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# Psychopathology in offspring of parents with bipolar disorder: three studies exploring risk

Freed, Rachel Deborah

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Dissertation

**PSYCHOPATHOLOGY IN OFFSPRING OF PARENTS WITH BIPOLAR  
DISORDER: THREE STUDIES EXPLORING RISK**

by

**RACHEL D. FREED**

B.A., Johns Hopkins University, 2002  
M.A., Boston University, 2007

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**2014**

Approved by

First Reader

---

Martha C. Tompson, Ph.D.  
Associate Professor of Psychology

Second Reader

---

Aude Henin, Ph.D.  
Co-Director, Child CBT Program  
Department of Psychiatry, Massachusetts General Hospital

Third Reader

---

Michael W. Otto, Ph.D.  
Professor of Psychology

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**PSYCHOPATHOLOGY IN OFFSPRING OF PARENTS WITH BIPOLAR  
DISORDER: THREE STUDIES EXPLORING RISK**

(Order No.            )

**RACHEL DEBORAH FREED**

Boston University Graduate School of Arts and Sciences, 2014

Major Professor: Martha C. Tompson, Ph.D., Associate Professor of Psychology

**ABSTRACT**

Offspring of parents with bipolar disorder (BD) are at high risk for psychiatric disorders, but mechanisms conferring risk are not well understood. Identifying and understanding factors that increase offspring vulnerability may inform intervention efforts. Three studies examined the following risk factors: (1) obstetric complications (OCs); (2) family functioning; and (3) clinical characteristics of parental BD.

Investigations included cross-sectional data from two Massachusetts General Hospital studies of 109 BD parents and 206 offspring.

Study 1 examined associations between: (1) maternal lifetime comorbid anxiety and OCs in pregnancy/delivery; (2) OCs and development of offspring psychopathology. Associations emerged between maternal anxiety and OCs. OCs, particularly during delivery, also correlated with offspring anxiety disorders. Path analyses revealed that delivery complications mediated the relationship between maternal and offspring anxiety.

Study 2 examined associations between family functioning (cohesion, expressiveness, conflict) and offspring psychopathology, and explored moderation by

offspring age and sex. Higher conflict and lower cohesion correlated with offspring internalizing and externalizing symptoms. Lower cohesion correlated with offspring mood disorders. Moderation analyses indicated that the link between cohesion and internalizing symptoms was stronger for younger compared to older children. Also, conflict and mood disorder were associated in younger boys, but not in older boys or in girls.

Study 3 classified parents according to BD course presentation using latent class analysis, and examined associations between parental class membership and offspring psychopathology. The best-fitting model yielded three parent groups that were based on 8 illness characteristics. Some notable patterns differentiated classes: Class 1 and 2 parents had earlier illness onset, whereas Class 3 parents had later onset; Class 2 consisted of parents with Bipolar-II Disorder, whereas Class 1 parents had Bipolar-I Disorder. Class differences emerged for offspring anxiety disorders, but only among females. Class 3 parents had girls with fewer anxiety disorders compared to the other classes, with girls of Class 2 parents at greatest risk.

Altogether, these studies identify several specific environmental mechanisms that increase psychopathology risk in offspring of BD parents. Such findings have important implications for targeted prevention and intervention.

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## LIST OF ABBREVIATIONS

ADHD	Attention deficit hyperactivity disorder
AIC	Akaike's Information Criterion
BCRP	Bipolar Clinic and Research Program
BD	Bipolar disorder
BD-I	Bipolar I disorder
BD-II	Bipolar II disorder
BIC	Bayesian Information Criterion
CD	Conduct disorder
CBCL	Child Behavior Checklist
DICA-P	Diagnostic Interview for Children and Adolescents-Parent Version
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
EO-I	Earlier-onset BD-I
EO-II	Earlier-onset BD-II
FES	Family Environment Scale
GAD	Generalized anxiety disorder
KSADS	Schedule for Affective Disorders and Schizophrenia for School-Aged Children-Epidemiologic Version
LCA	Latent class analysis
LO	Later-onset BD
LRT	Likelihood ratio test

M	Mean
MDD	Major depressive disorder
MRS	Magnetic Resonance Spectroscopy
OC	Obstetric complication
OCD	Obsessive compulsive disorder
ODD	Oppositional defiant disorder
PTSD	Posttraumatic stress disorder
SD	Standard deviation
SCID	Structured Clinical Interview for DSM-IV Axis I Disorders

## **CHAPTER ONE**

### **GENERAL INTRODUCTION**

#### **OVERVIEW**

Offspring of parents with bipolar disorder are at increased risk for developing psychiatric disorders themselves. According to a meta-analysis of studies of child and adult offspring of parents with bipolar disorder (Lapalme, Hodgins, & LaRoche, 1997), these offspring are over 2.5 times more likely to develop any psychiatric disorder and 4 times more likely to develop an affective disorder compared to offspring of parents with no psychiatric history. In a review of studies from 1966 to 2000, DelBello and Geller (2001) report that in all research comparing offspring of parents with bipolar disorder with offspring of parents with no psychiatric history, the former were at increased risk for developing a wide range of psychopathology, including depressive, substance use, conduct, oppositional defiant, and anxiety disorders.

Although syndromal disorders (particularly mood disorders) often do not onset until adolescence or young adulthood, offspring of parents with bipolar disorder appear to be at risk for psychiatric illnesses at multiple stages of their lives (Henin et al., 2005). In fact, the presence of early psychopathology in these offspring may increase risk for later mood disorder and/or represent prodromal forms of later mood disorder. Carlson and Weintraub (1993) found that childhood behavior and attention problems were significantly associated with mood disorders in young adulthood in offspring of parents with bipolar disorder. Of interest, this relationship was unique to the offspring of parents with bipolar disorder; in offspring of parents with other (non-bipolar) psychiatric

disorders and in offspring whose parents had no psychiatric disorder, childhood behavior and attention problems were associated only with non-mood disorders in young adulthood. Duffy and colleagues (2007) similarly found that a variety of psychiatric diagnoses occurred prior to bipolar spectrum disorders in offspring of parents with bipolar disorder, suggesting that non-specific psychopathology may be a precursor to later bipolar disorder in offspring at genetic risk. In fact, these researchers recently proposed a clinical “staging hypothesis” of the course of bipolar disorder, whereby high-risk offspring who go on to develop bipolar disorder do so in a predictable sequence, beginning with anxiety and sleep disturbances in childhood, non-clinical mood symptomatology in early adolescence, then major depressive episodes, and finally hypomanic/manic episodes (Duffy, Alda, Hajek, Sherry, & Grof, 2010; Duffy et al., 2014).

Despite the link between parental bipolar disorder and offspring psychopathology, mechanisms conferring risk to offspring are not fully known. Genetic factors undeniably contribute substantially to an offspring’s vulnerability, and it is clear that bipolar disorder, in particular, is highly heritable (Smoller & Finn, 2003). However, twin studies estimate concordance rates for bipolar disorder among monozygotic twins that are between 39% and 44%, suggesting that environmental factors also play a role in the development of bipolar disorder (Cardno et al., 1999; Kendler, Pedersen, Johnson, Neale, & Mathé, 1993; Kieseppä, Partonen, Haukka, Kaprio, & Lönqvist, 2004; McGuffin et al., 2003). In addition, estimates suggest that a large number of offspring of parents with

bipolar disorder do not go on to develop psychiatric illness (Chang, Steiner, & Ketter, 2000; DelBello & Geller, 2001).

Advancing the knowledge of environmental factors increasing risk in offspring of parents with bipolar disorder has important implications for intervention efforts. By identifying potential factors that put offspring at heightened risk, we can intervene early to curtail adverse developmental trajectories, decreasing the burden to individuals, families, and communities. In the following chapters, three sets of potential risk factors were examined among families where a parent has bipolar disorder to better understand the relationships between these factors and psychopathology in offspring.

#### *Obstetric Complications*

Study 1 (Chapter 2) focused on obstetric complications (OCs) as very early risk factors in the later development of psychopathology in offspring of parents with bipolar disorder and the role of comorbid parental anxiety in impacting OCs. OCs (i.e., adverse events during pregnancy or birth) have been shown to have substantial implications for later health outcomes, including child and adult physical diseases and psychiatric disorders and impaired neural and cognitive development (Barker, 2004; Klevzon, Gross, & Reichenberg, 2007; O'Donnell, O'Connor, & Glover, 2009; Schlotz & Phillips, 2009). A number of studies have linked OCs to increased risk for a range of psychiatric disorders (Hirshfeld-Becker et al., 2004; Robinson et al., 2008), including mood disorders (Costello, Worthman, Erkanli, & Angold, 2007; Guth, Jones, & Murray, 1993; Kinney, Yurgelun-Todd, Levy, & Medoff, 1993; Kinney, Yurgelun-Todd, Tohen, & Tramer, 1998; S. W. Lewis & Murray, 1987; Patton, Coffey, Carlin, Olsson, & Morley, 2004;

Pavuluri, Henry, Nadimpalli, O'Connor, & Sweeney, 2006). However, many prior studies have failed to account for parental psychopathology in examining these associations. This oversight is problematic given evidence that women with psychopathology, including those with bipolar disorder, may be more likely to experience OCs during pregnancy (Diego et al., 2006; Field, Diego, & Hernandez-Reif, 2006; Jablensky, Morgan, Zubrick, Bower, & Yellachich, 2005; Lee & Lin, 2010), potentially due to disturbances in the prenatal environment resulting from psychiatric symptoms or stress (Rice et al., 2010). In particular, anxiety has been implicated as a contributing factor in the occurrence of OCs (Alder, Fink, Hösli, & Holzgreve, 2007; Pluess, Bolten, Pirke, & Hellhammer, 2010). Therefore, in addition to evaluating the links between OCs and psychopathology, research must also examine the role of maternal anxiety in this association.

### *Family Environment*

Study 2 (Chapter 3) focused on the role of family environment in increasing risk for psychopathology among offspring of parents with bipolar disorder, as well as offspring characteristics that may moderate this association. Previous research has shown that families with a parent who has bipolar disorder may experience family functioning difficulties, even during periods of symptom remission (Barron et al., 2014; Chang, Blasey, Ketter, & Steiner, 2001; Du Rocher Schudlich, Youngstrom, Calabrese, & Findling, 2008; Romero, Delbello, Soutullo, Stanford, & Strakowski, 2005; Vance, Huntley Jones, Espie, Bentall, & Tai, 2008; Weinstock, Keitner, Ryan, Solomon, & Miller, 2006). Given the already increased biological risk faced by offspring of parents with bipolar disorder, disruptions in family functioning may place offspring at even

greater risk for developing adjustment and psychiatric problems. Evidence from both the adult and child literature suggests that family functioning can significantly affect the course of bipolar disorder (Geller, Tillman, Craney, & Bolhofner, 2004; D. J Miklowitz, Goldstein, Nuechterlein, Snyder, & Mintz, 1988) and therefore may impact the development of bipolar disorder and other psychiatric disorders in populations at risk (Du Rocher Schudlich et al., 2008; Meyer et al., 2006; Reichart et al., 2007). In addition, associations between family functioning and offspring psychopathology may be complex and may differ based on offspring characteristics such as sex and age. Girls have been shown to be more sensitive to interpersonal stressors than boys (Hops, 1995; Rudolph, 2002), and therefore may be more strongly affected by family functioning difficulties (Davies & Lindsay, 2004; Davies & Windle, 1997). There may also be developmental differences in how children perceive and respond to family functioning difficulties (Grych, 1998), such that younger children are more negatively impacted and therefore more prone to the development of psychopathology. Additional studies are needed to clarify the associations between family functioning and offspring adjustment in families where a parent has bipolar disorder and to determine whether offspring are differentially affected based on their age and sex.

#### *Parental Bipolar Disorder Course Characteristics*

Study 3 (Chapter 4) examined patterns in course characteristics of parental bipolar disorder and how these patterns may be differentially associated with offspring psychopathology. Children living with a parent with bipolar disorder experience the fallout of their parent's episodes of mania and depression and associated psychosocial

impairment and stress. However, given the heterogeneity of bipolar disorder course presentation, children's experience of parental bipolar disorder may differ substantially depending on the nature and course of parental symptoms. Additionally, offspring might be at higher genetic risk of certain types of psychopathology depending on parental bipolar disorder characteristics. Particular bipolar disorder course characteristics, including bipolar disorder type (I or II), age of illness onset, polarity at illness onset, primary episode polarity, rapid cycling, history of psychosis, history of anxiety disorders, and history of substance dependence, have been linked with greater illness severity and poorer patient outcomes (Treuer & Tohen, 2010). Such findings have led to speculations that many of these features may be associated with discrete bipolar disorder subtypes, perhaps with different patterns of familial risk (e.g., M. S. Bauer et al., 1994; Benazzi, 2009; Potash et al., 2001; Schurhoff et al., 2000; N. M. Simon et al., 2004; Wozniak et al., 2010). However, few published studies to date have examined specifically the impact of these characteristics on offspring. These studies generally report associations between characteristics of parental illness (e.g., bipolar disorder illness severity, number of manic and mixed episodes, age of illness onset, bipolar disorder type, and psychosis) and the presence of offspring psychopathology (Chang et al., 2000; Garcia-Amador et al., 2013; Grigoriu-Serbanescu et al., 1989; Oquendo et al., 2013). However, these studies warrant replication in a larger sample that examines a range of offspring psychopathology. In addition, rather than examining correlations between various individual bipolar disorder illness characteristics and offspring psychopathology, it may be important to instead

evaluate relationships with empirically derived patterns of parental bipolar disorder course and clinical characteristics.

## **SPECIFIC AIMS OF THE PRESENT STUDIES**

### *Study 1 (Chapter 2)*

The aims of this study were to examine the relationships between OCs and psychopathology in offspring of parents with bipolar disorder and to explore whether parental comorbid anxiety disorders influenced risk for OCs and/or offspring psychopathology. First, associations between OC history and offspring psychopathology were assessed, with the hypothesis that OC history would be linked with increased rates of psychopathology in these offspring. Second, this study identified whether and what categories of OCs (i.e., maternal prenatal complications, delivery complications, neonatal characteristics) were associated with offspring psychopathology. Third, associations between lifetime maternal comorbid anxiety disorder and OCs were examined, with the prediction that anxiety comorbidity (particularly when onset occurs prior to the offspring's birth) would be associated with increased rates of OCs. As an additional control, these relationships were also examined in fathers with bipolar disorder to determine whether the potential influence of anxiety pathology was specific to mothers. Fourth, to further elucidate the relationship between OCs and offspring psychopathology, path models tested whether OCs mediated the association between comorbid maternal anxiety disorder and offspring psychopathology.

*Study 2 (Chapter 3)*

The first aim of this study was to examine the cross-sectional associations between family functioning variables (cohesion, expressiveness, and conflict) and multiple categories of current offspring psychopathology. Offspring psychopathology was assessed dimensionally as well as categorically to capture the full range of current offspring symptomatology. As a second aim, this study assessed whether age and sex moderated the above associations, with the hypothesis that the connection between family functioning and offspring psychopathology would be stronger in girls and in younger children. This study also tested the three-way interaction between family functioning, age, and sex, anticipating that the associations between family functioning and psychopathology would be strongest in younger boys and older girls.

*Study 3 (Chapter 4)*

The aims of this study were to examine whether particular patterns of illness characteristics would emerge among parents with bipolar disorder and to determine if these patterns were associated with differential risk for psychopathology in offspring. First, latent class analysis (LCA) was used to identify phenotypic subtypes of bipolar disorder in parents based on relevant characteristics of bipolar disorder illness course: bipolar disorder type (I or II), age of illness onset, polarity at illness onset, polarity of primary episode, rapid cycling, history of psychosis, history of anxiety disorders, and history of substance dependence. LCA models with 2-, 3-, and 4-class solutions were compared to determine optimal class compositions. Second, this study examined associations between parental latent class membership and rates of psychopathology in

offspring. Multiple categories of offspring psychopathology were examined. Third, separate analyses were conducted for male and female offspring to determine potential sex differences.

## **GENERAL METHODS**

Detailed methods specific to Studies 1, 2, and 3 are described in Chapters 2, 3, and 4, respectively. This section provides a general overview of relevant study procedures and sample characteristics.

### *Procedure*

The present series of investigations involve cross-sectional secondary analyses of data from two larger studies examining offspring of patients with bipolar disorder: *Identifying Children at Risk for Bipolar Disorder* (Child at Risk study; PI: Andrew Nierenberg, MD) and *Magnetic Resonance Spectroscopy (MRS) in Children at Risk for Bipolar Disorder* (MRS study; PI: Aude Henin, Ph.D.)<sup>1</sup>. Both investigations compared at-risk youth to a control group of offspring of parents with no psychiatric disorder; however, only the families in which a parent had bipolar disorder were included in this secondary analysis of the data.

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Participants were recruited from the Massachusetts General Hospital Bipolar Clinic and Research Program (BCRP). Similar recruitment strategies were utilized for both studies: parents were recruited through advertisements posted in the waiting room of the BCRP and letters to clinicians. Those who were interested in participating contacted the study coordinator who confirmed their diagnosis of bipolar disorder via a screening questionnaire. Eligible families meeting study entry criteria then received a diagnostic assessment with a structured interview, and those who received a positive diagnosis of bipolar disorder were included in the final analysis. To be eligible for participation, parents had to have at least one biological child between the ages of 4 and 18. Participants were excluded if they had current severe acute mania or psychosis, pervasive developmental disability, or an inadequate command of the English language.

Upon entrance in the study, parents were interviewed about their own psychiatric history as well as the psychiatric history of their children. Offspring ages 12 and older were also interviewed directly. Interviews gathered detailed information about lifetime and current psychiatric diagnoses, severity of impairment, ages of onset/offset, and treatment history. Interviews were conducted by master- or bachelor-level psychometricians who were extensively trained and supervised in interview procedures and diagnostic criteria. Psychometricians were blind to all study hypotheses, and they interviewed parents about their children prior to obtaining diagnostic information about the parents themselves to maintain blindness to information about the parents. Parents and offspring over the age of 12 also completed a variety of questionnaires, including

measures of offspring symptoms and family functioning. Detailed information about these measures is presented in the following chapters.

All study procedures were approved by the Massachusetts General Hospital Subcommittee for Human Studies. All parents, and offspring who were age 18 or older, provided informed consent prior to participate. Offspring under age 18 provided assent for study participation. Participants were compensated for their involvement.

### *Participants*

The full sample of participants included 119 parents who received treatment at the Massachusetts General Hospital BCRP and their 206 offspring, ages 4 to 33. Data were only available for one parent in each family (i.e., the parent who had a bipolar disorder diagnosis). The family compositions were as follows: 47 patients had one offspring in the study; 58 patients had two offspring in the study; 13 patients had three offspring in the study; and 1 patient had four offspring in the study. Of the full sample, 73% of families were recruited as part of the Child at Risk study, 24% were part of the MRS study, and 3% participated in both studies. There also were multiple waves of data for some participants. When this occurred, the most recent complete set of data was selected.

The parent sample was composed of 79 females and 35 males (sex data were missing for five parents). Sixty-six percent of offspring ( $n = 131$ ) had a mother with bipolar disorder. Approximately half of the offspring sample (46.6%) was female. Most offspring were Caucasian (93.2%) and came from families in the top two income classes on the Hollingshead scale (82.0%). Sixty-three percent of offspring came from an intact family (i.e., biological parents were married or co-habiting), whereas 37% had biological

parents who were separated or divorced from one another. Participant demographic data vary for each study given that participants were excluded from some analyses due to missing data on study-relevant measures. In addition, for Study 2, only offspring age 18 years and under were included (see Chapter 3 for explanation).

### *Analyses*

All analyses were conducted using *SPSS* and *Mplus* (Muthén & Muthén, 1998-2010) software. The sample contains multiple siblings from some families, violating assumptions of independence of observations. Therefore, multilevel modeling (with the type=complex feature in *Mplus*) was utilized for all regression and path analyses to adjust standard errors to account for nested data. Detailed descriptions about each set of analyses are included in the following chapters.

Power calculations for the present analyses were based upon standard methods to demonstrate the adequacy of the sample to study the hypotheses proposed using the tables published by Cohen (1988). Assuming a Type I error rate of 0.05, the present sample size of 206 offspring of bipolar disorder parents should be sufficient to achieve 95% power to detect a medium effect size even in the most complex models. Some analyses are restricted to offspring of mothers with bipolar disorder. Given that approximately 80% of parents with bipolar disorder in this study were mothers, therefore reducing the sample size, the power to detect a medium effect size may be lower (0.85) in these analyses. Other analyses were restricted to female offspring and male offspring separately, thus cutting sample size approximately in half for these analyses; again, the power to detect a medium effect size may be lower in these analyses.

