A R T I C L E

Studies of Offspring of Parents With Bipolar Disorder

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Children and adolescents who are the biological offspring of individuals with bipolar disorder (BD) (bipolar offspring) represent a population rich in potential for revealing important aspects in the development of BD. Multiple cross-sectional assessments of psychopathology in bipolar offspring have confirmed high incidences of BD, as well as mood and behavioral disorders, and other psychopathology in this population. Longitudinal studies of offspring have begun to shed light on precursors of BD development. Other assessments of bipolar offspring have included dimensional reports of psychiatric and psychosocial functioning, temperament assessments, and descriptions of family environments and parenting styles. Neurobiological studies in bipolar offspring are just beginning to yield findings that may be related to the underlying neuropathophysiology of BD. The future holds promise for longitudinal studies of bipolar offspring incorporating all of these facets, including genetic analyses, to further elucidate the factors involved in the evolution of BD.   © 2003 Wiley-Liss, Inc.

INTRODUCTION

Children and adolescents who are the biological offspring of individuals with bipolar disorder (BD) (hereafter referred to as bipolar offspring) represent a population rich in potential for revealing important aspects in the development of BD. Bipolar offspring are at relatively high genetic risk for development of BD, as well as other psychopathology. Therefore, a greater understanding of familial transmission of BD can be gained through studying bipolar offspring. Furthermore, through having a parent with BD who may have had significant mood episodes that impacted the child, environment–gene interactions can be evaluated. Their status as at risk for developing BD also allows for study of trait vs. state determinations of any biological findings.

The ultimate reason for studying bipolar offspring may be for early intervention and prevention purposes. The concept of kindling in affective disorders, as proposed by Post [1992], argues for the need for such early identification of individuals at high risk for developing BD. The kindling theory suggests that mood disorders are created by an interplay between a susceptible genetic diathesis and environmental stressors that causes biological changes at the genetic level, which over time lead to the crossing of a neurobiological threshold for a mood episode. With the onset of each successive episode of mania or depression, these biological changes accrue, leading to more frequent and spontaneous episodes. If applicable to BD, in order to lessen future morbidity, it is important to intervene at as early a stage as possible in bipolar development. Therefore, studies of populations at high risk for developing BD are necessary to inform researchers and clinicians as to the most appropriate individuals in which to institute early intervention. This review will summarize the evidence establishing bipolar offspring as a high-risk group, discuss the extant studies of psychiatric phenomenology and other characterization of bipolar offspring, report on the few neurobiological studies in bipolar offspring, and propose future directions for research in this area.

RETROSPECTIVE DATA OF EARLY-ONSET SYMPTOMS OF BD

Retrospective reports of childhood disorders in adults with BD provide insight into possible early expressions of BD. In a questionnaire-based study, support group members with BD reported symptoms of depressed mood, hyperactivity, suicidality, and manic behavior occurring before their first manic episode. Thirty-one percent of respondents described experiencing these symptoms before the age of 15 years and 17% before the age of 10 years [Lish et al., 1994]. Similarly, in a study of adults hospitalized in New York for their first psychotic episode, 67% of those with BD reported childhood-onset psychiatric disturbance, with 21% having disruptive behavioral disorders [Carlson et al., 2000].

These retrospective data point to possible early stages in BD development. Collection of prospective data would provide more reliable data, but in order

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to collect relevant data, a sample at high risk for BD development would need to be studied.

PHENOMENOLOGICAL STUDIES OF BIPOLAR OFFSPRING

The heritability of BD may be 40–70%, based on both studies of relatives of bipolar probands and twin concordance studies [for review, see Craddock and Jones, 1999]. Therefore, offspring of parents with BD should be at high risk themselves for BD development. Formal studies of children with manic-depressive parents were not conducted until the 1970s. Kestenbaum [1979] reported that 13 children with a bipolar parent had a preponderance of temper tantrums, dysphoric symptoms, obsessive and compulsive tendencies, hyperactivity, mood lability, and impulsivity. McKnew et al. [1997] found over half of 30 children of inpatients with affective disorder (unipolar or bipolar) to have depressive disorders themselves.

