2 (2.0)	$\chi^2 = 12.21$	<.001
ODD	14 (11.5)	5 (4.9)	$\chi^2 = 3.70$	.07
2 axis-I disorders	21 (17.2)	7 (6.9)	$\chi^2 = 5.42$	.02

Values are bolded in order to denote statistical significance.

ADHD, attention deficit hyperactivity disorder; ODD, oppositional defiant disorder; FET, Fisher's exact test.

^a Bipolar disorder not otherwise specified (2 offspring) and depressive disorder (1 offspring).

^b Generalized anxiety, separation anxiety, panic disorder, obsessive-compulsive disorder and posttraumatic stress disorder.

Table 3

Mean raw scores of Child Behavior Checklist (CBCL), Dysregulation Profile (CBCL-DP), Early Child Inventory (ECI) and Emotionality Activity Sociability (EAS) scale in offspring of parents with BP and offspring of control parents

	Offspring of parents with BP (<i>n</i> = 120)	Offspring of control parents (<i>n</i> = 98)	<i>F</i> stat	Unadjusted <i>p</i> -value	Adjusted <i>p</i> -values ^a	Adjusted <i>p</i> -values ^b
CBCL, mean (<i>SD</i>)						
Total	46.97 (30.2)	23.64 (18.7)	44.59	<.001	.05	.02
Internalizing	11.78 (9.6)	5.38 (5.8)	33.60	<.001	.13	.31
Externalizing	18.53 (12.5)	9.73 (7.9)	36.67	<.001	<.01	.03
Emotionally reactive	3.72 (3.5)	1.63 (2.1)	26.79	<.001	.07	.36
Anxious/depressed	3.76 (3.3)	1.89 (2.2)	23.30	<.001	.50	.84
Somatic complaints	2.05 (2.1)	0.82 (1.5)	24.02	<.001	<.01	.03
Withdrawn	2.25 (2.5)	1.04 (1.6)	17.74	<.001	.14	.29
Sleep problems	4.37 (3.2)	2.31 (2.4)	27.60	<.001	<.01	<.01
Attention problems	3.39 (2.7)	1.83 (1.8)	24.98	<.001	.13	.38
Aggressive behavior	15.13 (10.4)	7.91 (6.7)	35.30	<.001	<.01	.03
CBCL-DP	22.18 (14.7)	11.62 (9.3)	16.53	<.001	.02	.03
ECI, mean (<i>SD</i>) ^c						
ADHD	20.79 (12.0)	13.29 (9.2)	26.03	<.001	.24	.56
ODD	9.15 (6.3)	5.11 (4.4)	27.54	<.001	.03	.14
Conduct disorder	3.11 (4.4)	1.23 (2.2)	14.49	<.001	.15	.17
MDD	5.69 (3.5)	4.13 (2.4)	13.56	<.001	.24	.52
Dysthymia	4.23 (2.9)	2.95 (2.0)	13.36	<.001	.22	.55
SAD	4.14 (4.3)	1.98 (2.3)	19.41	<.001	.10	.15
Generalized Anxiety	7.66 (4.6)	4.55 (3.6)	28.78	<.001	.03	.15
Sleep disorder	3.83 (2.6)	2.45 (2.0)	17.79	<.001	<.01	<.01
EAS, mean (<i>SD</i>) ^d						
Total	65.27 (7.3)	61.36 (6.8)	16.32	<.001	.01	.05
Emotionality	14.90 (5.1)	11.38 (4.4)	28.74	<.001	<.01	<.01
Shyness	12.71 (4.6)	12.56 (4.2)	0.06	.81	.60	.54
Activity	20.57 (3.4)	20.43 (3.1)	0.18	.76	.39	.48
Sociability	17.00 (3.3)	16.67 (3.1)	0.62	.43	.25	.25

Values are bolded in order to denote statistical significance.

^aOverall *p*-values are adjusted for proband's race, current GAF, ADHD, DBD, anxiety disorders and SUD, co-parent's any axis-I disorder.

^b Adjusting for parental factors as mentioned plus offspring's ADHD and ODD.

^c *n* = 209 (113 offspring of parents with BP, 96 offspring of controls).

^d *n* = 217 (119 offspring of parents with BP, 98 offspring of controls).