The present series of investigations utilized cross-sectional data. Therefore, it is important to note that throughout the investigations, any references to directionality of findings are merely speculative. Further, in the following chapters, any use of the word “risk factor” in describing the present findings will denote *potential* risk for the development of psychopathology (see Alloy, Abramson, Smith, Gibb, & Neeren, 2006).

## CHAPTER TWO

### STUDY 1

#### **Early Risk Factors for Psychopathology in Offspring of Parents with Bipolar Disorder: The Role of Obstetric Complications and Maternal Comorbid Anxiety<sup>2</sup>**

#### **INTRODUCTION**

Offspring of parents with bipolar disorder (BD) are at increased risk for developing BD and various other psychiatric disorders, compared with offspring of parents with no psychiatric history (DelBello & Geller, 2001). Despite the link between parental BD and offspring psychopathology, mechanisms conferring risk are not fully understood. Genetic factors contribute substantially to vulnerability, and BD is highly heritable (Smoller & Finn, 2003). Yet, estimated concordance rates for BD among monozygotic twins (approximately 0.40) suggest that environmental factors also play a role (Kieseppä et al., 2004). In addition, many offspring of parents with BD do not go on to develop psychiatric illness (Chang et al., 2000). Identifying environmental factors that

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<sup>2</sup> This chapter was previously published: Freed, R. D., Tompson, M. C., Hirshfeld-Becker, D., Otto, M. W., Nierenberg, A. A., Wang, C. H., & Henin, A. (2014). Early risk factors for psychopathology in offspring of parents with bipolar disorder: The role of obstetric complications and maternal comorbid anxiety. *Depression and Anxiety*. DOI: 10.1002/da.22254.

increase vulnerability to psychopathology in high risk samples, and understanding mechanisms of risk, may inform preventative interventions for children and families.

Environmental factors conferring risk for psychopathology may occur at the very initial stages of development. Obstetric complications (OCs), adverse events during pregnancy or birth, can have substantial implications for later health outcomes. OCs include events or circumstances in pregnancy, such as heavy bleeding, excessive nausea/vomiting, and gestational diabetes (maternal prenatal complications); during labor or delivery, such as breech delivery, cesarean section, and premature birth (delivery complications); or immediately after delivery, such as low birth weight and hospitalization in a neonatal intensive care unit (neonatal characteristics). OCs have been linked with a number of psychiatric disorders in children and adults (Schlotz & Phillips, 2009), with the most robust evidence for the association with later schizophrenia (Cannon, Jones, & Murray, 2002); however, studies have also demonstrated associations between OCs and risk for non-schizophrenic disorders including anxiety (Hirshfeld-Becker et al., 2004), disruptive behavior (Robinson et al., 2008), and depressive disorders (Patton et al., 2004). Findings are mixed for BD, with some studies reporting higher rates of OCs during the pregnancy/birth of individuals with BD, compared with both individuals with other psychiatric disorders and healthy controls, and others not finding such associations (Scott, McNeill, Cavanagh, Cannon, & Murray, 2006). One problem with prior studies is the failure to account for important “third variables,” such as parental psychopathology, that may influence risk for both OCs and offspring disorders.

Women with BD may have an increased risk of experiencing OCs during pregnancy with their offspring than women with no psychiatric history (Jablensky et al., 2005; Lee & Lin, 2010). Although the reasons for these higher rates remain unclear, two consistent findings suggest that comorbid anxiety in mothers with BD may be a contributing factor. First, anxiety disorders frequently co-occur with BD (Merikangas et al., 2007; Merikangas et al., 2011); and second, stress and anxiety in pregnancy are associated with OCs, independent of other biomedical risk factors (Alder et al., 2007). However, to date no study has examined the role of anxiety comorbidity on the risk for OCs in women with BD.

Given the heightened risk of OCs among women with BD and/or anxiety disorders, risk for psychopathology in offspring may be partially conferred indirectly via OC risk. The current study aimed to clarify the relationship between OCs and psychopathology in offspring of parents with BD. First, associations between OC history and offspring psychopathology were examined, with the hypothesis that OC history would be linked with increased rates of psychopathology in these offspring. Second, the present study identified whether and what categories of OCs (i.e., maternal prenatal complications, delivery complications, neonatal characteristics) predicted offspring psychopathology. Third, associations between lifetime maternal comorbid anxiety disorder and risk for OCs were examined, with the prediction that anxiety comorbidity (particularly when onset occurs prior to the offspring's birth) would be associated with increased risk for OCs. As an additional control, the present study also examined these relationships in fathers with BD to determine whether the potential influence of anxiety

pathology is specific to mothers. Fourth, to further elucidate the relationship between OCs and offspring psychopathology, path models tested whether OCs mediate the relationship between comorbid maternal anxiety disorder and offspring psychopathology.

## **METHODS**

The present investigations examined data from two studies examining characteristics of and risk factors for offspring of parents with BD (Henin et al., 2005; Henin et al., submitted). Parents were recruited through advertisements posted in waiting rooms of Massachusetts General Hospital psychiatry units, letters to clinicians, and advertisements to the general public. Potential participants were evaluated using a structured diagnostic interview, and those with a positive BD diagnosis were included. Study procedures were approved by the Massachusetts General Hospital Subcommittee for Human Studies. All participants age 18 or older provided informed consent prior to participation. Offspring under age 18 provided written assent. Participants were compensated for their participation.

### *Measures*

*Psychiatric history.* Parents with BD were interviewed about their own current and past diagnoses using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID; First & Gibbon, 2004). Psychiatric information about the unaffected (i.e., non-BD) parent was not collected. Parents and offspring over age 12 were interviewed about lifetime offspring diagnoses. The Schedule for Affective Disorders and Schizophrenia for School-Aged Children-Epidemiologic Version (KSADS; Orvaschel, 1995) was used for subjects under age 18 years. When offspring were over age 18, parents and offspring

were interviewed about offspring diagnoses using the SCID, supplemented by KSADS modules to assess childhood diagnoses (e.g., attention deficit hyperactivity disorder). In cases where offspring were also interviewed directly about their symptoms, a symptom was considered present if endorsed by either the parent or the offspring. Interviews were conducted by master- or bachelor-level psychometricians who were extensively trained and supervised in interview procedures and diagnostic criteria and were blind to study hypotheses. Psychometricians conducted offspring evaluations prior to parental evaluations in order to maintain blindness to parental information. For analyses, parent and offspring emotional and behavioral diagnoses were grouped in the following categories: BD (BD-I or BD-II); depressive disorder (major depressive disorder and/or dysthymic disorder); attention deficit hyperactivity disorder; disruptive behavior disorder (oppositional defiant disorder and/or conduct disorder); and anxiety disorder (panic disorder, agoraphobia, social phobia, specific phobia, obsessive compulsive disorder, generalized anxiety disorder, posttraumatic stress disorder, and/or separation anxiety disorder).

*Obstetric complications.* History of OCs (presence or absence) for each offspring was established from the Perinatal and Early Development Section of the Diagnostic Interview for Children and Adolescents-Parent Version (DICA-P; Herjanic & Reich, 1982). This module of the DICA-P asks about the mother's pregnancy, including questions about complications having occurred, including maternal prenatal complications, delivery complications, and neonatal characteristics. Studies report high test-retest reliability for this section, with the majority of items having a Kappa of 0.70 or

greater (Reich, 2000). A number of studies have also shown maternal retrospective reports of obstetric events are highly consistent with chart reviews (Gayle, Yip, Frank, Nieburg, & Binkin, 1988; Olson, Shu, Ross, Pendergrass, & Robison, 1997; Sanderson et al., 1998). An obstetrician<sup>3</sup> was consulted prior to conducting analyses to determine which items on the DICA-P represented indicators of fetal distress. The present study subsequently only included these items in analyses to ensure assessment of reliable markers of risk (see Table 2.3). For example, items such as “spotting or light bleeding” were excluded, as such mild bleeding during the first trimester is not routinely indicative of major problems.

### *Analyses*

Data were analyzed using *Mplus v.6* (Muthén & Muthén, 1998-2010) and *SPSS* software. Bivariate analyses determined whether demographic factors (e.g., parent and offspring sex, parent and offspring age, socioeconomic status, and parental marital status) were associated with the constructs of interest. The sample contains multiple offspring (i.e., siblings) from some families. Therefore, multilevel modeling (with the type=complex feature in *Mplus*) was utilized for regression and path analyses to adjust standard errors to account for nested data. Weighted least squares estimation with mean- and variance-adjustment was also used. When multiple waves of data were present for some participants, the most recent wave was selected for analyses.

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<sup>3</sup> Debra G. Knee, MD of Winchester Hospital, Winchester, MA.

Probit regression analyses examined associations between OCs and offspring psychopathology, with presence/absence of lifetime emotional and behavioral disorders as dependent variables and OC history as the predictor. Probit regressions then examined whether, and the extent to which, different categories of OCs (maternal prenatal characteristics, delivery complications, and neonatal characteristics) predicted offspring psychopathology. Next, probit regression analyses were run in the subsample of mothers with BD, examining associations between maternal lifetime anxiety diagnoses and OCs in pregnancy/delivery with their offspring. Identical analyses were run in the subsample of fathers with BD to clarify specificity of findings to mothers. Path analyses tested whether OCs mediate the relationship between parental lifetime anxiety disorders and offspring lifetime psychopathology. Path analysis was selected in order to incorporate all hypotheses concurrently, estimating indirect and direct effects in one model.

## **RESULTS**

### *Participant characteristics*

The sample included 206 offspring of 119 parents (mother or father) with BD. Of these families, 47 included one offspring, 58 included two offspring, 13 included three offspring, and 1 included four offspring. As Table 2.1 illustrates, 66.4% of offspring ( $n = 131$ ) had a mother with BD. Offspring age ranged from 4–33 years ( $M = 13.6$ ,  $SD = 6.10$ ), and approximately half were female. Most offspring were Caucasian (93.2%) and came from families in the top two income classes on the Hollingshead scale (82.0%). Almost 75% were born after the occurrence of their parent's first manic episode.

Most offspring (77.2%) had a lifetime history of emotional or behavioral

disorders, with 53.1% having more than one diagnosis and 38.2% having more than two diagnoses (Table 2.2). Among parents, 66% had lifetime diagnoses of comorbid anxiety disorders (Table 2.3); and in 90% of cases, the anxiety disorder(s) onset prior to their child's birth (Mean age of onset = 13.5 years;  $SD = 9.79$ ). Of the full sample of offspring, information about OCs was available for 77% ( $n = 159$ ). Seventy-two percent of these offspring had a history of at least one OC, and over half of these offspring (56%) had had multiple OCs (Table 2.3; Range: 1–8,  $M = 2.16$ ,  $SD = 1.46$ ). There were no differences in rates of OCs between offspring of BD mothers versus BD fathers (*Fisher's Exact Test*  $p = .51$ ).

Bivariate analyses revealed that, of the demographic variables, only offspring age and parent age were significantly associated with the constructs of interest: both age variables were correlated with prenatal OC history (offspring age:  $t = 3.43$ ,  $p < .001$ ; parent age:  $t = 2.54$ ,  $p < .01$ ) and offspring lifetime anxiety disorder (offspring age:  $t = 3.25$ ,  $p < .001$ ; parent age:  $t = 3.09$ ,  $p < .01$ ). The pattern of findings did not change when controlling for these variables; therefore, results of analyses without the inclusion of age variables are presented below.

#### *Associations of OCs with offspring psychopathology*

Probit regression analyses tested associations between OC history and offspring lifetime diagnoses. Only offspring lifetime anxiety disorders ( $\beta = .25$ ,  $p < .01$ , *R-square* = .06) were significantly associated with OC history. Controlling for parental lifetime anxiety disorders, results remained significant ( $\beta = .21$ ,  $p < .05$ , *R-square* = .08). To examine associations between particular categories of OCs and offspring lifetime

disorders, the analyses were repeated using the following predictors: maternal prenatal complications, delivery complications, and neonatal characteristics. Offspring anxiety disorders were significantly associated with delivery complications ( $\beta = .27, p < .01, R\text{-square} = .07$ ) and remained so controlling for parental lifetime anxiety disorders ( $\beta = .24, p < .01, R\text{-square} = .10$ ). Offspring anxiety disorders were not associated with the other OC categories, nor were other offspring lifetime disorders associated with OCs.

The sample was then divided into offspring of BD mothers ( $n = 96$ ) and offspring of BD fathers ( $n = 56$ ), and ran identical probit regression analyses in each group separately (these analyses excluded offspring [ $n = 7$ ] for whom parent gender data were missing). A small but significant association was observed between OCs and anxiety disorders in offspring of BD mothers ( $\beta = .23, p < .05, R\text{-square} = .05$ ) and an association that approached significance in offspring of BD fathers ( $\beta = 0.28, p = .09, R\text{-square} = .08$ ). In offspring of BD mothers, but not fathers, anxiety disorders were significantly associated with delivery complications ( $\beta = .33, p < .01, R\text{-square} = .11$  versus  $\beta = .18, p = .29, R\text{-square} = .03$ ). Offspring anxiety disorders were not associated with the other OC categories in either group.

#### *Associations of co-morbid parental anxiety disorders and OCs*

Probit regression analysis using the full sample revealed an association between parental lifetime anxiety disorders and OCs ( $\beta = .27, p < .05, R\text{-square} = .07$ ). When the 10% of parents whose anxiety had onset after their child's birth were removed, there was an even stronger association ( $\beta = .34, p < .01, R\text{-square} = .12$ ). Identical probit regressions were then conducted separately for BD mothers and BD fathers. OCs were

significantly associated with parental lifetime anxiety disorders in BD mothers ( $\beta = .35$ ,  $p < .05$ ,  $R\text{-square} = .12$ ) but not fathers ( $\beta = 0.13$ ,  $p = .52$ ,  $R\text{-square} = .02$ ). Again, results were strengthened when excluding mothers whose anxiety onset after their child's birth ( $\beta = .42$ ,  $p < .01$ ,  $R\text{-square} = .18$ ). There were no significant associations between maternal lifetime anxiety disorders and each OC category separately.

#### *Path Analyses*

Path analysis tested whether OCs mediate the relationship between maternal lifetime anxiety disorders and offspring lifetime anxiety disorders. The chi-square statistic ( $\chi^2 = 1.12$ ,  $df = 1$ ,  $p = .29$ ), as well as incremental fit indices ( $RMSEA = .04$ ;  $CFI = 0.99$ ;  $TLI = .96$ ) indicated good model fit (Hu & Bentler, 1999). Model fit was improved when excluding mothers whose anxiety onset after their child's birth ( $RMSEA = .00$ ;  $CFI = 1.00$ ;  $TLI = 1.27$ ). Figure 1 shows the standardized path coefficients for the model. Results confirmed a direct effect of maternal lifetime anxiety disorders on OCs ( $\beta = .42$ ,  $p < .01$ ,  $R\text{-square} = .17$ ) and a direct effect of OCs on offspring lifetime anxiety disorders ( $\beta = .32$ ,  $p < .05$ ,  $R\text{-square} = .11$ ). The indirect effect of maternal lifetime anxiety disorders on offspring lifetime anxiety disorders (via OCs) approached statistical significance ( $\beta = .14$ ,  $p = .07$ ).

The path model testing mediation by delivery complications also fit the data well ( $\chi^2 = 1.14$ ,  $df = 1$ ,  $p = .29$ ;  $RMSEA = .04$ ;  $CFI = 0.98$ ;  $TLI = .95$ ), and model fit was again improved when excluding mothers whose comorbid anxiety onset after their child's birth ( $RMSEA = .00$ ;  $CFI = 1.00$ ;  $TLI = 1.23$ ). As shown in Figure 1, results confirmed a direct effect of maternal lifetime anxiety disorders on delivery complications ( $\beta = .32$ ,  $p < .05$ ,

*R-square* = .10) and a direct effect of delivery complications on offspring lifetime anxiety disorders ( $\beta = .48, p < .05, R\text{-square} = .23$ ). The indirect effect of maternal lifetime anxiety disorders on offspring lifetime anxiety disorders (via delivery complications) was statistically significant ( $\beta = .15, p < .05$ ).

## **DISCUSSION**

The present study examined relationships between OCs and psychopathology in offspring at risk for BD and explored whether parental comorbid anxiety disorders influenced risk for OCs and/or offspring psychopathology. Data replicated earlier research demonstrating high rates of psychopathology in offspring of parents with BD. Results also indicated an association between maternal lifetime anxiety disorders and OCs and a link between OCs, particularly delivery complications, and increased risk for offspring anxiety disorders. Finally, path analyses revealed that delivery complications act as a mediator in the relationship between maternal comorbid anxiety disorders and offspring anxiety disorders, suggesting that the association between maternal and offspring anxiety may be influenced in-part by very early environmental factors occurring at birth.

Consistent with prior studies of offspring at risk for BD (Chang et al., 2000; DelBello & Geller, 2001), the present sample had high rates of psychopathology, and there was significant comorbidity among diagnoses. Over three quarters of the sample had a history of one or more emotional or behavioral disorders, more than half had at least two diagnoses, and almost a quarter had BD themselves. Anxiety disorders were the most prevalent category of offspring disorder, affecting approximately half the sample;

this is consistent with findings that anxiety disorders are the most common disorders among both high-risk youth (Nurnberger et al., 2011) and U.S. adolescents in general (Merikangas et al., 2011). These data underscore the need to assess offspring of parents with BD for a range of psychopathology in addition to mood disorders. Although parents with BD may be cognizant of the risk for mood disorders in their offspring, the presence of anxiety disorders may be less easily recognized.

Offspring with anxiety diagnoses were more likely to have a history of OCs. This was the case for offspring of both BD mothers and BD fathers. Although these results were not statistically significant (i.e.,  $p > .05$ ) for offspring of BD fathers, this may be a result of limited power given the similar effect sizes between offspring of BD mothers and BD fathers. A relationship between OCs and subsequent offspring anxiety has been observed in previous studies of offspring of parents with and without psychopathology (Hirshfeld-Becker et al., 2004; E. Simon, Bögels, Stoel, & De Schutter, 2009). The present findings suggest this relationship may exist in offspring of parents with BD as well. When examining OCs in separate categories based on timing of their occurrence (e.g., prenatal maternal complications, delivery complications, neonatal characteristics), only delivery complications remained associated with offspring anxiety disorders. Alternatively, other studies have shown that prenatal complications are associated with offspring anxiety (Hirshfeld-Becker et al., 2004; E. Simon et al., 2009). Differences between studies may result from different indicators of prenatal OCs and/or differences in base rates of certain prenatal OCs. For example, although the present study used the same measure to assess OCs as Hirshfeld-Becker and colleagues, unlike these researchers, the

present study excluded certain items that might be confounds with maternal psychopathology (e.g., serious family problems during pregnancy, emotional problems requiring counseling). Compared to Hirshfeld-Becker and colleagues' study, the present study also had lower base rates of certain prenatal OCs which they found to be associated with offspring anxiety (e.g., heavy bleeding, hypertension or excessive fluid, illnesses requiring medical attention). Simon and colleagues examined other prenatal factors which the present study did not examine, such as sexually transmitted disease, bacterial/viral infection, lead poisoning, mercury poisoning, radiation, and substance use. Additionally, these authors included as prenatal OCs prematurity and low birth weight, which the present study conceptualized as delivery problems. These measurement discrepancies may have contributed to the inconsistencies in findings across studies. Larger scale studies are needed in order to examine the associations of specific OCs with offspring psychopathology.

Consistent with prior research examining offspring of parents with BD (Singh et al., 2007), the present study did not find an association between OCs and any offspring mood disorders, including BD. However, the mean age of offspring was 13, and therefore most of the sample had not yet entered the period of greatest risk for mood-disorder onset (Kessler et al., 2005). Childhood anxiety disorders often precede major mood disorders (by 8 years, on average; Duffy et al., 2010), and therefore longer-term follow-up may have revealed a link between OCs and offspring mood disorder. Future research following at-risk offspring into adulthood is needed to fully examine the relationship between OCs, offspring anxiety disorders, and subsequent development of BD.

As hypothesized, comorbid maternal lifetime anxiety disorder was associated with OCs. However, this relationship was not present when the father was the affected parent, suggesting that anxiety in the mother (the individual carrying the child) may impact perinatal outcomes. Both human and animal research suggests anxiety and stress during pregnancy may increase risk of OCs by inducing alterations in the fetal environment (Wadhwa, 2005). It is important to note that associations were between lifetime maternal anxiety disorders and OCs, and anxiety symptoms were not necessarily acute during the pregnancy. However, for the vast majority, anxiety disorders had onset prior to their child's birth, and results were strengthened when only this group of mothers was included in analyses. Furthermore, studies show that previous diagnoses of anxiety disorders are strongly correlated with anxiety disorders occurring during pregnancy (Buist, Gotman, & Yonkers, 2011), so it is likely that many mothers in the present sample had elevated anxiety during pregnancy. These results lend support to the hypothesis that maternal anxiety may be driving associations between BD and OC risk observed in previous studies (Jablensky et al., 2005; Lee & Lin, 2010).