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Phenomenological bipolar offspring studies published between 1983 and 1993 [Kuyler et al., 1980; Waters and Marchenko-Bouer, 1980; LaRoche et al., 1981, 1985, 1987; Decina et al., 1983; Gershon et al., 1985; Kashani et al., 1985; Klein et al., 1985; Hammen et al., 1987, 1990; Weintraub, 1987; Zahn-Waxler et al., 1988; Nurnberger et al., 1988b; Grigoroiu-Serbanescu et al., 1989; Radke-Yarrow et al., 1992; Carlson and Weintraub, 1993] were analyzed in a meta-analysis [Lapalme et al., 1997] (Table I). Of these 17 studies, 11 also included a comparison group of offspring of parents with no major mental disorder. There were

772 children with a bipolar parent and 626 children of healthy parents included in the meta-analysis. Over half (52%) of the bipolar offspring met Diagnostic and Statistical Manual (DSM)-III or DSM-III-R criteria for a psychiatric disorder, compared to 29% of the children of healthy parents. Relative risk analysis revealed bipolar offspring to be more than 2.5 times as likely to develop a psychiatric disorder

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and 4.0 times more likely to develop an affective disorder than the control group. Furthermore, 5.4% of bipolar offspring were diagnosed with BD, compared to 0% of the control group [Lapalme et al., 1997]. As all of these studies except three were cross-sectional, the number of offspring developing BD may eventually be higher, given that many of the bipolar offspring would not yet have been at the most common age of onset of BD, between 15 and 19 years [Goodwin and Jamison, 1990].

Studies conducted after this meta-analysis have reported about a 50% incidence of some psychiatric disorder in cross-sectional assessments of child and adolescent bipolar offspring [Duffy et al., 1998; Chang et al., 2000; Soutullo, 2000]. BD itself has been increasingly diagnosed in bipolar offspring, perhaps in part due to the inclusion of BD not otherwise specified (NOS) and bipolar II disorder in DSM III-R and DSM-IV [American Psychiatric Association, 1994]. Duffy et al. [1998] found five of 36 bipolar offspring to have bipolar spectrum disorders, and Chang et al. [2000] found nine of 60 offspring to have

bipolar I or II disorder. Soutullo [2000] reported that 50% of 24 bipolar offspring had a bipolar spectrum disorder, compared to 9% of 13 healthy controls. It is unclear whether this increase in BD incidence in bipolar offspring is due simply to the widening of the bipolar spectrum in DSM-IV or to other factors, such as more accurate diagnoses through structured interviews geared toward childhood affective disorders [for discussion, see DelBello and Geller, 2001]. It is also possible that familial BD incidence is growing due to genetic or environmental influences.

A study from the Netherlands of a Dutch cohort gives a perspective different from the North American studies discussed above [Wals et al., 2001]. In this study, only 3% of 140 bipolar offspring had a lifetime diagnosis of BD. The authors proposed that the relatively low incidence might be due to less prescribing of potentially mania-inducing antidepressants or stimulants to children in Europe compared to the United States.

Externalizing and behavioral disorders also have been increasingly recognized in bipolar offspring. Attention deficit hyperactivity disorder (ADHD) was first reported in bipolar offspring in 1983 [Decina et al., 1983]. Since 1988, ADHD or significant behavioral or attention problems have been reported in approximately 27% of bipolar offspring studied (Table I).

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> *ADHD in children with strong family histories of BD may be the first sign of a developing BD. Family studies of probands with ADHD and BD have supported this comorbidity as representing a familial type of early-onset BD.*

TABLE I. Phenomenological Studies of Bipolar Offspring*

First author (Year)	N (Families)	% with BD	% with ADHD	% with any Dx	Rating[a]	Comments
McKnew [1979]	30 (13)			16	★★	Depression was only diagnosis found
Kuyler et al. [1980]	49 (27)	0	0	22 (45%)	★★	
Laroche et al. [1981]	17 (10)	0	0	0 (0%)	★★	
Cytryn [1982]	19 (13)			11/13 families	★★★★★	Same cohort as McKnew [1979], but with blinded raters and control group
Decina et al. [1983]	31 (18)	0 (5)	2 (6%)	16 (52%)	★★★★1/2	Children interviewed with the Mental Health Assessment form
Gershon et al. [1985]	29	1 (3%)	4 (14%)	21 (72%)	★★★★ control group included, but unclear if blinded interviewers	8 children had atypical depression, which included cyclothymic disorder
Kashani et al. [1985]	9 (5)	0	1 (11%)	?	★★★1/2 Parent not assessed directly	Bipolar offspring not significantly different from unipolar offspring
Klein et al. [1985]	37 (24)	10 (27%)		16 (43%)	★★★★	Subjects 15–21 years old. Parents not interviewed about children
LaRoche et al. [1985]	39	0	0	9 (23%)	★★1/2	13% with cyclothymic personality traits
Weintraub [1987]	134 (58)			27 (20%)	★★★	Subjects assessed at age >18 years
Nurnberger et al. [1988a]	53 (32)	?	?	38 (72%)	★★★★	Subjects 15–25 years old
Zahn-Waxler [1988]	7 (7)	0	2 (29%)	6 (86%)	★★★★	Children assessed at age 6 years
Grigoroiu-Serba-nescu et al. [1989]	72 (47)	1 (1%)	15 (21%)	44 (61%)	★★★★1/2	Parents interviewed clinically. Controls with 25% psychopathology
Hammen [1990]	18 (14)	0	1 (6)	13 (72%)	★★★★★	All mothers with BD. 82% of unipolar comparison group with psychopathology
Radke-Yarrow [1992]	44 (22)			(56%)	★★★★1/2	Results from subjects 8–11 years old reported here
Carlson and Weintraub [1993]	128	6/125 (5%)	39 (30%) (at baseline)	?	★★★★★	Longitudinal follow-up at over age 18 years
Duffy et al. [1998]	36 (23)	5 (14%)	1 (3%)	19 (53%)	★★★	Subjects 10–25 years old
Soutullo [1999]	24	12 (50%)	16 (67%)	?	★★★★★	High rate of BP and ADHD in controls (9%, 18%)
Chang et al. [2000]	60 (37)	8 (13%)	16 (27%)	31 (52%)	★★★★	Parents with retrospective ADHD more likely to have offspring with BD
Wals et al. [2001]	140 (86)	4 (3%)	7 (5%)	61 (44%)	★★★★	Netherlands, age 12–21, 27% had a mood disorder

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[a]Ratings guidelines

★★Offspring interviewed with semi-structured interviews (children directly interviewed).

★★★Offspring interviewed with semi-structured interviews, parents interviewed about children.

★★★★Parents and offspring interviewed with semi-structured interviews, parents interviewed about children, children directly interviewed.

★★★★★Parents and offspring interviewed with semi-structured interviews, parents interviewed about children, children directly interviewed, interviewers blinded to parental status, control group assessed.

BP, bipolar spectrum disorders (bipolar I, II, or NOS, or cyclothymia); ADHD, attention-deficit/hyperactivity disorder; Dx, diagnosis; ?, not reported. Blank cells indicate uncertainty whether interview used allowed for possibility of such a diagnosis.

of probands with ADHD and BD have supported this comorbidity as representing a familial type of early-onset BD [Faraone et al., 1997a,b]. Furthermore, Chang et al. [2000] found that seven of eight offspring with BD had first met criteria for ADHD. Also in this study, parents with BD who retrospectively reported a history of ADHD during their own childhood were more likely to have children already with BD than bipolar parents without a history of ADHD. Thus, it is possible that this increase in the prevalence of ADHD in bipolar offspring may actually reflect an overall increase in early forms of evolving BD.

One longitudinal study that supports this link between behavioral disorders and BD in children at risk for BD followed 134 bipolar offspring and 108 healthy controls from childhood to early adulthood. At baseline, 27.6% of bipolar offspring had behavioral problems, and 30.4% had attention problems, as defined by various rating scales. Upon reassessment after age 18 years, behavioral or attention problems in childhood were found to be associated with development of a mood disorder in young adulthood only in the bipolar offspring. This was the first study to make such a link between behavioral disorders and later development of mood disorders in a population at high risk for BD.