It is also possible that comorbid anxiety disorders indicate more severe BD psychopathology; and therefore BD illness severity, rather than anxiety per se, is actually responsible for increasing risk for OCs. Among BD patients, anxiety comorbidity is linked with greater symptom severity and impairment (N. M. Simon et al., 2004). Although this has not been tested directly, research examining BD onset (another marker of illness severity) has shown associations with OCs (Jablensky et al., 2005). Future studies will need to clarify whether illness severity may be responsible for increasing the

risk of OCs for BD mothers.

Path analyses indicated that delivery complications partially mediated the relationship between maternal anxiety disorder and offspring anxiety disorder. In other words, part of the relationship between maternal and offspring anxiety may be accounted for by the presence of difficulties during childbirth. Taken together, these findings suggest that: 1) women with BD and comorbid anxiety are at greater risk for OCs; 2) OCs, particularly delivery complications, put offspring at increased risk for anxiety disorders; and 3) offspring of mothers with BD and comorbid anxiety, who also experience OCs, are at greater risk for the development of anxiety disorders themselves. The relationship between maternal and offspring anxiety has been well documented (Micco et al., 2009). The present results add to the literature by suggesting that mothers may confer some of the risk for anxiety in offspring indirectly through influences on fetal environment.

However, it is possible that a third variable may be influencing these relationships. For example, as noted above, prenatal anxiety may alter the fetal environment; in addition to increasing risk for OCs, such alterations may adversely impact fetal brain development and, in turn, affect later child development (Van den Bergh, Mulder, Mennesa, & Glover, 2005). Post-natal environmental factors may also play a role. For example, both maternal anxiety and OCs may indirectly increase the risk of child psychopathology by acting as risk factors for maternal postpartum psychopathology. In fact, previous research indicates that anxiety during pregnancy predicts postpartum depression (Coelho, Murray, Royal-Lawson, & Cooper, 2011); and

severe OCs have been linked with postpartum depression, independent of depression or anxiety disorder during pregnancy (Verdoux, Sutter, Glatigny-Dallay, & Minisini, 2002). Experiencing complications during pregnancy or delivery may also influence a mother's parenting style and mother-child interactions in a way that increases risk for offspring psychopathology. For example, compared to mothers of full-term infants, mothers of premature infants have been found to be less sensitive and more controlling in mother-infant interactions (Muller-Nix et al., 2004). Such interactions may be heightened in mothers who are already pre-disposed to anxiety. Evidence suggests that parental over-control and anxious rearing may contribute to the development of offspring anxiety disorders (Bögels & Brechman-Toussaint, 2006; Van Brakel, Muris, Bögels, & Thomassen, 2006). Regardless of whether events during delivery are directly or indirectly contributory, the present findings suggest that comorbid anxiety in mothers with BD may set in motion a chain of events that increase risk for offspring anxiety disorders. Additionally, these findings speak to the importance of attending to and accounting for both maternal anxiety and OCs when working with mothers and offspring.

Despite the contribution that this research adds to the literature, additional study limitations warrant mention. First, the sample was comprised exclusively of parents with BD and their offspring, so the present study cannot determine the specificity of these findings to BD. Second, ascertainment of OCs was through self-report only, and parents may not clearly remember events during pregnancy and delivery. However, studies have shown parental retrospective reports of perinatal factors and infant birth weight are highly consistent with chart reviews, and reliability is not affected by time between delivery and

interview (Olson et al., 1997; Sanderson et al., 1998). Third, data were collected using the DICA-P which is not primarily used to assess OCs and does not assess OC severity. An obstetrician was consulted in an attempt to exclude items that were not indicative of risk for fetal distress. However, the same complication (maternal bleeding, for example) may vary greatly in intensity, duration, and timing. As Scott and colleagues (2006) point out, such measurement issues are widespread in the literature on the impact of OCs on psychopathology and speak to the need for a more narrow and concise definition of OCs that accounts for nature, timing, duration, and intensity. Fourth, the sample was comprised primarily of Caucasian families in the top income classes on the Hollingshead scale. It is possible that the present findings may not generalize to families of other racial/ethnic groups or income classes.

Despite these limitations, the present findings have implications for interventions for pregnant mothers and high-risk offspring. Identifying anxiety in pregnant mothers with (and potentially without) BD may be an important step in reducing risk of OCs and/or offspring psychopathology. Although in recent years, screening for depression during pregnancy has become an important priority for health care providers (Freed, Chan, Boger, & Tompson, 2012), identification of anxiety during pregnancy has received less attention (Meades & Ayers, 2011). Obstetricians and gynecologists indicate more confidence and accuracy in identifying depressive symptoms than anxiety symptoms (Coleman, Carter, Morgan, & Shulkin, 2008a). This speaks to the need for better training for medical providers working with pregnant women with psychiatric disorders. Identifying OCs as early vulnerability factors for psychopathology may also facilitate

earlier detection and intervention for children at familial risk.

Psychotherapy for pregnant women with BD and/or comorbid conditions is also potentially important. Despite an expanding literature on psychosocial treatments for BD (D. J Miklowitz, 2008), no published BD treatment studies have focused specifically on pregnant women. In addition to helping women manage their BD during pregnancy and postpartum, and addressing issues salient to pregnant women (role transition, parenting expectations, pregnancy-related physical and social constraints, eliciting practical and emotional support), treatments should emphasize anxiety reduction. Such interventions may decrease maternal OC risk and provide secondary benefits to offspring, both during fetal development and throughout childhood.

## TABLES AND FIGURES

Table 2.1. Participant Demographic Characteristics

Demographic Factor	Mean $\pm$ <i>SD</i> (Range) or Percentage
Offspring age (in years)	13.61 $\pm$ 6.14 (4–33)
Offspring sex	
Female	46.6%
Male	53.4%
Parent age (in years)	44.68 $\pm$ 7.79 (25–63)
Sex of parent with bipolar disorder	
Female	66.2%
Male	33.8%
Parent age at offspring's birth (in years)	30.88 $\pm$ 5.5 (15–50)
Child born before or after parent's onset of mania	
Born before	26.0%
Born after	74.0%
Family social class (Hollingshead, 1= highest)	1.88 $\pm$ 1.00 (1–5)
Intactness of family	
Parents married	63.1%
Parents separated or divorced	36.9%

Table 2.2. Lifetime Offspring Psychopathology

History of Emotional and Behavior Disorders	Percentage
Bipolar disorder	23.8%
Depressive disorder	24.3%
Major depressive disorder	23.8%
Dysthymic disorder	1.5%
Anxiety disorder	52.7%
Panic disorder	6.8%
Agoraphobia	16.1%
Specific phobia	22.1%
Social phobia	15.1%
Obsessive compulsive disorder	7.4%
Generalized anxiety disorder	21.1%
Posttraumatic stress disorder	4.9%
Separation anxiety disorder	27.3%
Attention deficit/hyperactivity disorder	28.3%
Disruptive behavior disorder	37.1%
Oppositional defiant disorder	36.1%
Conduct disorder	10.2%
Any emotional or behavioral disorder (listed above)	77.2%

Table 2.3. Frequency of Obstetric Complications and Intercorrelations in Offspring ( $n = 159$ )

Obstetric Complication	%	1	2	3	4	5	6	7	8	9	10	11	12	13
Maternal prenatal complications	44.7%													
1. Heavy bleeding requiring bed rest	5.1%													
2. Excessive nausea or vomiting lasting more than three months	7.5%	.15												
3. Weight loss over 10 lbs	5.7%	.07	-.07											
4. Infection requiring medical attention	12.0%	.18*	.04	-.01										
5. High blood pressure and/or excessive fluid in your body	19.5%	.25**	.16*	.22**	.16*									
6. Convulsions	0.6%	-.02	-.02	-.02	-.03	-.04								

7. Accidents requiring medical care	3.8%	-0.05	.19*	-0.05	.13	-0.01	-0.02							
8. Other illnesses requiring medical care	14.5%	.07	.29**	-.10	.12	.11	-.03	.11						
Delivery complications	55.3%													
9. Born breech	3.1%	.12	.22**	-.04	-.07	.18*	-.01	.15	.23**					
10. Cesarean section	17.7%	-.02	.13	-.11	-.01	.20*	-.04	-.01	.20*	.30**				
11. Other delivery complication <sup>1</sup>	47.8%	.13	.21*	.04	.23**	.20*	-.08	.08	.15	.01	.11			
Neonatal characteristics	16.1%													
12. Put in an incubator	10.3%	.11	-.02	.01	.00	.10	.24**	-.07	.04	.18*	.17*	.23**		
13. Weight less than 5 lbs	3.2%	.12	-.05	-.05	.15	.19*	-.02	-.04	-.08	-.03	.20*	.19*	.42**	
14. Long stay in hospital	6.6%	.07	-.07	-.07	.15	-.06	-.02	-.05	-.03	-.05	-.06	.12	.08	.10

<sup>1</sup> e.g., born 2 weeks early/late, forceps delivery, cord wrapped around neck, labor > 24 hours; \*  $p < .05$ ; \*\*  $p < .01$

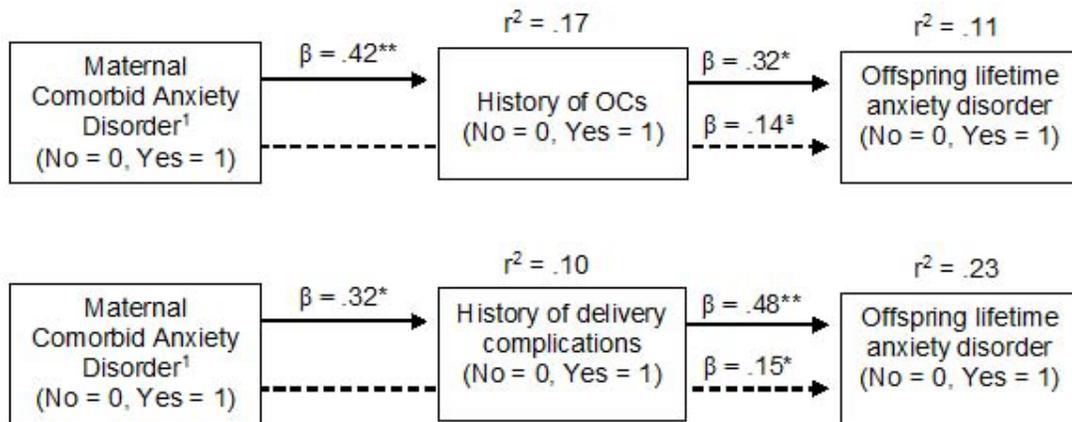


Figure 2.1. Path analyses testing mediation via history of OCs (top) and via delivery complications (bottom). NOTE: Solid arrows indicate direct effects, and dotted arrow indicates indirect effect. Standardized Regression Weights are shown. <sup>1</sup> Occurring prior to birth of offspring,  $** p < .01$ ,  $* p < .05$ ,  $^a p = .07$ .

## CHAPTER THREE

### STUDY 2

#### **Family Functioning in the Context of Parental Bipolar Disorder: Associations with Offspring Age, Sex, and Psychopathology**

#### **INTRODUCTION**

Bipolar Disorder (BD) is a chronic disorder characterized by high rates of relapse and recurrence (Harrow, Goldberg, Grossman, & Meltzer, 1990), and individuals with BD may experience substantial functional impairment, even when receiving treatment (Judd, Akiskal, Schettler, Coryell, Maser, et al., 2003; Judd et al., 2005). Offspring of parents with BD are at high risk for developing BD and other psychiatric problems (DelBello & Geller, 2001; Hirshfeld-Becker et al., 2006; Lapalme et al., 1997). Although syndromal disorders (particularly mood disorders) often do not onset until adolescence or young adulthood, offspring of parents with BD appear to be at risk for psychiatric symptoms and adjustment problems at multiple stages of development (Henin et al., 2005). In fact, the presence of early, general psychopathology in these offspring may increase risk for later mood disorder (Carlson & Weintraub, 1993; Duffy, Alda, Crawford, et al., 2007). Although genetic factors have been implicated in the intergenerational transmission of mood disorders among BD families, environmental factors also play salient roles in increasing vulnerability (Alloy et al., 2005; Kieseppä et al., 2004). Additionally, early psychosocial stress may hasten age of onset in individuals with genetic vulnerability to BD (Post & Leverich, 2006), heralding more severe disease courses and greater impairment (Perlis et al., 2004). Therefore, identifying and

understanding the role of environmental factors for high-risk offspring may inform efforts at prevention and early identification and therefore reduce the intergenerational impact of BD on families.

One critical environmental variable that may impact the developmental trajectory of offspring of parents with BD is family functioning. Studies conducted to date suggest that when a parent has BD, families experience more interpersonal difficulties, including less cohesion and expressiveness and more conflict, compared to families without a parent who has been diagnosed with BD (Barron et al., 2014; Chang et al., 2001; Du Rocher Schudlich et al., 2008; Romero et al., 2005; Vance et al., 2008). Parents with BD also rate themselves as being more negative in interactions with their children than either parents with unipolar depression or parents without psychopathology (Davenport, Zahn-Waxler, Adland, & Mayfield, 1984; Inoff-Germain, Nottelmann, & Radke-Yarrow, 1992; Vance et al., 2008). Such disruptions in family functioning continue to persist during periods of BD symptom remission (Weinstock et al., 2006), indicating that family impairment may be a somewhat stable construct in this population. These findings suggest that, even when the parent is well, offspring of parents diagnosed with BD are at risk for continued exposure to high family stress and discord.

In the unipolar depression literature, evidence consistently suggests that poor family functioning has a detrimental influence on the psychosocial adjustment of high-risk offspring, whereas positive family factors can exert protective effects (Downey & Coyne, 1990; Goodman & Gotlib, 2002). However, less is known about family processes in families where a parent has been diagnosed with BD. Given that such families may

experience levels and patterns of impairment similar to those families in which a parent has unipolar depression (Weinstock et al., 2006), findings of associations between family functioning and offspring psychopathology from the unipolar depression literature may also hold true for offspring of parents with BD. Indeed, Meyer and colleagues (2006) found that offspring of parents with BD who were exposed to extreme maternal negativity were at five times greater risk for BD than offspring who were not exposed to this risk variable. In a retrospective study of adult offspring of parents with BD, those offspring who themselves had BD reported more rejection by their fathers and mothers compared with offspring with other diagnoses or without diagnosis, as well as compared with individuals from the general population (Reichart et al., 2007). In addition, Ostiguy and colleagues (2011) found an association between interpersonal stress and cortisol levels (a potential biomarker for affective disorders) in offspring of parents with BD, which was not observed among offspring of healthy controls. Du Rocher Schudlich and colleagues (2008) found that among offspring of parents with BD, family functioning was associated with general psychopathology risk, but was not specifically linked to offspring BD. Thus, poor family functioning may be associated with multiple types of psychopathology among high-risk offspring of parents with BD.

Furthermore, associations between family functioning and offspring adjustment may be complex and may differ based on offspring characteristics. For example, sex differences may impact the relationship between family functioning and offspring psychopathology. Hops (1995) proposed that the family may be a more salient context for girls' behavior, as girls are socialized to be more dependent and oriented toward family

issues, and therefore may be more strongly affected by family functioning difficulties. Rudolph (2002) similarly suggested that girls possess more interpersonal sensitivity than boys, and therefore respond with more negative emotion when confronted by interpersonal stressors. Therefore, the relationship between poor family functioning and psychological difficulties may be stronger in girls than boys (Davies & Lindsay, 2004; Davies & Windle, 1997). However, no research has investigated sex differences in the association between family environment and adjustment in offspring of parents with BD. One bottom-up study showed that girls who develop BD (not necessarily high-risk offspring) may be more likely to experience family hostility, criticism, and emotional over-involvement than boys who develop BD (Coville, Miklowitz, Taylor, & Low, 2008).

Offspring age may also influence the association between family functioning and offspring adjustment. For example, Grych (1998) suggested that there are developmental differences in how children perceive and respond to family conflict, in that younger children feel more threatened and helpless, and may use less sophisticated coping strategies, than older children. Given these differences, younger children may be more negatively impacted by family conflict and therefore more prone to the development of psychopathology. Furthermore, the impact of developmental differences may be complicated by child sex. For example, boys may be more vulnerable to the impact of family functioning impairment during childhood; whereas, during adolescence, girls may have heightened vulnerability (see Davies & Lindsay, 2004). This possibility needs to be further explored in families with a parent with BD.

Additional studies are needed to elucidate whether family functioning is associated with offspring adjustment in families where a parent has been diagnosed with BD, and if so, whether offspring are differentially affected based on their sex and developmental stage. A better understanding of family functioning in the context of parental BD and associations with offspring psychopathology may enhance the knowledge of environmental risk factors for BD and thus inform prevention and intervention efforts. The current investigation examined family functioning in a large sample of offspring of parents with BD and identified family environment factors associated with offspring psychopathology. Specifically, the present study examined cross-sectional associations between family functioning variables (i.e., higher conflict, poorer cohesion, lower expressiveness) and offspring psychopathology. The present study assessed psychopathology dimensionally as well as categorically given prior findings that, even before developing clinically significant psychiatric disorders, offspring of parents with BD typically have high rates of non-specific psychiatric symptomatology (Diler et al., 2011). The present study also examined offspring age and sex differences in these associations, hypothesizing that the connection between family functioning and offspring psychopathology would be stronger in girls and in younger children. Last, the present study tested the three-way interaction between family functioning, age, and sex, anticipating that younger boys and older girls might be more vulnerable to family functioning difficulties.

## **METHODS**

The current investigation combined data from two studies examining characteristics of and risk factors for offspring of parents with BD (Henin et al., 2005; Henin et al., submitted). Parents were recruited through advertisements posted in waiting rooms of Massachusetts General Hospital psychiatry units, letters to clinicians, and advertisements to the general public. Potential participants and their offspring were evaluated using a structured diagnostic interview, and parents with a positive BD diagnosis were included. When parents were separated or divorced, the parent with bipolar disorder was required to have primary or joint custody of offspring.

All study procedures were approved by the Massachusetts General Hospital Subcommittee for Human Studies. Parents provided informed consent prior to participation. Offspring provided assent for study participation. Participants were compensated for their involvement.

Parent and offspring diagnostic interviews were conducted by master- and bachelor-level diagnosticians who were extensively trained and supervised in interview procedures and diagnostic criteria. Diagnosticians discussed each interview with experienced, board-certified child and adult psychiatrists and licensed psychologists for review and to resolve diagnostic uncertainties. Kappa coefficients of agreement were examined by having experienced, board certified child and adult psychiatrists and licensed clinical psychologists diagnose subjects from audio taped interviews made by the assessment staff. Based on 500 assessments from interviews of children and adults, the median kappa coefficient was .98. Kappa coefficients for individual diagnoses

included: attention deficit/hyperactivity disorder (ADHD; 0.88), conduct disorder (CD; 1.0), oppositional defiant disorder (ODD; .90), depression (1.0), mania (0.95), separation anxiety (1.0), agoraphobia (1.0), panic disorder (.95), obsessive compulsive disorder (OCD; 1.0), generalized anxiety disorder (GAD; 0.95), specific phobia (0.95), posttraumatic stress disorder (PTSD; 1.0), social phobia (1.0), and substance use disorder (1.0). These measures indicated excellent reliability between ratings made by the non-clinician raters and experienced clinicians. The reliability of the diagnostic review process was examined by computing kappa coefficients of agreement between clinician reviewers. For these clinical diagnoses, the median reliability between individual clinicians and the review committee assigned diagnoses was .87. Kappa coefficients for individual diagnoses included: ADHD (1.0), CD (1.0), ODD (.90), depression (1.0), mania (0.78), separation anxiety (0.89), agoraphobia (.80), panic disorder (.77), OCD (.73), GAD (.90), specific phobia (0.85), PTSD (0.8), social phobia (0.9), and substance use disorder (1.0).

### *Measures*

*Parent psychopathology.* To confirm the presence of BD, parents were interviewed about current and past symptoms using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID; First & Gibbon, 2004). Information about history of comorbid Axis I diagnoses was also gathered through these interviews. The current analyses controlled for comorbid anxiety and substance use disorders, given that these comorbid disorders have been associated with poorer quality of life and greater role impairment in patients with BD (B. I. Goldstein & Levitt, 2008; Mazza et al., 2009; Otto

et al., 2006). Comorbid anxiety disorder was indicated based on the presence of one or more of the following diagnoses: panic disorder, agoraphobia, social phobia, specific phobia, obsessive compulsive disorder, generalized anxiety disorder, posttraumatic stress disorder. Comorbid substance use disorder included the presence of a diagnosis of substance abuse or dependence and/or alcohol use or dependence. Psychiatric information about the unaffected (i.e., non-BD) parent was not collected.

*Offspring psychopathology.* Offspring emotional and behavioral psychopathology was measured by examining both symptom measures and diagnostic data in order to explore fully the effects of environmental risk factors on child outcomes. Parents were administered the 118-item Child Behavior Checklist (CBCL; Achenbach, 1991) as a measure of current offspring emotional and behavioral symptoms. The CBCL is normed for age, allowing for comparisons of children across a wide range of ages and has the advantage of capturing the presence of child symptoms that may not meet full diagnostic criteria. The CBCL has excellent test-retest reliability and good inter-parental agreement (McConaughy, 1993) and shows good convergent and discriminant validity (Clarke, Lewinsohn, Hops, & Seeley, 1992). The present analyses examined *T* scores from the Internalizing and Externalizing problem scales from the CBCL. These scales were examined separately; despite being correlated, these scales are conceptualized as distinct constructs and have been shown to predict divergent patterns of risk from early childhood to adolescence in children at risk (Petty et al., 2008).

Current DSM-IV emotional and behavioral diagnoses were assessed via interviews with parents and offspring over the age of 12 (when available) using the

Schedule for Affective Disorders and Schizophrenia for School-Aged Children-Epidemiologic Version (KSADS; Orvaschel, 1995). The KSADS has demonstrated good validity and reliability (for a review see Ambrosini, 2000). In cases where offspring were also interviewed directly about their symptoms, a symptom was considered present if endorsed by either the offspring or the parent. Diagnoses were rated on a 3-point scale, with a rating of 3 assigned when the offspring's symptoms met full DSM-IV criteria for a particular disorder. A rating of 2 indicated a subclinical presentation of a disorder and was assigned based on specific guidelines for each disorder (e.g., the offspring met more than half of the symptoms for a disorder; the offspring met all symptom criteria but did not meet the time frame criteria). A rating of 1 indicated that the disorder was not present at a clinical or a subclinical level. Mood disorder data were re-coded for analyses such that, if the offspring met full criteria for a depressive disorder (major depressive disorder [MDD] or dysthymia) and had subthreshold manic symptoms that did not meet DSM-IV criteria for BD type I or type II (BD-I or BD-II), a rating of 2 was assigned for BD and a rating of 1 was assigned for depressive disorder. This decision was made based on findings that high-risk offspring who meet full diagnostic criteria for MDD and have subthreshold mania are more likely to progress to full BD over time than those with MDD and no manic symptoms (Axelson et al., 2011; Zimmermann et al., 2009).

To assist with analyses, offspring emotional and behavioral diagnoses were grouped in the following categories: BD (BD-I or BD-II); depressive disorder (MDD and/or dysthymic disorder); disruptive behavior disorder (ODD or CD); anxiety disorder (panic disorder, agoraphobia, social phobia, specific phobia, OCD, GAD, PTSD, and/or

separation anxiety disorder); and ADHD (inattentive type, hyperactive type, or combined type). As an additional category, the present study examined “mood disorders” (i.e., depressive disorder and BD); these mood categories were combined given the wide age range among offspring in the sample and the fact that early manifestations of BD in high risk offspring often reflect depressive polarity and pre-pubertal mania is rare (Duffy, 2009).

*Family functioning.* Parents reported on family functioning using the Family Environment Scale (FES; Moos & Moos, 2009), relationship dimension subscales: Cohesion, Expressiveness, and Conflict. The Cohesion subscale assesses the degree of commitment, help, and support family members provide for one another. The Expressiveness subscale taps into the extent to which family members are encouraged to express their feelings directly. The Conflict subscale represents the amount of openly expressed anger and conflict among family members. Example items from each subscale include: “Family members really help and support one another” (Cohesion scale); “Family members often criticize one another” (Conflict scale); “We tell each other about our personal problems (Expressiveness Scale). Items are rated as true or false (scored as 0 or 1, respectively), and each subscale consists of nine items. FES subscale scores range from 0 to 9, with higher scores reflecting greater cohesion, conflict, and expressiveness. The FES subscales have been found to be valid and reliable measures of family functioning (Holahan & Moos, 1982; Moos & Moos, 2009; Sanford, Bingham, & Zucker, 1999). Coefficient alphas in this sample were .88 (Cohesion scale), .67 (Expressiveness scale), and .79 (Conflict scale).

### *Analyses*

Data were analyzed using *Mplus* v.6 (Muthén & Muthén, 1998-2010) and *SPSS* software. The sample contains multiple siblings from some families, violating assumptions of independence of observations. Therefore, multilevel modeling (with the `type=complex` feature in *Mplus*) was utilized for analyses to adjust standard errors to account for nested data. Multiple waves of data were present for a small number of participants (20%); when this occurred, the most recent wave of complete data was selected (e.g., both FES and CBCL data collected).

First, correlational analyses and *T* tests were run to examine the bivariate associations among the variables of interest. Second, moderation effects were assessed by conducting a series of multiple regression analyses to test: a) whether offspring sex and age moderates the association between the FES scales and CBCL Internalizing and Externalizing *T* scores, and b) whether a three-way interaction exists among these variables in predicting CBCL *T* scores. For each outcome variable, separate models were run for each FES subscale. After centering variables, two-way interaction terms were calculated and included in the models for offspring sex by each FES subscale score, offspring age by each FES subscale score, and offspring age by sex. Three-way interaction terms (offspring age by sex by each FES subscale score) were also calculated and included in the models. Probit regression analyses were then run for presence of DSM-IV diagnostic categories versus absence (i.e., not present and subclinical presentations) using the same predictor variables as above. Finally, all analyses were re-run, controlling for parental comorbid anxiety and substance use disorders.

## RESULTS

### *Participant characteristics*

The full sample contained 119 parents with BD and their 206 offspring; however offspring who were over age 18 and/or those families whom had missing FES data were excluded from analyses. This smaller subsample (75 parents and 117 offspring) was compared with the sample as a whole on demographic variables and outcome variables and found no significant differences between the two groups.

Table 3.1 shows the demographic and family environment data for the 75 parents and 117 offspring (mean age = 11.81,  $SD = 3.70$ ) included in the current analyses. Of these families, 39 included one offspring, 31 included two offspring, 4 included three offspring, and 1 included four offspring. The vast majority of offspring were Caucasian (91.5%) and came from families in one of the top two income classes on the Hollingshead scale (84.0%). Mean scores for the FES scales fell within the average range.

As shown in Table 3.2, mean  $T$  scores on the CBCL scales were also within the non-clinical range for externalizing and internalizing scales; 27.6% of offspring had Externalizing  $T$  scores in the clinical range, and 23.5% had Internalizing  $T$  scores in the clinical range. At the time of assessment, 56.5% of offspring met diagnostic criteria for at least one emotional or behavioral disorder (Table 3.2).

### *Preliminary analyses*

Bivariate analyses tested associations between each outcome variable and demographic variables: parent sex, parent age, SES (measured using the Hollingshead

scale, where lower numbers indicate higher income), intactness of family (i.e., parents married/co-habiting versus separated/divorced), and race (i.e, Caucasian versus non-Caucasian). Results indicated that Internalizing and Externalizing  $T$  scores were associated with parent age, parent sex, and SES. Specifically,  $T$  scores were: negatively correlated with parental age (Internalizing:  $r = -.27, p < .01$ ; Externalizing:  $r = -.27, p < .01$ ); higher in offspring of mothers with BD, as compared to offspring of fathers with BD (Internalizing:  $t = 2.12, p < .05$ ; Externalizing:  $t = 2.86, p < .01$ ); and correlated with SES such that scores were higher in lower SES homes (Internalizing:  $r = .33, p < .01$ ; Externalizing:  $r = .41, p < .01$ ). Offspring behavioral disorders were associated with family intactness, and SES. Specifically, offspring of divorced or separated parents were more likely to have a behavioral disorder diagnosis, as compared to offspring living in intact homes ( $\chi^2 = 7.44, df = 2, p < .05$ ); and offspring with behavioral disorder diagnoses came from lower SES homes ( $t = -3.96, p < .01$ ). Finally, offspring with ADHD were more likely to come from lower income homes ( $t = -2.93, p < .01$ ). Demographic variables that had significant associations with outcome variables were included as covariates in regression analyses. The pattern of findings did not change when controlling for these variables; therefore, presented below are results of analyses without the inclusion of demographic variables.

#### *Associations between FES and offspring variables*

Correlational analyses,  $T$  tests, and chi-square tests examined offspring sex and age differences on FES scores, CBCL scores, and current diagnoses. Offspring age was correlated with the Expressiveness scale such that higher expressiveness was associated

with younger age ( $r = -.27, p < .01$ ); offspring age was not significantly correlated with the other FES scales. No offspring sex differences emerged on any of the FES scales (Cohesion:  $t = -1.71, p = .09$ ; Expressiveness:  $t = .54, p = .59$ ; Conflict:  $t = .90, p = .37$ ). On the CBCL,  $T$  tests revealed no significant differences in scores between boys and girls for  $T$  scores on either scale (Externalizing  $T$  Scores:  $t = 1.58, p = .12$ ; Internalizing  $T$  Scores:  $t = .66, p = .51$ ). In addition, boys and girls did not differ on rates of any diagnostic category. Offspring with current behavioral disorders were significantly younger than offspring without behavior disorders ( $t = 2.32, p < .05$ ). There were no age differences for any other diagnostic category.

Next, the present study identified associations between FES scales and offspring psychopathology. Expressiveness was not correlated with any outcome measures. Higher Conflict was significantly correlated with higher  $T$  scores on the Internalizing ( $r = .27, p < .01$ ) and Externalizing ( $r = .28, p < .01$ ) scales. Lower Cohesion was also associated with higher Internalizing ( $r = -.23, p < .05$ ) and Externalizing ( $r = -.31, p < .01$ )  $T$  scores, and offspring with mood disorders had lower mean scores on the Cohesion scale (51.03 versus 41.24;  $t = 2.08, p < .05$ ). For other diagnostic categories, there were no differences in Conflict or Cohesion between offspring who met diagnostic criteria and those who did not.

#### *Moderation analyses for symptom measures*

A series of regression models were run in *MPlus* to test for moderation by offspring age and sex in the association of FES variables and CBCL Externalizing and Internalizing scales. For the models that included Expressiveness and Conflict, no

interaction terms were significant in predicting CBCL *T* scores. In the models that included Cohesion, offspring age emerged as a significant moderator such that the interaction term of age by Cohesion significantly predicted Internalizing *T* scores ( $\beta = .28, p < .01$ ). Specifically, in younger offspring, lower scores on Cohesion were associated with higher Internalizing *T* scores (age = 1 *SD* below the mean:  $p < .01$ ); whereas for older offspring, Cohesion and Internalizing *T* scores were not significantly associated (age = 1 *SD* above the mean:  $p = ns$ ). When analyses were re-run controlling for parental comorbid anxiety and substance use disorders, findings remained the same.

#### *Moderation analyses for diagnostic data*

Probit regression models were then run using presence or absence of clinical disorders as dichotomous outcome variables. For the models that included Cohesion and Expressiveness, no interaction terms were significant in predicting any of the outcome variables. For the models that included Conflict, the three-way interaction of age by sex by Conflict reached statistical significance for current mood disorders ( $\beta = -.534, p < .05$ ). Specifically, there was a significant association between Conflict and current mood disorder in younger males (age = 1 *SD* below the mean:  $p < .05$ ) but not in younger females, older males, or older females ( $p$ 's = *ns*). For the models that included Conflict, no other interaction terms reached statistical significance in predicting any of the other diagnostic categories. When analyses were re-run controlling for parental comorbid anxiety and substance use disorders, findings remained the same.

#### *Post-hoc analyses*

As indicated above, there were three categories for each diagnostic group (i.e., clinical, subclinical, and not present). There were also relatively high rates of subclinical presentations of offspring mood disorders in the sample (subclinical BD: 7.8%; subclinical depressive disorder: 5.2%). Due to concerns that failing to account for subclinical presentations of mood disorders might lead to loss of potentially important information, the present study re-ran probit regression analyses with the data dichotomized into clinical/subclinical versus not-present categories. This decision was made due to findings that subthreshold mood symptoms are quite impairing and are likely to convert to full mood disorders over time (Axelson et al., 2011; Duffy et al., 2014; Keenan et al., 2008). These analyses produced the same pattern of results such that the three-way interaction of age by sex by Conflict predicted current offspring mood disorders; however, the Beta value was reduced ( $\beta = -3.96, p < .05$ ).

## **DISCUSSION**

The current study examined the links between family functioning (cohesion, expressiveness, and conflict) and psychopathology in a large sample of offspring of parents with BD. Age and sex differences in these associations were also examined. Correlational analyses indicated, first, that higher family conflict and poorer cohesion were associated with higher internalizing and externalizing symptoms in offspring. Second, lower family cohesion was also associated with current offspring mood disorders. Moderation analyses indicated, first, that the link between family cohesion and internalizing symptoms was stronger for younger, compared to older, offspring. Second, family conflict and current mood disorder were associated in younger boys only. Results

remained the same after controlling for parental anxiety or substance use comorbidity, indicating that the relationship between family functioning and offspring psychopathology was not accounted for by other common parental comorbidities.

In the present study, there was a specific association between FES scales and offspring mood diagnoses, and there were not broader associations with other psychiatric diagnoses in youth. Early-onset mood disorder, particularly in younger youth, may be considered a severe clinical phenotype whereby individuals experience heightened irritability and mixed episodes (in the case of BD), high rates of comorbidity, and greater psychosocial impairment (Biederman et al., 2004; Weissman et al., 1999). This may be particularly true during mood episodes (T. R. Goldstein et al., 2009). Youth with mood diagnoses have also been found to be highly vulnerable to poor family functioning, as well as responsive to improvements in family functioning (Asarnow, Goldstein, Tompson, & Guthrie, 1993; D. J. Miklowitz, Biuckians, & Richards, 2006)). Alternatively, youth with mood disorders may provoke family-related stress (Chan, Doan, & Tompson, 2013) and/or have other risk factors contributing to family environment, such as temperamental vulnerabilities (West, Schenkel, & Pavuluri, 2008).

Findings of moderation effects suggest that the association between family functioning and offspring psychopathology are complex, and other factors may affect how offspring experience and/or how they are impacted by family environment. Results suggest that family cohesion is linked more strongly with internalizing symptoms in younger offspring. This makes sense given that younger children are more entwined in the family system and dependent on family members for social support (W. A. Collins &

Laursen, 2004). Results also suggest that conflict is associated with BD only in younger males, which is consistent with Gordis and colleagues' (2001) findings that family conflict is linked with internalizing psychopathology in boys, but not girls, aged 8-11. At least three potential explanations exist for these findings. First, young boys may be more adversely affected by family conflict than girls. Second, both boys and girls may be impacted by family conflict to the same degree, but there may be sex differences in the manifestation of symptoms, with boys more likely to outwardly express their distress and therefore be diagnosed with a mood disorder. Third, it may be the case that the presence of mood disorders in young boys is particularly pernicious to the family system. This might be related to evidence that negative affectivity in boys is characterized by more difficulty and intensity as compared to girls, and that girls display a better ability to inhibit inappropriate responses and behaviors than boys (Else-Quest, Hyde, Goldsmith, & Van Hulle, 2006). Future research using longitudinal designs and multiple indicators of child functioning are needed to clarify these relationships.

As implied above, any suggestions of a causal association between family functioning and offspring outcome based on the present data are speculative. It is equally possible that offspring psychopathology brings about conflict and poor cohesion in the family, as it is that negative family environment impacts offspring psychopathology. Schenkel and colleagues (2008) found that youth BD diagnosis was associated with family functioning, even after controlling for the presence of parental mood disorder. Conversely, others have suggested that parent factors may have a more prominent role in determining family functioning, as compared to child factors (Chang et al., 2001).

However, such conclusions cannot be definitively made without further, longitudinal research. It is most plausible that there is a reciprocal, mutually influential association between family factors and the emergence in psychopathology in all family members over time (Miklowitz, 2011).

Furthermore, FES scores in the sample were comparable to population means (Moos & Moos, 2009). This is in contrast to previous studies that found families with a BD parent report less cohesion and expressiveness and more conflict on the FES, as compared to families without a BD parent and to population means (Barron et al., 2014; Chang et al., 2001; Romero et al., 2005). It is possible that the present results differed from these prior studies because parents in the present study were currently receiving treatment for their BD. Although family functioning has been shown to be impaired even when the BD patient is not acutely symptomatic (Weinstock et al., 2006), there is also evidence to suggest that family functioning may fluctuate as a result of the BD patients' current mood state (Uebelacker et al., 2006). Therefore, it is possible that the difference in FES scores in the present sample is due to fluctuations in family functioning as the BD parent is receiving treatment.

Additionally, in the present sample, family expressiveness was not correlated with any measure of offspring psychopathology. Ferreira and colleagues (2013) also failed to find associations between the expressiveness scale and psychopathology in offspring of parents with BD. Several possibilities could account for these null findings in the literature. The expressiveness scale measures the extent to which family members are encouraged to express their feelings, but does not distinguish between expression of

positive and negative emotion. One might expect that negative emotional expressiveness exert a harmful effect, whereas positive emotional expressiveness would be protective (see Bariola, Gullone, & Hughes, 2011). Therefore, the lack of association with offspring psychopathology may have arisen because the scale tapped both types of emotional valence.

Several study limitations warrant mentioning. First, the present study was limited by the measures of family functioning and child psychology. For example, parents completed the FES scale, and offspring did not report on their perceptions of family functioning. Some of the associations among measures may also be a consequence of having parents report on multiple measures. It may be the case that variables particular to the parent or his or her illness (e.g., BD severity) caused them to respond to both FES and CBCL scales in a certain way. However, Romero and colleagues (2005) found no differences in FES scores when the measure was completed by the parent with BD versus the non-BD parent; and research by Weinstock and colleagues (2013) indicates that parents with BD might be better reporters of family functioning than their child and adolescent offspring. Evidence also suggests that parents with a history of mood disorders may be accurate reporters of their children's symptoms, particularly for younger children (K. J. Lewis et al., 2012). Despite these findings, future research should include multiple measures (including youth-report and observational) of the constructs of interest.

As a second limitation, the present study did not assess other offspring, parent, or family characteristics, which may interact with family environment to affect offspring psychopathology. For example, Ellenbogen and Hodgins (2004) showed that high levels

of neuroticism in BD parents influenced parenting, which subsequently impacted child functioning. Du Rocher Schudlich and colleagues (2008) found that deficits in family problem solving and communication mediated the association between parental mood disorder and family conflict, which in turn predicted child BD. Third, a significant limitation of the study is the lack of a comparison group. The present study cannot determine whether findings are specific to offspring of parents with BD or whether such findings also generalize to families with other types of psychopathology and/or healthy controls. Future studies are needed that test associations in families with other types of psychopathology as well as healthy controls.

In spite of these limitations, the present findings are highly relevant for informing prevention and intervention efforts. Identifying subgroups of offspring who are at greatest risk for maladjustment is necessary to develop targeted prevention programs. Results suggest that preadolescent offspring of parents with BD, particularly boys and those with elevated scores on the CBCL, are more strongly impacted by high family conflict and low family cohesion, and therefore may be at greatest need for interventions aimed at enhancing family functioning. Fortunately, preventative interventions that involve family members and target family processes are currently in development, and these programs show promise for youth at risk for BD. For example, Nadkarni and Fristad (2010) found that participation in a multi-family psychoeducation group treatment was associated with a four-fold reduction in risk for conversion from depression to BD. Similarly, Miklowitz and colleagues (2013) found that Family-Focused Therapy was associated with better outcomes for symptomatic youth who had a first degree relative with BD, and effects

were more pronounced for families with high versus low expressed emotion. These results, combined with the present findings, underscore the profound importance of focusing on family processes in prevention efforts for youth BD, particularly for preadolescents. Advancing the knowledge of psychosocial risk factors has the potential to curtail the adverse developmental trajectories of offspring at risk for BD and other forms of psychopathology as well as to decrease the cost and burden to society of such disorders.