While ADHD has been established as a precursor for early-onset BD, other diagnoses that have a high comorbidity with pediatric BD, including anxiety disorders, may precede full BD development. In one outpatient sample, only 23.5% of children and adolescents with bipolar I or II disorder did *not* have a comorbid anxiety disorder [Masi et al., 2001]. Several bipolar offspring studies reported the presence of anxiety disorders, predominantly separation anxiety and generalized anxiety, in offspring who did not yet meet the criteria for BD [Cytryn et al., 1982; Decina, 1983; Hammen, 1987, 1990; Radke-Yarrow, 1992; Chang, 2000]. Thus, early symptoms of anxiety in some offspring may represent another pathway toward later BD development. Similarly, other beha-

vioral disorders such as oppositional defiant disorder and conduct disorder have high comorbidity with BD (up to 71% and 54%, respectively) [Kovacs and Pollock, 1995; Geller et al., 2000] and are present in bipolar offspring [Chang et al., 2000]. It is possible that the presence of any early psychopathology in bipolar offspring could result in increased experienced stress, thus increasing the likelihood of BD development in an individual already at genetic risk.

It should be noted that the aforementioned studies of bipolar offspring usually did not take into account the presence of comorbid disorders in the bipolar parent or psychiatric disorders in the spouse. That is, these cohorts may have been contaminated by the presence of multiple psychiatric conditions on either parent's side. For example, the presence of unipolar depression in these genealogies may account for some amount of mood disorder development and psychosocial morbidity of the offspring. A few studies of bipolar offspring included a comparison group of children with a parent with unipolar major depressive disorder. While two of these studies reported no differences in amount of psychopathology in unipolar compared to bipolar offspring [Kashani et al., 1985; Weintraub, 1987], two others reported that children with unipolar parents had higher rates of psychopathology. Therefore, the presence in bipolar offspring lineages of disorders other than BD may account for some of the findings discussed here.

Data from these phenomenological studies support bipolar offspring as a cohort at high risk for development of numerous psychiatric disorders, specifically ADHD, depression, and BD. However, it may be difficult to disentangle the effects of genetics from the effects of parenting and other environmental factors in the etiology of this increased risk. Furthermore, additional longitudinal studies are needed to delineate the significance of these disorders in bipolar offspring as they relate to future psychopathology and functioning.

OTHER CHARACTERIZATIONS OF BIPOLAR OFFSPRING

CBCL

Besides making categorical diagnoses, another way of characterizing bipolar offspring is by a dimensional approach, which does not rely only on DSM-IV criteria and clusters disturbances in several independent and interrelated domains. One frequently used example of the dimensional approach is the Child Behavior Checklist (CBCL) [Achenbach and Edelbrock, 1983; Achenbach, 1991], a standardized format for reporting the behavioral problems and competencies of children ages 4–18 as reported by their parents or guardians [Bird et al., 1987]. Three studies have used the CBCL to differentiate between BD and ADHD in children [Biederman et al., 1995; Geller et al., 1998; Hazell et al., 1999]. Wals et al. [2001] reported on CBCL scores in a population of bipolar offspring, finding that girls scored higher on eight of the 11 clinical scales and boys scored higher on four of the 11 clinical scales than a group of healthy controls. However, CBCL scores were not stratified by different diagnostic groups within the offspring group.

These studies, conducted in bipolar offspring from infancy to adolescence, indicate a tendency of bipolar offspring to possess temperaments that may result in less than optimal reactions to psychosocial stressors and predispose them to development of affective psychopathology.

In an offspring cohort with a higher incidence of psychopathology than that of Wals et al. [2001], Dienes et al.

[2002] found that bipolar offspring had elevated scores on every clinical scale of the CBCL. Bipolar offspring with BD were more pervasively disturbed than the offspring with other disorders. However, compared to the ADHD group, the BD group scored higher only on the Withdrawn, Anxious/Depressed, and Aggressive Behavior subscales of the CBCL. In a past study of a clinical cohort not selected for offspring status, children with ADHD had lower scores than children with mania on the Delinquent Behavior, Aggressive Behavior, Withdrawn, Somatic Complaints, Anxious/Depressed, and Thought Problems subscales [Biederman et al., 1995]. It is possible that Dienes et al. [2002] may have detected a group of offspring with ADHD with early symptoms of BD, leading to a greater similarity between offspring with BD and those with only ADHD than found in previous studies of nonbipolar offspring.