## TABLES AND FIGURES

Table 3.1. Participant Characteristics (Demographic and Family Environment)

Variable	Mean $\pm$ SD (Range) or Percentage
Offspring age (in years)	11.81 $\pm$ 3.70 (5-18)
Offspring sex	
Female	46.6%
Male	53.4%
Parent age (in years)	43.62 $\pm$ 6.77 (26-59)
Sex of parent with bipolar disorder	
Female	67.8%
Male	32.2%
Family social class (Hollingshead, 1= highest)	1.82 $\pm$ 0.86 (1-5)
Intactness of family	
Parents married or co-habiting	61.9%
Parents separated or divorced	38.1%
Family Environment (measured using FES)	
Cohesion	49.14 $\pm$ 17.16 (4-65)
Expressiveness	48.67 $\pm$ 13.41 (21-71)
Conflict	52.65 $\pm$ 13.21 (33-80)

FES = Family Environment Scale

Table 3.2. Rates of Current Offspring Psychopathology

	% or Mean $\pm$ SD (Range)
Bipolar Disorder (I or II)	8.7%
Depressive Disorder (MDD or DD)	9.5%
Anxiety Disorder*	35.8%
Disruptive Behavior Disorder (ODD or CD)	28.7%
ADHD (Inattentive, Hyperactive, or Combined Type)	29.5%
CBCL Externalizing T-Score	55.16 $\pm$ 13.80 (32-87)
CBCL Internalizing T-Score	55.17 $\pm$ 12.98 (31-83)

\* Includes panic disorder, agoraphobia, social phobia, specific phobia, obsessive compulsive disorder, generalized anxiety disorder, posttraumatic stress disorder, and/or separation anxiety disorder. MDD = major depressive disorder, DD = dysthymic disorder, ODD = oppositional defiant disorder, CD = conduct disorder, ADHD = attention deficit/hyperactivity disorder, CBCL = Child Behavior Checklist.

## **CHAPTER FOUR**

### **STUDY 3**

#### **A Latent Class Analysis of Parental Bipolar Disorder: Associations with Offspring Psychopathology**

##### **INTRODUCTION**

Bipolar disorder (BD) is a chronic illness characterized by high rates of relapse and recurrence (Harrow et al., 1990), and patients with BD experience psychosocial impairment that often persists between episodes and impacts essentially all areas of functioning (Coryell et al., 1993; Yatham et al., 2004). However, BD is also a complex and heterogeneous disorder, with profound variations in the severity, length, and number of manic/hypomanic and depressive episodes and patterns of comorbidity (Akiskal et al., 2000). Further, variations in the course of BD can lead to more or less favorable patient outcomes, psychosocial impairment, and stress (M. S. Bauer, Kirk, Gavin, & Williford, 2001), including interpersonal and family stress (Dore & Romans, 2001). Given the vast variations in BD illness course and characteristics, the current diagnostic system does not provide for the identification of which families may be in greatest need of intervention and support (Ghaemi et al., 2008). Uncovering this information would assist in the prevention of long-term maladaptive outcomes for patients with BD and their families. Additionally, this information would inform targeted intervention for offspring of individuals with BD, as parental illness course may have implications for both environmental and genetic offspring risk.

### *Characteristics of BD*

Several BD illness characteristics are associated with greater illness severity and poorer functional outcome in patients with BD (Treuer & Tohen, 2010); these include the course variants included in the current classification systems (e.g., BD type, rapid cycling, psychosis), age of illness onset, patterns of psychiatric comorbidity (particularly anxiety and substance use disorders), and characteristics associated with episode polarity (polarity at first episode, pole of the majority of episodes).

*Bipolar Type.* The two major types of BD, Bipolar I Disorder (BD-I) and Bipolar-II Disorder (BD-II) are conceptualized as qualitatively distinct subtypes that exist along a continuum (Benazzi, 2007). BD-I and BD-II are differentiated only by the severity of manic episodes (i.e., the presence of a manic versus hypomanic episode, respectively); however, research suggest that the BD types also have different profiles in terms of chronicity, comorbidity, and clinical features. For example, although BD-I may be a more severe form of disorder (e.g., the presence of psychosis, more acute impairment), BD-II is generally shown to be more chronic, with higher rates of depression, more episode switching, and higher rates of anxiety disorder comorbidity (Judd, Akiskal, Schettler, Coryell, Endicott, et al., 2003; Judd, Akiskal, Schettler, Coryell, Maser, et al., 2003; Kupka, Luckenbaugh, Post, Leverich, & Nolen, 2003; Vieta, Gasto, Otero, Nieto, & Vallejo, 1997).

*Rapid Cycling.* Another major BD course specifier in the current classification system is the presence of rapid cycling, defined as four or more mood episodes per year. Rapid cycling is reported to occur in 13–56% of BD patients (see Kilzieh & Akiskal,

1999) and is associated with more depressive morbidity, greater illness severity, higher risk for suicide, and poorer response to treatment (Coryell et al., 2003; Kupka et al., 2003; Nierenberg et al., 2010; Tondo, Hennen, & Baldessarini, 2003). Given such distinctions, some suggest that rapid cycling may be a discrete subtype of BD (M. S. Bauer et al., 1994). However, others suggest that rapid cycling is a transient manifestation of BD rather than a stable marker (Kilzieh & Akiskal, 1999); and cycling may be on a continuum (Schneck et al., 2008), and therefore may not be considered a qualitative indicator.

*Psychosis.* Approximately half of all BD patients will experience psychotic features at some point (Azorin, Akiskal, & Hantouche, 2006). Current classification systems indicate that the presence of psychotic symptoms is a marker of more severe manic episodes. Indeed, research has linked psychosis to BD episode severity, higher hospitalization rates, and poorer treatment response (Ozyildirim, Cakir, & Yazici, 2010; van Rossum et al., 2008). However, other research suggests that psychosis in mania may be due only in part to the severity of the episode, with other factors also influencing the presence of psychosis (Azorin et al., 2007); and those with and without a history of psychosis do not differ significantly in morbidity and psychosocial functioning (Keck et al., 2003). Further, patients who experience psychosis are more likely to have family members with a psychotic form of BD, leading investigators to propose that BD with psychotic features may delineate a BD subtype (Potash et al., 2001).

*Age of illness onset.* Research has consistently indicated that age of BD onset is inversely associated with poorer illness course and outcome, including greater severity

and chronicity, higher rates of comorbidity, and greater likelihood of suicide attempts (Perlis et al., 2004; Suppes et al., 2001; Yatham, Kauer-Sant'Anna, Bond, Lam, & Torres, 2009), and this is true irrespective of polarity of episode at illness onset (Ortiz et al., 2011). Patients under age 21 with mood disorders (BD-II and major depressive disorder) have been shown to have high recurrence of episodes, compared to patients 21 and older, and this does not appear to be related to a longer duration of illness (Benazzi, 2009). Another large study of adult patients with BD showed that, compared to those who had a mood onset after age 18, those who had a childhood onset (before age 13) experienced fewer days out of episode and greater impairment in functioning and quality of life (Perlis et al., 2009). These differences in clinical expression and outcome between earlier and later onset BD, along with data indicating different patterns of familial risk between the groups (Somanath, Jain, & Reddy, 2002), has led researchers to suggest that age of onset could be a valid alternative to polarity for classifying mood disorders (Benazzi, 2009; Schurhoff et al., 2000).

*Comorbidity.* Patients with BD frequently meet criteria for other psychiatric disorders, with the most common being anxiety and substance use disorders (McElroy et al., 2001). Epidemiological studies estimate that 60-75% of patients with BD have had at least one lifetime comorbid anxiety disorder, and the lifetime comorbidity with any substance use disorder is 42-60% (Merikangas et al., 2007; Regier et al., 1990; Sala et al., 2012). Both comorbid disorders have been shown to be more common among patients with BD than patients with major depressive disorder (Schaffer et al., 2010), and one study showed that comorbid substance abuse or dependence was more common in BD

than any other Axis I disorder (Regier et al., 1990). Anxiety disorder comorbidity has shown associations with BD severity (e.g., suicidality, mental health service use, and hospitalization), chronicity, negative treatment outcomes, and impaired psychosocial functioning (Gaudiano & Miller, 2005; B. I. Goldstein & Levitt, 2008; Otto et al., 2006; Sala et al., 2012; N. M. Simon et al., 2004). Comorbid substance use disorders in patients with BD have similarly been linked to impairments in psychosocial functioning, higher rates of psychiatric hospitalizations, and poorer treatment response (Cassidy, Ahearn, & Carroll, 2001; Goldberg, Garno, Leon, Kocsis, & Portera, 1999; Mazza et al., 2009). Substance use may also hasten BD episode recurrence and maintain high levels of inter-episode symptoms, and may be associated with impulsivity and suicidality (see Salloum & Thase, 2000). Although anxiety and substance use disorders tend to overlap with one another in patients with BD, research suggests that the disorders have different patterns of associations with BD course and may uniquely contribute to BD severity and outcome (M. S. Bauer et al., 2005; B. I. Goldstein & Levitt, 2008; N. M. Simon et al., 2004; Tsai et al., 2012).

*Polarity:* Evidence suggests that episodes of depression and mania/hypomania may differ in terms of their impairment such that depression accounts for most of the morbidity and mortality due to BD (Mitchell & Malhi, 2004; Rosa et al., 2010). In addition, it takes longer for patients to recover from depression compared to mania/hypomania (Solomon et al., 2010). Given these findings, it is not surprising that the number of past depressive episodes appears to be a stronger determinant of functioning and wellbeing than the number of past manic episodes (MacQueen et al.,

2000). There is also evidence that the course of BD is predominantly characterized by episodes of the same polarity, and there may be important clinical differences between patients with predominantly manic episodes and those with predominantly depressive episodes (Colom, Vieta, Daban, Pacchiarotti, & Sanchez-Moreno, 2006; Rosa et al., 2008). For example, patients with predominantly depressive episodes tend to have less severe manic episodes, a more chronic course of illness, and higher number of suicide attempts than patients with predominantly manic episodes (Colom et al., 2006; Judd, Akiskal, Schettler, Coryell, Endicott, et al., 2003; Judd, Akiskal, Schettler, Coryell, Maser, et al., 2003; Rosa et al., 2008). Patients with predominant mania/hypomania, on the other hand, have higher rates of psychosis (Ozyildirim et al., 2010).

The course of BD may also be associated with the polarity of the initial index episode. For example, Daban and colleagues (2006) showed that patients who had an initial depressive episode had a more chronic illness course (e.g., a higher number of total episodes and a longer illness duration), were more likely to have attempted suicide, had a later illness onset, had fewer hospitalizations, and were less likely to develop psychotic symptoms, compared to patients with manic episode onset. Other researchers have found that polarity at onset is a familial feature of BD, such that relatives have the same episode type at onset (Kassem et al., 2006), suggesting that this clinical feature may delineate different BD subtypes.

#### *Associations with Offspring Outcomes*

Although abundant literature exists identifying illness characteristics associated with poorer outcomes in patients with BD, few published studies to date have examined

specifically the impact of these characteristics on offspring. The vast majority of studies have instead compared rates of psychopathology in offspring of parents with versus without BD, without examining parental illness course and characteristics as moderators of risk. Such research overwhelmingly shows that offspring of parents with BD are at increased risk for developing psychiatric disorders themselves, including depressive, conduct, oppositional defiant, and anxiety disorders than children of psychiatrically healthy parents (DelBello & Geller, 2001; Lapalme et al., 1997).

However, given the heterogeneity of BD, offspring living with parents with BD may have vastly different experiences, including variable levels of stress and unpredictability. Additionally, offspring might be at higher genetic risk of certain types of psychopathology depending on parental BD characteristics. An early report by Grigoriou-Serbanescu and colleague (1989) found that the presence and severity of psychopathology (i.e., any DSM-III diagnosis) in 72 offspring of parents with BD was associated with parent's BD illness severity, number of manic and mixed episodes, and age of BD onset. More recently, in a sample of 50 offspring of 36 BD parents, Garcia-Amador and colleagues (2013) found that offspring of parents with a lifetime history of psychotic symptoms or BD-II were more likely to have been diagnosed with an Axis-I disorder. Two additional studies point to the role of age of parental BD onset in increasing offspring risk for mood disorder specifically (Chang et al., 2000; Oquendo et al., 2013). However, Goldstein and colleagues (2010) failed to find any relationship between parental BD illness characteristics (e.g., BD type, rapid cycling, age of onset, suicidality, psychosis, comorbidity) and the presence of BD, specifically, in offspring.

These discrepancies and the fact that many of the studies were limited by small sample sizes, and thus low power to detect associations, warrant replication in a larger sample that examines a range of offspring psychopathology. In addition, rather than examining correlations between various individual illness characteristics and offspring psychopathology, it may be important to instead evaluate relationships with empirically derived patterns of parental BD course and clinical characteristics.

### *Current Study*

Taken together, the above research suggests that a number of BD illness characteristics—some within and some outside of the current nosology—may predict severity and outcome. Data also indicate that many of these course characteristics co-occur, and it is therefore unclear which indicators may be driving associations with patient outcomes. Finally, some studies suggest that there may be relationships between BD illness characteristics and offspring psychopathology, although this literature is sparse. The current study used latent class analysis (LCA) to identify more accurate and parsimonious phenotypic subtypes of BD in a sample of parents diagnosed with BD. LCA is a statistical modeling technique used to identify substantively meaningful subgroups in a population based on similarities in responses to measured variables (L. M. Collins & Lanza, 2010). Next, the present study examined associations between parental latent class membership and rates of emotional and behavioral disorders in offspring.

## **METHODS**

The current investigation combined data from two studies examining patients with BD and their offspring (Henin et al., 2005; Henin et al., submitted). Parents were

recruited through advertisements posted in waiting rooms of Massachusetts General Hospital psychiatry units, letters to clinicians, and advertisements to the general public. Potential participants and their offspring were evaluated using a structured diagnostic interview, and parents with a positive BD diagnosis were included. All study procedures were approved by the Massachusetts General Hospital Subcommittee for Human Studies. Parents provided informed consent prior to participation. Offspring provided assent for study participation. Participants were compensated for their involvement.

Parent and offspring diagnostic interviews were conducted by master- and bachelor-level diagnosticians who were extensively trained and supervised in interview procedures and diagnostic criteria. Diagnosticians discussed each interview with experienced, board-certified child and adult psychiatrists and licensed psychologists for review and to resolve diagnostic uncertainties. Kappa coefficients of agreement were computed by having experienced, board certified child and adult psychiatrists and licensed clinical psychologists diagnose subjects from audio taped interviews made by the assessment staff. Based on 500 assessments from interviews of children and adults, the median kappa coefficient was 0.98. Kappa coefficients for individual diagnoses included: attention deficit/hyperactivity disorder (ADHD; 0.88), conduct disorder (CD; 1.0), oppositional defiant disorder (ODD; 0.90), depression (1.0), mania (0.95), separation anxiety (1.0), agoraphobia (1.0), panic disorder (0.95), obsessive compulsive disorder (OCD; 1.0), generalized anxiety disorder (GAD; 0.95), specific phobia (0.95), posttraumatic stress disorder (PTSD; 1.0), social phobia (1.0), and substance use disorder (1.0). These measures indicated excellent reliability between ratings made by the non-

clinician raters and experienced clinicians. The reliability of the diagnostic review process was estimated by computing kappa coefficients of agreement between clinician reviewers. For these clinical diagnoses, the median reliability between individual clinicians and the review committee assigned diagnoses was 0.87. Kappa coefficients for individual diagnoses included: ADHD (1.0), CD (1.0), ODD (0.90), depression (1.0), mania (0.78), separation anxiety (0.89), agoraphobia (0.80), panic disorder (0.77), OCD (0.73), GAD (0.90), specific phobia (0.85), PTSD (0.8), social phobia (0.90), and substance use disorder (1.0).

### *Measures*

*Parent psychopathology.* Parents with BD were interviewed about their own current and lifetime symptoms using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID; First & Gibbon, 2004). Psychiatric information about the unaffected (i.e., non-BD) parent was not collected. Detailed information about BD course was gathered through these interviews, including age of onset, episode types, number of episodes, and presence of psychosis. Age of onset was defined by the age at onset of the first major syndromal mood (mania or major depression) episode (as suggested by Benazzi, 2009). Rapid cycling was defined as an average of 4 or more mood episodes per year and was calculated by dividing the total number of episodes (of any polarity) by the number of years since illness onset. This enabled determination of those patients for whom rapid cycling may be a more stable characteristic, rather than just a transient phenomenon (e.g., only occurring in one year of illness; see discussion in M. Bauer, Beaulieu, Dunner, Lafer, & Kupka, 2008)

Details about lifetime comorbid Axis I diagnoses were also gathered through these interviews. The present study was particularly interested in examining comorbid anxiety and substance dependence, given that these comorbid disorders have been most consistently associated with poorer quality of life and greater role impairment in patients with BD (B. I. Goldstein & Levitt, 2008; Mazza et al., 2009; Otto et al., 2006). Comorbid anxiety disorder was indicated based on a history of one or more of the following diagnoses: panic disorder, agoraphobia, social phobia, specific phobia, obsessive compulsive disorder, generalized anxiety disorder, posttraumatic stress disorder. Comorbid substance dependence included lifetime history of a diagnosis of substance dependence and/or alcohol dependence.

*Offspring psychopathology.* Offspring lifetime DSM-IV emotional and behavioral diagnoses were assessed via interviews with parents and offspring over the age of 12 (when available) using the Schedule for Affective Disorders and Schizophrenia for School-Aged Children-Epidemiologic Version (KSADS; Orvaschel, 1995). The KSADS has demonstrated good validity and reliability (for a review see Ambrosini, 2000). In cases where offspring were also interviewed directly about their symptoms, a symptom was considered present if endorsed by either the offspring or the parent. To assist with analyses, offspring emotional and behavioral diagnoses were grouped in the following categories: BD (BD-I or BD-II); depressive disorder (MDD and/or dysthymic disorder); disruptive behavior disorder (ODD or CD); anxiety disorder (panic disorder, agoraphobia, social phobia, specific phobia, OCD, GAD, PTSD, and/or separation anxiety disorder); and ADHD (inattentive type, hyperactive type, or combined type). As

an additional category, “mood disorders” (i.e., depressive disorder and BD) was examined; these mood categories were combined given the wide age range among offspring in the sample and the fact that early manifestations of BD in high risk offspring typically reflect depressive polarity and pre-pubertal mania is rare (Duffy, 2009).

### *Analyses*

Data were analyzed using *Mplus v.6* (Muthén & Muthén, 1998-2010) and *SPSS*. The sample contains multiple siblings from some families, violating assumptions of independence of observations. Therefore, multilevel modeling (with the `type=complex` feature in *Mplus*) was utilized for analyses to adjust standard errors to account for nested data. Multiple waves of data were present for some participants (20%); when this occurred, the most recent wave of complete data was selected for inclusion in analyses.

Latent Class Analysis (LCA) empirically classified parents into groups according to BD course presentation. Based on the literature, eight features were extracted that capture salient characteristics of illness course: BD type (BD-I or BD-II), age of illness onset, polarity at illness onset, polarity of primary episode, rapid cycling, history of psychosis, history of anxiety disorders, and history of substance dependence. All were dichotomous variables, except for age of onset which was measured as a continuous variable. Models with 2-, 3-, and 4-class solutions were compared to determine the optimal substantive and statistical fit. Statistical model comparisons were made using Akaike’s Information Criterion (AIC; Akaike, 1987) and the Bayesian Information Criterion (BIC; Schwartz, 1987), with lower values indicating the optimal number of latent classes that should be extracted from the variables. Entropy, a measure of class

separation, was also examined, with values closer to 1 indicating better classification. Finally, the Lo-Mendell-Rubin Adjusted Likelihood Ratio Test (LRT; Nylund, Asparouhov, & Muthen, 2007) was examined. The LRT assesses the statistical significance of the improvement in the model when an additional class is extracted. A parent was assigned to the class for which he or she had the highest probability of belonging (i.e., most likely class membership).

To examine associations between parental class membership and offspring psychopathology, each offspring diagnostic category was regressed onto parents' assigned most likely class membership. Prior to running regression models, demographic factors (e.g., offspring and parent age, offspring and parent sex, socioeconomic status, parent marital status) were examined to identify class differences; variables showing significant differences were entered as covariates in models. Next, dummy variables were created to form dichotomous predictors corresponding to the presence/absence of each parental latent class, and these variables were included as predictors of offspring diagnoses. Separate regression models were run for male and female offspring to examine sex differences.

## **RESULTS**

### *Participant characteristics*

The full sample contained 119 parents with BD and 206 offspring; however those offspring who had missing parental diagnostic data were excluded ( $n = 10$  parents,  $n = 18$  offspring). Table 4.1 shows the demographic data for the 109 parents and 188 offspring included in the current analyses. Of these families, 43 included one offspring, 52 included

two offspring, 12 included three offspring, and 1 included four offspring. Offspring age ranged from 4–33 years, however the majority (84.0%) was 18 years of age or under ( $M = 13.46$ ,  $SD = 5.90$ ). The vast majority of the offspring sample was Caucasian (93.1%) and came from families in one of the top two income classes on the Hollingshead scale (84.0%).

#### *LCA of Parental Diagnostic Data*

Eight indicators were included in the LCA: BD type (BD-I or BD-II), age of illness onset, polarity at illness onset, primary episode polarity, rapid cycling, history of psychosis, history of anxiety disorders, and history of substance dependence. Table 4.2 lists the LCA model fit indices for two-, three-, and four-class solutions. Entropy was high ( $> .80$ ) for all solutions. The BIC and AIC favored different models, with the BIC suggesting that a two-class solution was optimal and the AIC suggesting that a three-class solution was optimal. However, the LRT indicated that a model with three latent classes significantly improved the model fit ( $p < .05$ ) over a two-class solution. A three-class model was therefore selected.

The three-class model was also acceptable on theoretical grounds. In examining the eight course indicators, various features differentiated classes, with some notable patterns (Table 4.3). First, Class 1 (50%) and Class 2 (28%) parents had earlier illness onset, whereas Class 3 (21%) parents had later onset. Second, parents in Class 1 had a 0.90 probability of having BD-I, whereas Class 2 consisted entirely of parents with BD-II. Class 1 was therefore labeled as the *Earlier-Onset Bipolar-I* class (EO-I) and Class 2 as the *Earlier-Onset Bipolar-II* class (EO-II). Class 3 was labeled the *Later-Onset*

BD class (LO). For parents assigned to each class, the average likelihood for being in that class were as follows: EO-I = .89; EO-II = .98; LO = .91.

In addition to class differences in age of onset ( $F = 111.95, p < .01$ ) and BD type ( $\chi^2 = 62.37, df = 2, p < .001$ ), classes differed on anxiety disorder comorbidity ( $\chi^2 = 12.40, df = 2, p < .01$ ), substance dependence ( $\chi^2 = 6.01, df = 2, p = .05$ ), rates of psychosis ( $\chi^2 = 37.23, df = 2, p < .001$ ), and primary episode type ( $\chi^2 = 5.97, df = 2, p = .05$ ). Specifically, post hoc tests showed that EO-I and EO-II did not differ from one another in terms of anxiety disorder comorbidity, but each had a higher probability rate than LO. EO-I had a higher probability than LO of substance dependence; however, EO-I and EO-II did not differ significantly on this variable, nor did EO-II and LO. EO-I also had a higher likelihood of having their primary episode type be depressed than EO-II but not LO, and EO-I and LO did not differ. For psychosis, EO-I had significantly higher rates than the other two classes.

#### *Prediction of Offspring Psychopathology by Parental Latent Class*

Prior to running regression models to predict offspring psychopathology, demographic factors were examined to determine class differences. EO-II parents were significantly more likely to be married/co-habiting versus separated/divorced than EO-I and LO parents ( $\chi^2 = 17.01, df = 2, p < .01$ ), who had a fairly equal likelihood of being married/co-habiting versus separated/divorced (Table 4.1). Offspring of EO-II parents were also significantly younger than offspring in the other two groups ( $F = 7.41, p < .01$ ), and offspring of EO-I parents had significantly lower socioeconomic status than offspring

of parents in the other classes ( $F = 5.96, p < .01$ ). Therefore, subsequent analyses controlled for offspring age, socioeconomic status, and parent marital status.

Table 4.4 shows the lifetime rates of psychopathology in the total offspring sample, as well as within parental latent class groups. To examine class differences, first, probit regression analyses in *MPlus* predicted offspring lifetime psychopathology by parents' assigned most likely class membership. Class differences emerged for offspring anxiety disorders only, such that offspring of LO parents had significantly lower rates than offspring of EO-I parents (34.9% versus 56.3%,  $p < .05$ ). Additionally, the difference in rates of anxiety disorders between offspring of LO versus EO-II parents approached statistical significance, with offspring of LO parents having lower rates (34.9% versus 55.1%,  $p < .07$ ).

Next, these analyses were repeated, examining male and female offspring separately. For analyses that included female offspring only (Table 4.5), the same patterns emerged as the analyses conducted using the full sample. Specifically, daughters of LO parents had significantly lower rates of anxiety disorders compared to daughters of EO-I (15.8% versus 57.4%,  $p < .01$ ) and EO-II (15.8% versus 75.0%  $p < .01$ ) parents. However, no class differences in offspring disorders were found in analyses that included male offspring only.

## **DISCUSSION**

Using LCA, patients with BD were classified empirically based on phenotypic indicators of BD course, and substantive and statistical fit indicators favored three classes, which were labeled *Earlier-Onset Bipolar-I* (EO-I), *Earlier-Onset Bipolar-II*

(EO-II), and *Later-Onset BD* (LO) based on some of the notable differences between classes. The present study next examined associations between patients' most likely class membership and lifetime psychopathology in their offspring. Differences in offspring anxiety disorders emerged between the classes, but only for female offspring.

The International Society for Bipolar Disorders Diagnostic Guidelines Task Force has emphasized the need for more attention to diagnostic validators, including course and comorbidities, in determining BD nosology (Ghaemi et al., 2008). The present findings support this process. Eight indicators were included in the LCA: BD type (BD-I or BD-II), age of illness onset, polarity at illness onset, primary episode polarity, rapid cycling, history of psychosis, history of anxiety disorders, and history of substance dependence. Some notable patterns differentiated classes. First, two classes (EO-I and EO-II) had an average illness onset during mid-adolescence, whereas the LO class had an average illness onset around age 30; and of the earlier onset classes, EO-I consisted primarily of individuals with BD-I, whereas individuals in EO-II had BD-II. These findings, in part, support the validity of the present BD nosology, classifying based on the presence of hypomania versus mania; however results also implicate other factors, such as age of onset, as an important classification variable. Other researchers have also pointed to age of onset as a valid alternative to polarity for classifying mood disorders (Benazzi, 2009; Schurhoff et al., 2000) based on a number of relevant findings. For example, correlation for age of onset has been demonstrated between BD sibling pairs (Leboyer et al., 1998), and age of onset is significantly heritable in families and may be associated with particular genetic markers (Faraone, Glatt, Su, & Tsuang, 2004).

Second, the class consisting of earlier onset BD-I individuals had a significantly higher probability of lifetime psychosis than the other two classes. This is not surprising given that: 1) by definition, BD-II is not characterized by psychosis, and 2) past research has found higher rates of psychosis in individuals with earlier- as compared to later-onset BD-I (Ortiz et al., 2011; Schurhoff et al., 2000; Suominen et al., 2007). Third, in the present study, individuals with earlier-onset BD-I had a higher probability than the earlier-onset BD-II class of having primarily depressive (as opposed to manic/hypomanic) episodes. This is consistent with past research showing that, although BD-II patients experience more mood episodes overall, the proportion of depressive-to-manic episodes experienced by BD-I patients is similar to the proportion of depressive-to-hypomanic episodes experienced by BD-II patients (Vieta et al., 1997). Conversely, Judd and colleagues (Judd, Akiskal, Schettler, Coryell, Maser, et al., 2003) observed that, when followed for 10 years, BD-II patients had more major and minor depressive episodes than BD-I patients; although BD-I patients presented with more mixed episodes. The present study did not assess specifically for the presence of mixed episodes, and it is therefore possible that some of the episodes labeled as depressive in the BD-I individuals may actually have been mixed in nature. This study also did not account for time spent in episode. Such information may have provided a better picture of illness burden, as patients with BD-II have been shown to have longer duration depressive episodes than patients with BD-I, and significantly more BD-I patients report a return to baseline mood between affective episodes (Judd et al., 2003a). It is also important to note that, in the present study, differences were apparent only between the earlier-onset groups.

According to post hoc analyses (not shown) comparing individuals with BD-I versus BD-II on the probability of having primarily depressive episodes (without accounting for age of onset), the two groups did not differ significantly ( $\chi^2 = 2.85$ ,  $df = 1$ ,  $p = .09$ ); this is consistent with findings from Kupka and colleagues (2007) who reported that depression/mania ratios were of a similar magnitude in the BD-I and BD-II outpatients in their sample.

Fourth, there were class differences in terms of comorbidity patterns. The individuals with earlier-onset BD-I had had the highest probability of lifetime substance dependence. Past research also suggests that earlier onset is associated with greater rates of comorbid substance use disorders (Perlis et al., 2004). However the literature has been inconsistent regarding substance use comorbidity and BD type, with some studies showing that substance use disorder risk is higher for BD-I than BD-II (Merikangas et al., 2007), other studies showing that individuals with BD-II are more likely to have comorbid substance use disorders (Mazza et al., 2009), and yet other studies showing no differences in substance use disorders between BD types (Judd, Akiskal, Schettler, Coryell, Maser, et al., 2003). It is possible that such inconsistencies are due to lack of attention to differences in age of onset in these studies; in the present study, although BD-I individuals had the highest risk of comorbid substance dependence, their risk was only significantly different from the later-onset class and was not different from the earlier-onset BD-II class.

Both earlier-onset classes had a significantly greater probability of anxiety disorder comorbidity than the later-onset class. Overall almost three-quarters of the

sample had a lifetime anxiety disorder diagnosis; however, it appears that an overwhelming majority of these cases were in the earlier-onset classes, as they each had approximately twice the probability of having an anxiety comorbidity than the later-onset class. This finding is highly consistent with past studies showing an inverse association between anxiety comorbidity and age of illness onset (Keller, 2006; Perlis et al., 2004; N. M. Simon et al., 2004). Both anxiety comorbidity and age of illness onset have been implicated as being markers of greater illness severity in BD (McIntyre et al., 2006) (Suominen et al., 2007) and, as suggested by Simon and colleagues (2004) may represent an inherent component of a more severe bipolar subtype. The present data suggest that anxiety comorbidity may be associated with two such severe subtypes, one consisting of BD-I individuals and one consisting of BD-II individuals.

Consistent with prior studies of children at risk for BD (Chang et al., 2000; DelBello & Geller, 2001), the present sample had high rates of psychopathology. Comparing parental classes on rates of lifetime offspring psychopathology, there were notable class differences in offspring anxiety, but no class differences for other disorders. Offspring of parents in the two earlier-onset classes had significantly higher rates of anxiety disorders compared to offspring of parents in the later-onset class. This might be explained by the fact that parents in former groups were themselves more likely to have a lifetime anxiety disorder diagnosis, and therefore the disorder in offspring may be due to higher familial risk of anxiety. However, past studies have failed to find significant evidence that anxiety in offspring of parents with BD could be explained by an increased familial risk of anxiety (Duffy et al., 2013; Hirshfeld-Becker et al., 2006). Duffy and

colleagues (2013) speculate that the presence of anxiety disorders in offspring of parents with BD reflects the BD diathesis, rather than a separate diathesis for anxiety disorders. Therefore, it is possible that had the current sample been followed over time, increased rates of BD might have emerged in the offspring of the earlier-onset classes. However, previous studies show that only a subset of individuals with BD have lifetime comorbid anxiety (Sala et al., 2012), suggesting that the presence of preceding anxiety may be associated with a specific BD subtype. Consistent with this idea, in the present full sample, parental and offspring anxiety disorders were not significantly associated (fisher's exact test  $p = .16$ ; data not shown). Additionally, family studies suggest a specific pattern of heritability for BD with comorbid anxiety (MacKinnon et al., 2002; Wozniak et al., 2010), and genetic linkage studies suggest that anxiety comorbidity marks a genetically distinct subtype of bipolar disorder (MacKinnon, McMahon, Simpson, McInnis, & DePaulo, 1997; MacKinnon et al., 1998).

It is also possible that anxiety in offspring of parents with earlier-onset BD stems from environmental stressors (e.g., chaotic home environment; family conflict, financial difficulties) that may be associated with having a parent with a potentially more severe and/or chronic form of BD (Ostiguy et al., 2009; Wals et al., 2005). In general, families with a member who has BD experience heightened stress and impairment, which appears to have a profound negative impact on interpersonal relationships (Dore & Romans, 2001; Michalak, Yatham, Kolesar, & Lam, 2006; Weinstock et al., 2006). Although it is unclear whether particular BD course characteristics impact offspring stress levels, a number of characteristics, including earlier-onset, anxiety, and predominance of

depressive episodes, are shown to adversely impact patients' own general functioning and quality of life (MacQueen et al., 2000; Otto et al., 2006; Perlis et al., 2009; Sala et al., 2012; N. M. Simon et al., 2004). Therefore, it is possible that increased environmental stress associated with particular parental course characteristics may explain the class differences in offspring anxiety disorders. However, this explanation is merely speculative given that environmental stress was not assessed for specifically in the present study.

When male and female offspring were examined separately, the observed class differences in offspring anxiety disorders were only significant among female offspring. Although anxiety disorders have been shown to be precursors to BD (Duffy et al., 2013), no studies to date have examined sex differences in the developmental progression of illness. However, in examining children who have already developed BD, girls have been shown to have higher rates of anxiety disorders than boys (Biederman et al., 2004). It is possible that females at the highest risk for BD are more likely to develop anxiety as a precursor than are males; however, this must be tested in a longitudinal design. If anxiety in offspring of parents with earlier-onset BD stems from environment factors (as speculated above), females might be expected to be more strongly impacted. Rudolph (2002) suggested that girls possess more interpersonal sensitivity than boys, and therefore respond with more negative emotion when confronted by interpersonal stressors such as those associated with parental illness severity. Bouma and colleagues (2008) similarly found that stressful life events were associated with greater depression symptoms in both

boys and girls of parents with depression, but were considerably stronger in girls than in boys.

These findings should be viewed in light of some limitations. First, although larger than in other studies of offspring of parents with BD, the present sample size may not have been large enough to detect smaller effect sizes. For this reason, negative findings should be interpreted with caution. For example, class differences in other offspring disorders may have emerged with a larger sample of families. Second, offspring age ranged from 4 to 33 years. Although the present study controlled for age, younger offspring are less likely to have experienced particular psychiatric disorders (e.g., MDD, BD) compared to offspring in early adulthood. Future studies would benefit from using a longitudinal design and following offspring throughout development. Third, the present data do not allow for examination of offspring age at time of exposure to parental illness. It is possible that offspring of parents with earlier-onset BD were younger when exposed to parental illness, and therefore more vulnerable to environmental variables associated with living with a parent with BD. Future studies using more detailed assessment of parental course and timeline would do well to evaluate the effects of age at exposure to parental illness. Fourth, the sample was comprised primarily of Caucasian families in the top income classes on the Hollingshead scale and therefore cannot be considered representative of all BD patients. It is possible that the present findings may not generalize to families of other racial/ethnic groups or income classes. Fifth, the present study did not include all potential course indicators in the LCA. The particular variables selected led to the specific classes described in the present study, but using different

variables might have generated a different set of classes. Future LCAs might include other potentially important course characteristics, such as response to lithium treatment (Grof, Duffy, Alda, & Hajek, 2009), suicidality (Novick, Swartz, & Frank, 2010), mixed states (Perugi et al., 1997), or the presence of other particular symptoms.

Despite these limitations, the present findings provide important information about the nature and course of BD. The patterns of class differences in the LCA generally replicated findings across a number of studies that examined bivariate associations between individual BD characteristics. The advantage of the LCA was the ability to aggregate *individuals* in groups based on these characteristics. Further investigation of this approach is needed to confirm the validity of the subgroups identified in the present study. If replicated, identification of these specific sub-groups of patients may have implications for research and treatment. Rather than examining the impact of a variety of separate, heterogeneous illness characteristics on patient outcomes, future research can examine particular profiles of individuals who may be more or less at risk for negative outcomes and/or may differentially respond to treatments. Such information will be valuable as the field continues to refine its diagnostic criteria and identify underlying causal mechanisms for BD. In addition, the present results suggest that by identifying and classifying patterns of BD illness course, we may be able to predict vulnerability in offspring of parents with BD and therefore provide targeted prevention and early intervention to the offspring most at risk.

## TABLES AND FIGURES

Table 4.1. Parent and Offspring Demographic Data

Variable	Mean $\pm$ <i>SD</i> (Range) or %			
	Total	EO-I	EO-II	LO
Offspring age (in years)**	13.46 $\pm$ 5.91 (4 – 33)	14.56 $\pm$ 6.48 (5 – 33)	10.78 $\pm$ 4.19 (4 – 19)	14.05 $\pm$ 5.38 (6 – 31)
Offspring sex				
Female	45.7%	49.0%	40.8%	44.2%
Male	54.3%	51.0%	59.2%	55.8%
Parent age (in years)	44.45 $\pm$ 7.79 (25 – 63)	44.66 $\pm$ 9.28 (25 – 63)	43.20 $\pm$ 5.92 (26 – 53)	45.40 $\pm$ 5.59 (36 – 58)
Sex of parent with BD				
Female	65.4%	64.6%	75.5%	55.8%
Male	34.6%	35.4%	24.5%	44.2%

Family social class (Hollingshead, 1= highest)**	1.87 ± 0.99 (1 – 5)	2.10 ± 1.15 (1 – 5)	1.59 ± 0.61 (1 – 4)	1.65 ± 0.84 (1 – 4)
Intactness of family**				
Parents married/co-habiting	62.2%	57.3%	85.7%	46.5%
Parents separated/divorced	37.8%	42.7%	14.3%	53.5%

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BD = Bipolar disorder; EO-I = *Earlier-Onset BD-I*; EO-II = *Earlier-Onset BD-II*; LO = *Later-Onset BD*; \*\* Significant class differences at the  $p < .01$  level.

Table 4.2. Latent Class Analysis Fit Indices and Class Composition

	2-Class	3-Class	4-Class
	Solution	Solution	Solution
Log-likelihood	-787.50	-772.20	-763.99
AIC	1611.00	1598.39	1599.97
BIC	1659.45	1671.06	1696.86
Sample-size adjusted BIC	1602.57	1585.74	1583.11
Entropy	0.87	0.84	0.88
Lo-Mendell-Rubin adjusted LRT	37.23	29.90	16.04
	$p = 0.02$	$p = .01$	$p = 0.31$
Class composition <sup>1</sup>	79%, 21%	28%, 50%, 21%	27%, 53%, 12%, 9%

<sup>1</sup> Approximate percentage of parents assigned to each class; *AIC* = Akaike's Information Criterion; *BIC* = Bayesian Information Criterion; *LRT* = Likelihood ratio test

Table 4.3. Latent Class Analysis Three-class Solution

Parental Course Characteristic	Estimated Mean/Probabilities			
	Overall	EO-I (50%)	EO-II (28%)	LO (21%)
1. Age of Onset (Mean)	18.46	14.49	15.26	31.65
2. Bipolar Disorder Type I	0.63	0.90	0.00	0.73
3. History of Anxiety Disorder	0.72	0.79	0.83	0.41
4. History of Substance Dependence	0.41	0.51	0.31	0.29
5. History of Psychosis	0.42	0.65	0.00	0.35
6. Polarity at Illness Onset = Depressed	0.71	0.68	0.86	0.55
7. Primary Episode Type = Depressed	0.51	0.66	0.34	0.46
8. Rapid Cycling	0.28	0.29	0.40	0.13

BD = Bipolar disorder; EO-I = *Earlier-Onset BD-I*; EO-II = *Earlier-Onset BD-II*;

LO = *Later-Onset BD*

Table 4.4. Lifetime Offspring Psychopathology (Full Sample)

Diagnostic Category	Total ( <i>n</i> = 188)	Offspring of EO-I ( <i>n</i> = 96)	Offspring of EO-II ( <i>n</i> = 49)	Offspring of LO ( <i>n</i> = 43)
Mood disorder <sup>3</sup>	45.2%	49.0%	36.7%	46.5%
Bipolar disorder <sup>1</sup>	20.7%	20.8%	20.4%	20.9%
Depressive disorder <sup>2</sup>	24.5%	28.1%	16.3%	25.6%
Anxiety disorder* <sup>4</sup>	45.7%	56.3%	55.1%	34.9%
ADHD	26.6%	28.1%	22.4%	27.9%
Disruptive behavior disorder <sup>5</sup>	34.0%	31.3%	32.7%	41.9%

<sup>1</sup> bipolar I or II; <sup>2</sup> major depressive disorder and/or dysthymic disorder; <sup>3</sup> depressive and bipolar disorders; <sup>4</sup> panic disorder, agoraphobia, social phobia, specific phobia, obsessive compulsive disorder, generalized anxiety disorder, posttraumatic stress disorder, and/or separation anxiety disorder; <sup>5</sup> oppositional defiant disorder or conduct disorder.

\* Significant class differences at the  $p < .05$  level.