Temperament

Temperament characterizations of bipolar offspring strive to assess inborn patterns of behavior and mood present since an early age, which may be genetically determined and avoid some contamination from environmental factors. However, it is often difficult to discern temperament in the context of longstanding psychopathology. Nevertheless, laboratory measures or parental report of temperament at very young ages could offer valuable insights. Chang et al. [2003b] compared parental reports of temperament in bipolar offspring to national means on the Dimensions of Temperament Survey-Revised (DOTS-R). Offspring with already syndromal BD had higher levels of general activity, less ability to stay on task, and lower flexibility or adaptability. This characterization resembles the temperament construct of behavioral disinhibition, which has been linked to the development of disruptive behavioral disorders [Hirshfeld-Becker et al., 2002].

Zahn-Waxler et al. [1984] noted that 2-year-old children of bipolar parents showed "heightened distress and preoccupation with the conflicts and

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suffering of others." These children also had problems socializing appropriately with peers, less inclination to share, and more aggression toward both peers and adults. Similarly, Gaensbauer et al. [1984] studied seven male bipolar offspring infants (12–18 months old) and noted that compared to infants of nondisordered parents, the bipolar offspring showed more negative effects and less ability to self-soothe when upset.

These studies, conducted in bipolar offspring from infancy to adolescence, indicate a tendency of bipolar offspring to possess temperaments that may result in less than optimal reactions to psychosocial stressors and predispose them to development of affective psychopathology. Further studies of temperament in bipolar offspring, preferably in laboratory situations and at very young ages, are necessary to clarify the importance of inborn traits to this area of study.

Family Environment

The characterization of the immediate social environments of bipolar children and offspring has received some attention. The impact of parental psychopathology in general on their children has been long established as significant. Bipolar offspring often demonstrate disordered functioning in domains that have been shown to be strongly influenced by deficient parenting, such as aggressive behavior [Patterson et al., 1989]. Furthermore, the question of the precise importance of environmental stressors in the precipitation of the disorder itself [Post, 1992] makes this a relevant area of study.

Several studies are examining the impact of parent-child interaction and the structural characteristics of the family environment of bipolar offspring. Com-

pared to depressed or healthy mothers, mothers with BD were found to be more negative in their interactions with their children [Inoff-Germain et al., 1992]. In a study of 39 bipolar offspring, presence of offspring psychopathology was correlated with levels of marital discord and exposure of offspring to parental illness before age 3 years [LaRoche et al., 1985]. In a study using the Family Environmental Scale, families with a bipolar parent were found to have less cohesion and organization and more conflict than families from a national, unscreened sample. However, specific psychopathology in the bipolar offspring could not be predicted based on a particular family environment profile. Other investigators have suggested correlations between pathological family environments and severity of illness in bipolar offspring [Kuyler et al., 1980; Grigoroiu-Serbanescu et al., 1989]. These findings are interesting and suggest that detailed studies of shared and nonshared environmental characteristics should shed further light on the relative contributions to BD development in bipolar offspring. An interesting candidate would be the expressed emotion construct, which has been shown to contribute to relapse in studies of other psychoses [Vaughn and Leff, 1976] and more recently in bipolar adults [Miklowitz et al., 1988]. Therefore, parental and extended familial interactions with bipolar offspring may have a critical role in development of BD as well.

Psychosocial Functioning

Regardless of specific psychopathology, bipolar offspring may represent a population at risk for poor psychosocial functioning. In one controlled study, bipolar offspring were found to have a relatively weak social support group with an absence of a best friend [Pellegrini et al., 1986]. One of the few prospective longitudinal studies of bipolar offspring is being conducted at the National Institute of Mental Health (NIMH) by Radke-Yarrow and colleagues, comparing offspring of mothers with BD to offspring of depressed or healthy mothers. At older ages, but not

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younger ages, bipolar offspring reported suicidal ideation more often than children of healthy mothers. Presence of hypomanic symptoms or a mother with past suicide attempts correlated with suicidal ideation in adolescent offspring of bipolar mothers [Klimes-Dougan et al., 1999]. Notably, in the same cohort at 3-year follow-up, significantly more offspring of affectively-ill parents had developed depressive and behavioral problems.

Another study measured externalizing and internalizing behaviors, school performance, and behavior in class, finding offspring of depressed mothers to have worse overall psychosocial functioning than offspring of bipolar, medically ill, or healthy mothers [Anderson and Hammen, 1993]. In a previously mentioned study, a cohort of 60 bipolar offspring had a mean Global Assessment of Functioning (GAF) of 76 ± 12, indicating fairly good functioning. Scores on the Wide Range Achievement Test, Third Edition (WRAT-3) an indicator of academic achievement, were also all at or above grade level. However, bipolar offspring with psychopathology compared to those without psychopathology had lower GAF scores but did not have differing levels of academic achievement [Chang and Steiner, 2003].