ADHD = Attention deficit hyperactivity disorder; BD = Bipolar disorder; EO-I = *Earlier-Onset BD-I*; EO-II = *Earlier-Onset BD-II*; LO = *Later-Onset BD*

Table 4.5. Lifetime Offspring Psychopathology (Females)

Diagnostic Category	Total ( <i>n</i> = 86)	Offspring of EO-I ( <i>n</i> = 47)	Offspring of EO-II ( <i>n</i> = 20)	Offspring of LO ( <i>n</i> = 19)
Mood disorder <sup>3</sup>	40.7%	46.8%	25.0%	42.1%
Bipolar disorder <sup>1</sup>	15.1%	19.1%	5.0%	15.8%
Depressive disorder <sup>2</sup>	25.6%	27.7%	20.0%	26.3%
Anxiety disorder* <sup>4</sup>	52.3%	57.4%	75.0%	15.8%
ADHD	15.1%	17.0%	10.0%	15.8%
Disruptive behavior disorder <sup>5</sup>	31.4%	25.5%	40.0%	36.8%

<sup>1</sup> bipolar I or II; <sup>2</sup> major depressive disorder and/or dysthymic disorder; <sup>3</sup> depressive and bipolar disorders; <sup>4</sup> panic disorder, agoraphobia, social phobia, specific phobia, obsessive compulsive disorder, generalized anxiety disorder, posttraumatic stress disorder, and/or separation anxiety disorder; <sup>5</sup> oppositional defiant disorder or conduct disorder.

\* Significant class differences at the  $p < .05$  level.

ADHD = Attention deficit hyperactivity disorder; BD = Bipolar disorder; EO-I = *Earlier-Onset BD-I*; EO-II = *Earlier-Onset BD-II*; LO = *Later-Onset BD*

## **CHAPTER FIVE**

### **GENERAL DISCUSSION**

The studies presented in the previous chapters examined three sets of factors hypothesized to be linked with psychopathology in offspring of parents with bipolar disorder. Although it is clear that these offspring are at heightened risk for psychopathology, the environmental mechanisms conferring risk are not fully known. For this reason, the overall goal of these investigations was to determine factors associated with risk for certain types of offspring disorders, and mechanisms and moderators of that risk. The results of the three present studies enhances the field's knowledge of environmental risk and may therefore inform efforts at prevention and early identification for offspring of parents with bipolar disorder and their families.

#### **MAIN FINDINGS**

Chapter 2 (Study 1) highlighted OCs, particularly during delivery, as factors associated with the development of anxiety disorders in offspring of parents with bipolar disorder. Data also indicated that comorbid anxiety in mothers with bipolar disorder is associated with higher rates of OCs, and part of the relationship between maternal and offspring anxiety may be accounted for by the presence of difficulties during childbirth. Although data did not allow for the assessment of whether events during delivery directly (e.g., via alterations in the fetal environment impacting brain development) or indirectly (e.g., via post-natal environmental factors) contributed to offspring anxiety, findings suggested that comorbid anxiety in mothers may set into motion a chain of events that

increase risk for offspring anxiety disorders. This information speaks to the importance of identifying and attending to anxiety in pregnant mothers with bipolar disorder and providing increased support to families of infants born from complicated deliveries, as such strategies may hinder the development of adverse outcomes in offspring.

Chapter 3 (Study 2) substantiated past research showing links between negative family environment and psychopathology in offspring, thereby supporting the potential importance of targeting family functioning variables in interventions for families with bipolar disorder. In particular, findings implicated conflict and poor cohesion in the associations with offspring internalizing and externalizing symptoms and mood disorders. However, findings also suggested that the connections between family functioning and offspring outcomes are complex and differ based on offspring sex and age. Specifically, associations with internalizing and externalizing symptoms were stronger for younger offspring, and links with mood disorders were stronger for younger boys, suggesting that these individuals may be at greatest need for interventions aimed at enhancing family functioning.

Chapter 4 (Study 3) empirically classified parents with bipolar disorder based on phenotypic indicators of bipolar disorder course, providing potentially important information about the nature and course of bipolar disorder. Although these findings need replication before any definitive conclusions can be made regarding bipolar disorder etiology, they are generally consistent with the larger literature regarding course patterns in bipolar disorder and interrelationships among particular illness characteristics. Associations also emerged between parental most likely class membership (indicating

particular patterns of bipolar disorder course characteristics) and offspring anxiety disorders, but only among female offspring. Specifically, daughters of parents with a bipolar disorder course that was characterized by earlier-onset and higher rates of anxiety comorbidity had significantly higher rates of anxiety disorders themselves, as compared to daughters of parents with later-onset bipolar disorder and lower rates anxiety comorbidity. These findings may have relevance for informing targeted intervention for offspring, suggesting that daughters of parents with particular course profiles may be at greatest risk.

## **ADDITIONAL OVERALL FINDINGS**

### *Offspring Psychopathology*

The sample of offspring described in the previous chapters had high rates of psychopathology. Of the overall sample, a little over 75% reported a lifetime diagnosis of an emotional or behavioral disorder, and more than half had at least two diagnoses. As shown in Table 5.1, rates of any offspring lifetime disorder were consistent with many of those reported in previous samples of offspring at risk for bipolar disorder (Birmaher et al., 2009; Chang et al., 2000; Duffy, Alda, Crawford, et al., 2007; Grigoriou-Serbanescu et al., 1989; Hillegers et al., 2005; Reichart et al., 2004). In examining specific disorder categories, rates of lifetime mood disorders and ADHD were in line with some of the previous high-risk samples, although tended to fall at the high end across estimates. However, rates of lifetime anxiety and behavior disorders in the present sample were much higher (approximately 2-5 times) than those reported in previous samples.

The reasons for these discrepant findings in rates of anxiety and behavior disorders cannot be explained by the fact that the present investigations included older offspring (up to age 33) than the other studies; even in Study 2 that included only individuals under age 18, rates of lifetime psychopathology were consistent with the overall offspring sample (data not shown; although Table 3.2 shows rates of current disorders). Also, compared to previous studies, there were no obvious differences in the present studies in terms of methodology, diagnostic measures, or demographic characteristics. However, it is possible that the parents in the present sample differed from parents in other samples on clinical variables. Although the majority of past studies did not report parental clinical information, all reported on recruitment sources, which may shed some light on potential differences in parental clinical variables. The parents in the present investigations were patients receiving care at a hospital-based specialty outpatient clinic and therefore may have had more severe or complex pathology, compared to what might be seen in other settings, by virtue of selection bias (see Regeer et al., 2009). Although some previous studies recruited parents through specialty clinics similar to the BCRP (e.g., Chang et al., 2000; Duffy, Alda, Crawford, et al., 2007), others utilized a variety of other strategies/settings such as general psychiatric outpatient clinics and bipolar disorder support groups. Such differences in recruitment, and therefore composition of the parent sample, might have potential implications for an elevation of offspring psychopathology, as seen in the present sample. The present investigations also did not include diagnostic information about the co-parents, which might also have shed

some light on the discrepancies across studies. Larger epidemiological studies may be needed to determine a more accurate estimate of offspring psychopathology.

In the present investigations, anxiety disorders were the most prevalent category of offspring lifetime disorder, diagnosed in approximately 50% of offspring. In Studies 1 and 3, anxiety emerged as the only diagnostic category associated with the examined risk factors (i.e., OCs and parental latent class membership, respectively). This might have been a function of statistical power; in other words, the fact that this group was largest may have meant that there was more power to detect effect sizes. Limits on statistical power may have particularly impacted our ability to find effects for disorders with lower base rates, such as bipolar disorder. However, compared to anxiety disorders, the percentage of offspring with a lifetime history of mood disorder was almost as high. Even so, the possibility remains that with a larger sample, significant findings might have emerged for other diagnostic categories as well.

Even so, there is reason to suspect that anxiety may be an important component in both the etiology of bipolar disorder and the intergenerational transmission of bipolar disorder diathesis. Early on, Hammen and colleagues (1990) noticed an especially high rate of anxiety symptoms in offspring of mothers with bipolar disorder. More recent studies have also pointed to the significance of anxiety in the diagnostic profiles of offspring of parents with bipolar disorder. For example, two independent researchers showed that childhood anxiety disorders in offspring of parents with bipolar disorder were associated with an increased (2.1- to 2.6-fold) risk for later mood disorders (Duffy et al., 2013; Nurnberger et al., 2011). In addition, Duffy and colleagues (2013) report

that, compared to control offspring, anxiety disorders tended to occur significantly earlier in the offspring of parents with bipolar disorder, and subsequent mood disorders often did not emerge for many years after the onset of the anxiety disorder. Given these findings, these authors propose that bipolar disorder unfolds in a predictable sequence of clinical stages in high-risk offspring, progressing from a broad spectrum of anxiety disorders, to non-clinical mood symptomatology, to major depressive episodes, and finally to hypomanic/manic episodes (Duffy et al., 2010; Duffy et al., 2013). The offspring in the present investigations were, on average, in early adolescence; and therefore most of the sample had not yet entered the period of greatest risk for mood disorder onset (Kessler et al., 2005). Therefore longer-term follow-up may have revealed more links between the proposed risk factors and offspring mood disorder.

Taken together, these data underscore the need to assess children of parents with bipolar disorder for the presence of anxiety in addition to mood disorders. Although parents with bipolar disorder may be cognizant of the risk for mood disorders in their offspring, the presence of anxiety disorders may be less easily recognized. Additionally, given that anxiety disorders have prognostic implications for subsequent development of mood disorders, they are an especially important target for early intervention in offspring. Focusing on anxiety disorders in parents with bipolar disorder may also hold value, as the relationship between parental and child anxiety may be partially mediated by parenting variables. For example, anxious behaviors and rearing practices in parents (e.g., through modeling and by encouraging anxious cognitions and avoidance behaviors) have been shown to contribute to the development of child anxiety (Bögels & Brechman-Toussaint,

2006; Van Brakel et al., 2006). Interventions for parents that target anxiety may therefore also have implications for improved offspring outcomes.

### *Sex Differences*

Past research has implicated sex as an important moderator in the effects of environment on psychopathology. As discussed in previous chapters, in general, compared to boys, girls have been shown to be more vulnerable to interpersonal and family stressors and may respond with more negative emotion when confronted by such stressors (Davies & Windle, 1997; Hops, 1995; Rudolph, 2002). For this reason, specific aims of Studies 2 and 3 included determining whether sex differences existed in the relationships between the risk factors under investigation and the presence of offspring psychopathology. Study 3 also included age as a moderating variable given previous findings that age may interact with gender in affecting the relationship between environmental variables and psychopathology (Davies & Lindsay, 2004).

Among the overall offspring sample, there were no differences in rates of psychopathology between males and females. However, offspring sex did indeed appear to influence the relationships between risk factors and offspring psychopathology. First, Study 3 indicated that daughters of parents in the earlier-onset bipolar disorder class had significantly higher rates of anxiety disorders, compared to daughters of parents in the later-onset bipolar disorder class; these differences did not emerge for sons. Conversely, Study 2 did not find stronger associations between environmental factors (in this case, family functioning) and psychopathology in daughters compared to sons. There are a number of potential possibilities for this inconsistency across studies. For one, it is

possible that the differences in findings were related to the fact that Study 2 utilized a younger (and smaller) subset of offspring. However, it might also reflect the fact that different types of environmental factors have different effects on offspring, and factors related to course of parental illness (e.g., increased unpredictability, parental hospitalization) might be more stressful/impactful for females, or lead to different types of responses, than family functioning difficulties. The instrument used to assess family functioning might also have been inadequate such that it did not fully or accurately capture interpersonal stressors occurring in the family. Alternately, it is possible that among offspring of parents with bipolar disorder (or at least in the present sample), females may not in fact be more highly sensitive to the impact of environmental factors. Indeed, Wals and colleagues (2005) showed that sex did not moderate the influence of stressful life events on the development of mood disorders among their sample of offspring of parents with bipolar disorder. Therefore, the sex differences found in Study 3 might be related to genetic/biological, rather than environmental, factors.

Second, Study 2 found that family conflict was associated with psychopathology only in younger *boys*, and only for current mood disorder. This finding suggests that, at least for bipolar disorder, age may interact with sex to impact associations between risk factors and psychopathology. Consistent with this, Coville and colleagues (2008) found that, among families who had a son with bipolar disorder, parents were most critical when their child's bipolar disorder onset in childhood versus adolescence (for daughters, this pattern was reversed). As discussed in Chapter 3, compared to girls, younger boys may be more adversely affected by family conflict and/or may manifest their symptoms

differently (e.g., more outward expressions of distress) such that they are more likely to be diagnosed with a mood disorder. If instead offspring psychopathology is viewed as influencing the family environment, it is possible that the presence of mood disorders in younger boys has a more pronounced effect on the family environment. Future research using longitudinal designs is needed to clarify this relationship. Regardless of directionality of effect, interventions that target family functioning in younger boys may be warranted.

Sex differences in the parent sample were not a focus of the present studies (other than in examining risk of OCs in Study 1). However, this variable may be an important focus of future investigations. Some studies exploring parent-of-origin effects in the transmission of bipolar disorder have shown a significantly higher risk for bipolar disorder, in particular, in offspring of affected mothers than in offspring of affected fathers (Currier, Mann, Oquendo, Galfalvy, & Mann, 2006; Gershon, Badner, Detera-Wadleigh, Ferraro, & Berrettini, 1996; McMahon, Stine, Meyers, Simpson, & DePaulo, 1995), although not all studies agree (Grigoriou-Serbanescu et al., 1998; Kato et al., 1996; Kornberg et al., 2000). Parental sex has also been shown to moderate the association between parenting practices and offspring bipolar disorder (Neeren, Alloy, & Abramson, 2008). Parent and offspring sex may also interact such that parenting style of the same-sex parent may be more predictive of mood disorders in offspring than the style of the opposite-sex parent (see Alloy et al., 2006).

## **OVERALL CONCLUSIONS AND FUTURE DIRECTIONS**

Taken together, the three studies included in the present series of investigations provide important contributions to the literature, furthering the understanding of potential risk factors for psychopathology in offspring of parents with bipolar disorder and informing future interventions for parents, offspring, and families. Currently, there are very few studies testing early psychosocial interventions for offspring at risk for bipolar disorder (D. J Miklowitz et al., 2013). Data presented in the previous chapters may be helpful in informing research aimed at developing new prevention and treatment paradigms that target those most at risk. Information from the present studies may also be helpful for providers working directly with both parents with bipolar disorder and their offspring to ameliorate current, and curtail future, suffering and impairment. Further, understanding mechanisms associated with vulnerability among individuals with or at risk for bipolar disorder has important implications from a public health perspective. Bipolar disorder carries great socioeconomic impact (Begley et al., 2001), and is one of the leading cause of disability worldwide among all medical illnesses (Murray & Lopez, 1996).

Overall, the present series of investigations gives credence to the notion that psychopathology in offspring of parents with bipolar disorder may not be solely a function of genetic factors. Environmental factors may also play an important role, both on their own and via interactions with parent and offspring characteristics. Each study presented here had its own particular focus, hypotheses, and results. However, taken together, several important messages can be gleaned.

First, anxiety in both parents and offspring should be an important target of intervention, perhaps particularly for mothers (as suggested by Study 1) and daughters (as suggested by Study 3). Few studies to date have examined psychosocial treatments specifically designed to address anxiety comorbidity in individuals with bipolar disorder. However, preliminary research findings suggest that cognitive-behavioral therapy and mindfulness-based cognitive therapy may hold promise for adults (Provencher, Hawke, & Thienot, 2011). Unfortunately, no treatment studies have focused specifically on pregnant women with bipolar disorder, with or without comorbid anxiety. The present findings suggest that future treatments for pregnant women with bipolar disorder should emphasize anxiety reduction. For children and adolescents, a number of cognitive-behavioral interventions have a strong evidence base in alleviating anxiety (Rapp, Dodds, Walkup, & Rynn, 2013). Addressing anxiety in both parents with bipolar disorder and their offspring, especially early on, would likely yield positive effects for families and may prevent the progression to bipolar disorder in offspring.

Second, as discussed in Chapter 3 and above, efforts to improve family functioning should be incorporated into interventions for parents and offspring and might be particularly important when offspring (particularly boys) are young. As discussed in Chapters 2 and 4, findings in Studies 1 and 3, respectively, may also be related to parenting or family factors, although this was not assessed specifically in either study. Past research shows that the burden and strain associated with caring for and living with a family member with bipolar disorder can have a substantial impact on family functioning (Dore & Romans, 2001). In turn, numerous studies have shown that family factors can

substantially impact the course of bipolar disorder (Geller et al., 2004; D. J Miklowitz et al., 1988). Such reciprocal, mutually influential associations between family functioning and psychopathology (D. J. Miklowitz, 2011b) speak to the need for family-based interventions that target all family members. Fortunately, family interventions have been shown to be efficacious for the treatment of bipolar disorder in adults, and efforts are underway to examine these interventions in youth at risk for bipolar disorder (D. J Miklowitz et al., 2013). Such interventions include a focus on enhancing communication and problem-solving skills, which have the potential to ameliorate family criticism and low cohesion.

Third, the present findings add to the general literature in highlighting the heterogeneity of bipolar disorder, in terms of both illness course/presentation and the interpersonal impact of the disorder. Findings also draw attention to the variability of experiences and outcomes for families with a bipolar disorder parent. For a patient with bipolar disorder, his or her illness has the potential to interact with variables related to pregnancy and delivery, family environment, comorbid psychopathology (e.g., anxiety), and a great number of other factors that were not measured in the present studies, both within the individual and in his or her environment. In turn, risk profiles for offspring vary substantially depending on the variables under investigation and the moderators selected, suggesting myriad pathways of risk. The present studies endeavored to disentangle some of the variability in the interactions between environmental factors and the development of psychopathology in these offspring and may shed light on some variables that may be particularly important to consider.

Future research can build upon the present findings by including a longitudinal design that follows offspring prospectively over time. Our findings, combined with past research (e.g., Duffy, Alda, Crawford, et al., 2007), suggest that psychopathology in high-risk offspring frequently begins early on, and therefore assessment should begin when offspring are young. Further, given that mood disorders often do not reach full clinical diagnostic criteria until late adolescence or early adulthood (Kessler et al., 2005), longitudinal research must continue to follow these youth for a number of years to best understand the etiology of their psychopathology and related risk factors.

Future investigations would also do well to incorporate a variety of measures of environmental stress. Study 1 examined OCs as a proxy for very early environmental stress, and Study 2 attempted to capture the stress inherent in family functioning difficulties. However, there are countless other types of psychosocial stress, as well as ways of operationalizing, and methods of measuring, stress and the stress response. Consistent evidence exists to suggest that stress in an individual's environment influences the onset of bipolar disorder (Horesh & Iancu, 2010; Tsuchiya, Byrne, & Mortensen, 2003). These stressors may affect neurobiological change in such a way that not only triggers initial mood episodes, but also creates vulnerability to future episodes (i.e., the "kindling" hypothesis; Post, 1992). A strong relationship has also been demonstrated between stressful life events and psychopathology in offspring at genetic risk for bipolar disorder (Hillegers et al., 2004). In fact, in the absence of genetic predisposition, there may be no impact of independent life stress on adolescent mood pathology (Silberg, Rutter, Neale, & Eaves, 2001) or stress response (Ostiguy et al., 2011).

Although there may be a general connection between stress and psychopathology in individuals at risk for bipolar disorder, certain individuals may be more strongly impacted by stressful life events based on internal (e.g., temperament; self-esteem) and external (e.g., poor social support) factors (Duffy, Alda, Trinneer, et al., 2007; L. Johnson, Lundstrom, Aberg-Wistedt, & Mathe, 2003; S. L. Johnson, Meyer, Winett, & Small, 2000). Additionally, both sex and timing of exposure should be accounted for in future research examining stress, as both the present investigations and previous research suggest moderation by these variables (see Post & Leverich, 2006). Interventions aimed at enhancing coping skills, increasing social support, and/or stabilizing social rhythms, such as cognitive-behavioral therapy (Lam et al., 2003), family-based approaches (D. J Miklowitz et al., 2013; D. J Miklowitz et al., 2000), and interpersonal and social rhythms therapy (Frank, Swartz, & Kupfer, 2000), respectively, may be important in counteracting the impact of stress on individuals with bipolar disorder and their offspring.

Finally, in addition to gaining a better understanding of psychosocial risk, future research must examine factors exerting a protective effect on offspring. It is important to realize that parental bipolar disorder does not guarantee poor outcomes in children. What has been largely ignored in the literature is the fact that many offspring of parents with bipolar disorder do not go on to develop psychiatric illness (Chang et al., 2000; DelBello & Geller, 2001) and may even adapt well and maintain psychosocial competence in the face of genetic risk. In other words, these offspring may be “resilient.” Importantly, in their longitudinal study, Duffy and colleagues (2007) showed that the high-risk offspring who were completely well and asymptomatic in their childhood and early to mid-

adolescent years remained well throughout the observation period. Future studies would do well to focus their efforts on these offspring and identify the internal and external factors promoting resilience. In turn, treatments can be developed and evaluated that work to strengthen protective factors in children and families in addition to diminishing risk.

In conclusion, it is clear that bipolar disorder interacts with a variety of factors in a patient's and his or her family's lives, resulting in effects for the individual and family members that are far from straightforward. In her personal memoir, Kay Redfield Jamison (1998) captures these complexities well:

My temperament, moods, and illness clearly, and deeply, affected the relationships I had with others and the fabric of my work. But my moods were themselves powerfully shaped by the same relationships and work. The challenge was in learning to understand the complexity of this mutual beholdenness (p. 88).

The present series of investigations have attempted to unpack some of the complexity and variability in the interactions between environmental factors and psychopathology, and findings shed some light on variables that may be important to consider in understanding the individual and interpersonal context of bipolar disorder. However, studies have only just begun to understand both the social context and the internal mechanisms (e.g., genetic factors, neurobiological pathways) involved in the onset and course of bipolar disorder, as well as the intricacies involved in the interactions between these variables. The field still has a long road ahead before we can ultimately gain a full understanding of this exceedingly complex, and potentially devastating, disorder.

## TABLES AND FIGURES

Table 5.1. Lifetime Psychopathology Across Studies of Offspring of Parents with Bipolar Disorder

Diagnostic Category	Present Sample	Grigoroiu-Serbanescu et al. (1989)	Chang et al. (2000)	Reichart et al. (2004) <sup>1</sup>	Hillegers et al. (2005)	Duffy et al. (2007)	Birmaher et al. (2009)	Nurnberger et al. (2011)
Sample size	<i>N</i> = 188	<i>N</i> = 72	<i>N</i> = 60	<i>N</i> = 132	<i>N</i> = 129	<i>N</i> = 127	<i>N</i> = 388	<i>N</i> = 141
Age <i>M</i> ± <i>SD</i>	13.6 ± 6.1	12.9 ± 2.3	11.1 ± 3.5		20.8 ± 2.7		11.9 ± 3.6	16.7 ± 3.3
(Range)	(4–33)	(10–17)	(6–18)	(13–23)	(16–26)	(8–25)	(6–18)	(12–21)
Any disorder	77%	61%	51%	49%	76%	68%	52%	60%
Mood disorder	48%	7%	30%	33%	40%	44%	21%	23%
Anxiety disorder	53%	12%	12%	11%	27%	25%	26%	26%
ADHD	28%	21%	28%	5%	6%	10%	25%	11%
Behavior disorder	37%	14%	10% <sup>2</sup>	7%	9%	1% <sup>3</sup>	19%	11%

ADHD = Attention deficit hyperactivity disorder; <sup>1</sup> Reichart et al. (2004) and Hillegers et al. (2005) reported on the same sample at different time points. <sup>2</sup>Only reported findings for oppositional defiant disorder, <sup>3</sup>Only reported findings for conduct disorder.

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- prospective survey of the MATQUID cohort. *Acta Psychiatrica Scandinavica*, *106*(3), 212-219.
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- Yatham, L. N., Lecrubier, Y., Fieve, R. R., Davis, K. H., Harris, S. D., & Krishnan, A. A. (2004). Quality of life in patients with bipolar I depression: data from 920 patients. *Bipolar Disorders, 6*(5), 379-385. doi: 10.1111/j.1399-5618.2004.00134.x
- Zimmermann, P., Bruckl, T., Nocon, A., Pfister, H., Lieb, R., Wittchen, H. U., . . . Angst, J. (2009). Heterogeneity of DSM-IV major depressive disorder as a consequence of subthreshold bipolarity. *Archives of General Psychiatry, 66*(12), 1341-1352. doi: 10.1001/archgenpsychiatry.2009.158

## CURRICULUM VITAE

**RACHEL D. FREED**

218 WATERMAN STREET, APT 304B  
 PROVIDENCE, RI 02906  
 (617) 935-9338  
 rachel\_freed@brown.edu • rfreed@bu.edu

### EDUCATION

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- July 2013– Present    **The Alpert Medical School of Brown University**  
 Providence, RI  
*APA Accredited Pre-doctoral Internship: Child Clinical Psychology*
- Sept 2007– Present    **Boston University**  
 Boston, MA  
*Doctoral Candidate: Clinical Psychology*
- 2006–2007            **Boston University**  
 Boston, MA  
*Master of Arts: Clinical Psychology*
- 1998–2002            **Johns Hopkins University**  
 Baltimore, MD  
*Bachelor of Arts: Psychology*

### HONORS AND AWARDS

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- March 2011            Clara Mayo Memorial Dissertation Fellowship, Boston University
- September 2006      Boston University Presidential Fellowship, Boston University
- May 2002             Julian C. Stanley Psychology Award, Johns Hopkins University
- May 2002             Phi Beta Kappa Society, Johns Hopkins University
- September 2000      Psi Chi, Psychology Honor Society, Johns Hopkins University
- September 2000      Golden Key National Honor Society, Johns Hopkins University
- 1998–2002            Johns Hopkins University Dean's List, awarded every semester

### PAPERS AND PUBLICATIONS

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**Peer-reviewed publications:**

**Freed, R. D.**, Tompson, M. C., Hirshfeld-Becker, D., Otto, M. W., Nierenberg, A. A., Wang, C. H., & Henin, A. (in press). Early risk factors for psychopathology in offspring of parents with bipolar disorder: The role of obstetric complications and maternal comorbid anxiety. *Depression and Anxiety*.

**Freed, R. D.**, Chan, P. T., Boger, K. D., & Tompson, M. C. (2012). Enhancing maternal depression recognition in health care settings: A review of strategies to improve detection, reduce barriers, and reach mothers in need. *Families, Systems, & Health, 30*(1), 1-18.

**Freed, R. D.**, & Tompson, M. C. (2011). Predictors of parental locus of control in mothers of pre- and early-adolescents. *Journal of Clinical Child and Adolescent Psychology, 40*, 100–110.

Tompson, M. C., Pierre, C. B., Boger, K. D., McKowen, J. W., Chan, P. T., & **Freed, R. D.** (2010). Maternal depression, maternal expressed emotion and child psychopathology. *Journal of Abnormal Child Psychology, 38*, 105–117.

Huang, L. N., **Freed, R.**, & Espiritu, R. (2006) Co-occurring disorders of adolescents in primary care: closing the gaps. *Adolescent Medicine Clinics, 17*, 453–467.

Petersen, T., Alpert, J. E., Papakostas, G. I., Bernstein, E. M., **Freed, R.**, Smith, M. M., & Fava, M. (2003). Early-onset depression and the emotional and behavioral characteristics of offspring. *Depression and Anxiety, 18*, 104–108.

Alpert, J. E., Petersen, T., Roffi, P. A., Papakostas, G. I., **Freed, R.**, Smith, M. M., Nierenberg, A. A., Rosenbaum, J. F., & Fava, M. (2003). Behavioral and emotional disturbances in the offspring of depressed parents with anger attacks. *Psychotherapy and Psychosomatics, 72*, 102–106.

#### **Book chapters:**

**Freed, R. D.**, Chan, P. T., Langer, D. A., & Tompson, M. C. (2013). Depression, bipolar disorder and suicidality in children and adolescents. In S. G. Hofmann, D. Dozois, J. A. J. Smits, & W. Rief (Eds.) *Cognitive Behavioral Therapy: A Complete Reference Guide*. Wiley Publishing.

Otis, J. D., **Freed, R. D.**, & Keane, T. M. (2012). Treatment of co-occurring PTSD and chronic pain. In R. A. McMackin, E. Newman, J. M. Fogler, & T. M. Keane (Eds.). *Trauma Therapy in Context: The Science and Craft of Evidence-Based Practice*. Washington, DC: APA Publications.

Nicholson, J., Cooper, J., **Freed, R.**, & Isaacs, M. (2008). Children of parents with mental illness. In Gullotta, T. & Blau, G. (Eds.) *Family Influences on Childhood Behavior and Development: Evidence-Based Prevention and Treatment Approaches*. New York: Taylor & Francis Group.

#### **Non-peer-reviewed publications:**

**Freed, R. D.** (2009). [Review of the book *An early preventive intervention for depressed mothers and their infants, its efficacy and predictors of maternal sensitivity*, by K. van Doesum]. *Psychiatric Rehabilitation Journal*, 33, 163.

**Freed, R.** (2006). *A Community Action Guide to Promote Wellness and Prevent and Treat Maternal Depression. Issue Brief #4*. Baltimore, MD: Annie E. Casey Foundation.

Huang, L. N., & **Freed, R.** (2006). *The Spiraling Effects of Maternal Depression on Mothers, Children, Families and Communities. Issue Brief #2*. Baltimore, MD: Annie E. Casey Foundation.

#### **PROFESSIONAL PRESENTATIONS**

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**Freed, R. D.**, Seaboyer, L. M., Davis, S., Spirito, A., & Wolff, J. C. (2013, November). *Relationships between perception of family functioning and depressive symptoms in adolescents and parents participating in concurrent depression treatment*. Child and Adolescent Depression SIG poster presented at the 2013 Association for Behavioral and Cognitive Therapies (ABCT) Annual Convention, Nashville, TN.

**Freed, R. D.**, Wang, C. H., Tompson, M. C., Hirshfeld-Becker, D., Otto, M. W., Nierenberg, A. A., & Henin, A. (2013, November). *Family functioning in the context of parental bipolar disorder: Associations with youth psychopathology*. Poster presented at the 2013 Association for Behavioral and Cognitive Therapies (ABCT) Annual Convention, Nashville, TN.

Seaboyer, L. M., Davis, S., **Freed, R. D.**, Spirito, A., & Wolff, J. C. (2013, November). *Fostering hope among adolescents and parents with depression: Results from a randomized controlled trial*. Child and Adolescent Depression SIG poster presented at the 2013 Association for Behavioral and Cognitive Therapies (ABCT) Annual Convention, Nashville, TN.

**Freed, R. D.**, Tompson, M. C., Hirshfeld-Becker, D., Otto, M. W., Nierenberg, A. A., Wang, C. H., & Henin, A. (2012, November). *Obstetric complications as an early environmental risk factor for psychopathology among offspring of parents with*

*bipolar disorder*. Poster presented at the 2012 Association for Behavioral and Cognitive Therapies (ABCT) Annual Convention, National Harbor, MD.

Rousseau, C., Chan, P. T., **Freed, R. D.**, Langer, D. A., & Tompson, M. C. (2012, November). *Family interpersonal stress, negative attributional style, and depressive symptoms in youth: A longitudinal analysis*. Poster presented at the 2012 Association for Behavioral and Cognitive Therapies (ABCT) Annual Convention, National Harbor, MD.

**Freed, R. D.**, & Otis, J. D. (2011, November). *Moderators in the relationship between chronic pain and depression: The role of support and adaptive coping*. Poster presented at the 2011 Association for Behavioral and Cognitive Therapies (ABCT) Annual Convention, Toronto, Canada.

**Freed, R. D.**, & Tompson, M. C. (2010, November). *Predictors of parental locus of control in mothers: cross-sectional and longitudinal findings*. Poster presented at the 2010 Association for Behavioral and Cognitive Therapies (ABCT) Annual Convention, San Francisco, CA.

Tompson, M. C., Pierre, C. B., **Freed, R. D.**, McKowen, J., Chan, P. T., Cruise, R. C., & Smetana, C. R. (2010, November) *Maternal expressed emotion and internalizing symptoms in youth*. Paper presented at the 2010 Association for Behavioral and Cognitive Therapies (ABCT) Annual Convention, San Francisco, CA.

**Freed, R. D.**, Pierre, C. B., & Tompson, M. C. (2010, June). *The effects of marital status and relationship quality on maternal depression and child psychopathology*. Poster presented at the 6th World Congress of Behavioral and Cognitive Therapies (WCBCT), Boston, MA.

**Freed, R. D.**, & Tompson, M. C. (2009, November). *Family factors predicting psychopathology and competence in children of mothers with depression: Gender differences*. Poster presented at the 2009 Association for Behavioral and Cognitive Therapies (ABCT) Annual Convention, New York, NY.

**Freed, R. D.**, Cruise, R. C., & Tompson, M. C. (2009, June). *Depression, support, child behavior, and other predictors of parental self-efficacy*. Poster presented at the 2009 International Society for Research in Child and Adolescent Psychopathology (ISRCAP) Conference, Seattle, WA.

Pierre, C. B., Cruise, R. C., **Freed, R. D.**, & Tompson, M. C. (2009, June). *Maternal depression, marital status, child stress, and family functioning*. Poster presented at

the 2009 International Society for Research in Child and Adolescent Psychopathology (ISRCAP) Conference, Seattle, WA.

Tompson, M. C., Trivedi, S., McKowen, J. W., & **Freed, R. D.** (2009, June). *Factors impacting cognitive style and depressive symptoms: Gender and pubertal status*. Poster presented at the 2009 International Society for Research in Child and Adolescent Psychopathology (ISRCAP) Conference, Seattle, WA.

**Freed, R. D.**, Pierre, C. B., Chan, P. T., Boger, K. D., McKowen, J. W., & Tompson, M. C. (2008, March). *Predictors of parental locus of control: The role of maternal depression, maternal expressed emotion, and child symptoms*. Poster presented at the 98th annual meeting of the American Psychopathological Association (APPA), New York, NY.

McKowen, J. W., Boger, K. D., **Freed, R. D.**, Chan, P. T., Pierre, C. B., & Tompson, M. C. (2008, March). *Social support as a buffer to youth depression: Do perceptions of support moderate the relationship between life stress, negative cognitions, and depressive symptoms?* Poster presented at the 98th annual meeting of the American Psychopathological Association (APPA), New York, NY.

Pierre, C. B., Chan, P., McKowen, J., Boger, K. D., **Freed, R. D.**, & Tompson M. C. (2008, March). *Maternal depression and expressed emotion in the prediction of child attachment cognitions and youth depressive symptoms*. Poster presented at the 98th annual meeting of the American Psychopathological Association (APPA), New York, NY.

**Freed, R.** (2007, July). *A review of the literature on maternal depression*. Presentation at the Substance Abuse and Mental Health Services Administration (SAMHSA) Maternal Depression Action Guide Experts Meeting. Arlington, VA.

Nicholson, J., Cooper, J., **Freed, R.**, Huang, L., Isaacs, M., Knitzer, J., Beardslee, W., & Bell, C. (2006, February). *Parental depression, children, care givers, and communities: Research, policy, practice, and advocacy*. Presentation at the 19th Annual Research Conference. A System of Care for Children's Mental Health: Expanding the Research Base. Tampa, FL.

## COMMUNITY PRESENTATIONS

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**Freed, R.** (2014, March). *Sadness, Badness and Madness: Parenting Depressed Adolescents*. Bradley Hospital's 24th annual Parenting Matters conference. Barrington, RI.

## RESEARCH EXPERIENCE

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- July 2013–  
Present                    **Adolescent Mood and Stress Research Clinic**  
**Bradley Hasbro Research Unit, Rhode Island Hospital**  
*Psychology Resident*  
*Supervisors: Anthony Spirito, Ph.D., ABPP, Jennifer Wolff, Ph.D.*
- August 2012–  
June 2013                **Institute for Anxiety and Mood Disorders**  
**NYU Child Study Center**  
*Research Associate/Project Diagnostician/Study Co-therapist*  
*Supervisors: Carrie Masia Warner, Ph.D., Kathleen Herzig, Ph.D.*
- August 2011–  
July 2012                **Systems of Support Study**  
**Family Development & Treatment Lab, Boston University**  
*Graduate Research Fellow/Project Diagnostician/Study Therapist*  
*Supervisors: Martha Tompson, Ph.D., David Langer, Ph.D.*
- November 2010–  
July 2011                **Pain Management Psychology Services**  
**VA Boston Healthcare System**  
*Research Assistant / Project Diagnostician*  
*Supervisor: John Otis, Ph.D.*
- August 2006–  
August 2010            **Families' and Children's Adjustment Study**  
**Family Development & Treatment Lab, Boston University**  
*Graduate Research Fellow / Project Diagnostician*  
*Supervisor: Martha C. Tompson, Ph.D.*
- June 2005–  
August 2006            **The Action Network for Parental Depression**  
*Project Assistant*  
*Supervisors: William Beardslee, M.D., Joanne Nicholson, Ph.D., Larke Huang, Ph.D.*
- August 2002–  
August 2006            **Technical Assistance (TA) Partnership for Child & Family Mental Health, American Institutes for Research**  
*Research Associate*  
*Supervisors: Regina Hicks, Ph.D., Sharon Hunt, Ph.D., Larke Huang, Ph.D.*
- Summer  
2001                        **Depression Clinical and Research Program**  
**Massachusetts General Hospital**  
*Volunteer Research Assistant*  
*Supervisor: Timothy Petersen, Ph.D.*

## CLINICAL EXPERIENCE

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- March 2014–  
Present      **Pediatric Anxiety Clinic**  
**Rhode Island Hospital and Hasbro Children’s Hospital**  
*Psychology Resident*  
*Supervisors: Abbe Garcia, Ph.D., Jennifer Herron, Ph.D.*
- March 2014–  
Present      **Center for Autism and Developmental Disabilities (CADD)**  
**Inpatient Unit, Bradley Hospital**  
*Psychology Resident*  
*Supervisor: Barbara Tylenda, Ph.D.*
- July 2013–  
March 2014      **Adolescent Mood and Stress Clinic**  
**Rhode Island Hospital and Hasbro Children’s Hospital**  
*Psychology Resident*  
*Supervisors: Jennifer Wolff, Ph.D., Sara Becker, Ph.D.*
- July 2013–  
March 2014      **The Bradley School**  
*Psychology Resident*  
*Supervisors: Lisa Freda, Psy.D., Francine D’Elia, Ph.D.,*  
*Jamie Hollenbeck, Psy.D., Matthew Young, Ph.D.*
- July 2013–  
November 2013      **Pediatric Sleep Disorders Clinic, Hasbro Children’s Hospital**  
*Psychology Resident*  
*Supervisors: Julie Boergers, Ph.D., Richard Millman M.D.,*  
*Stephanie Hartselle, M.D.*
- September 2010–  
May 2012      **Pediatric Psychopharmacology Clinical & Research Program**  
**Massachusetts General Hospital**  
*Practicum Training Fellow*  
*Supervisors: Aude Henin, Ph.D., Dina Hirshfeld-Becker, Ph.D.*
- September 2009–  
June 2010      **The Manville School, Judge Baker Children’s Center**  
*Practicum Training Fellow*  
*Supervisor: Mitchell Abblett, Ph.D.*
- September 2008–  
August 2009      **The Danielsen Institute**  
*Practicum Training Fellow*  
*Supervisors: James Burns, Ph.D., David Rupert, Psy.D.*
- September 2007–  
August 2008      **Boston University Psychological Services Center**  
*Practicum Training Fellow*  
*Supervisors: Wendy Lippe, Ph.D., Rosemary Toomey, Ph.D.*

September 2007–  
August 2008      **Center for Anxiety and Related Disorders at Boston University  
Eating Disorders Program**  
*Practicum Training Fellow*  
*Supervisor: Heather Thompson-Brenner, Ph.D.,*

#### **TEACHING EXPERIENCE**

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January 2013–  
May 2013      **Advanced Seminar on Anxiety Disorders**  
**Graduate School of Arts and Sciences, New York University**  
*Adjunct Co-Professor (with Chad Brice, Ph.D.)*

January 2010–  
May 2010      **Introduction to Social Psychology**  
**College of Arts and Sciences, Boston University**  
*Teaching Fellow (Course Instructor: David Shim, Ph.D.)*

September 2009–  
December 2009      **Introduction to Personality Psychology**  
**College of Arts and Sciences, Boston University**  
*Teaching Fellow (Course Instructor: Richard Ely, Ph.D.)*

#### **CONSULTANT WORK**

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Summer 2007      **Mental Health America**

Spring 2006      **Annie E. Casey Foundation**

#### **AD HOC REVIEWS**

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Journal of Adolescent Health (with David Langer)  
Depression and Anxiety (with Jennifer Wolff)  
Journal of Child and Adolescent Psychology (with Anthony Spirito)  
Psychotherapy (with John Otis)  
Clinical Journal of Pain (with John Otis)  
Journal of Rehabilitation Research & Development (with John Otis)  
Journal of Traumatic Stress (with John Otis)

#### **PROFESSIONAL AFFILIATIONS**

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American Psychological Association (APA), student member  
    Division 53: Society of Clinical Child and Adolescent Psychology  
    Division 37: Society for Child and Family Policy and Practice  
Association for Behavioral and Cognitive Therapies (ABCT), student member  
    Child and Adolescent Depression Special Interest Group