Bipolar offspring, particularly those who develop psychopathology, appear at risk for poor psychosocial and academic functioning. However, psychosocial interventions, including psychotherapy,

have not yet been investigated in this group as a whole.

Psychological and Biological Markers

Presence of identifiable biological traits in bipolar offspring could lead to early identification of those at highest risk for BD development and to a better understanding of the pathophysiology of BD development. Therefore, some effort has been made to identify such biological markers. IQ testing of bipolar offspring, an indirect indicator of neurobiology, has had mixed results, including findings of decreased [McDonough-Ryan et al., 2000], normal [Waters et al., 1981], and increased IQ scores [as reported by Kestenbaum, 1980; Decina et al., 1983]. Furthermore, one study reported some increased incidence of a verbal–performance IQ split in bipolar offspring, with verbal scores higher than performance scores [McDonough-Ryan et al., 2002]. However, in this study other signs of nonverbal learning disorders, including worse mathematics performance, were not found. Eye-tracking abnormalities have been reported in offspring of parents with schizophrenia [Erlenmeyer-Kimling, 2000], but no such abnormalities have been found in bipolar offspring [Rosenberg et al., 1997]. A study of electrodermal activity in bipolar offspring compared to healthy controls did not find any differences at rest [Zahn et al., 1989]. However, when performing a mental arithmetic task, bipolar offspring showed higher electrodermal activity, correlating with a higher self-report of anxiety [Zahn et al., 1991]. Another study examined melatonin suppression by light of 25 bipolar offspring 15–25 years old and 20 healthy controls [Nurnberger et al., 1988b]. Bipolar offspring showed significantly higher suppression of melatonin levels after bright light exposure than controls. Furthermore, the group of seven offspring with two bipolar parents had the highest percentage of subjects (57%) with marked melatonin suppression, with only 21% of controls and 33% of offspring with one bipolar parent show-

ing marked melatonin suppression. There may be a correlation between the degree of melatonin suppression and genetic loading for BD [Nurnberger et al., 1988b], as 91% of a sample of adults with BD also were reported to have marked melatonin suppression [Lewy et al., 1985]. However, further studies investigating melatonin reactivity in bipolar offspring have not since been conducted.

The development of relatively safe and noninvasive magnetic resonance imaging (MRI) technologies has led to increased neuroimaging studies of children, including studies of bipolar offspring. DelBello et al. [2000] reported increased hippocampal size in bipolar offspring who did not meet criteria for BD, but who ranged from symptom-free to mood disordered. Using magnetic resonance spectroscopy (MRS), Chang et al. [2003a] reported decreased N-acetylaspartate (NAA)/creatine ratios in right dorsolateral prefrontal cortex of bipolar offspring with BD. It remains

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to be seen whether offspring without BD, or with other psychopathology, have similarly decreased prefrontal NAA.

Neuroimaging studies in adults and children with BD have revealed findings that could guide future study in bipolar

offspring. Volumetric MRI studies overall suggest that patients with BD may have prefrontal, temporal, cerebellar, ventricular, and deeper structural (striatum and amygdala) volume changes, as well as white matter abnormalities as indicated by white matter hyperintensities [for reference, see Strakowski et al., 2000, 2002]. Results from positron emission tomography (PET) studies of bipolar patients have been varied; perhaps the most consistent findings have been decreased blood flow in the prefrontal cortex during bipolar depressed states and a general implication of the prefrontal cortex (DLPFC, ACC, and orbitofrontal cortex), limbic structures (amygdala, insula), striatum, and thalamus in the neuropathophysiology of BD [Blumberg et al., 2002]. Studies of adults with familial BD have reported abnormalities in the subgenual prefrontal cortex [Drevets et al., 1997; Ongur et al., 1998], cerebellum (particularly the cerebellar vermis), and lateral ventricles [Brambilla et al., 2001]. These brain regions may have structural or functional alterations in familial BD and therefore could be reasonably investigated in bipolar offspring. Additional volumetric, spectroscopic, and functional MRI studies of bipolar offspring would aid in further identifying neurobiological characteristics that could represent vulnerability traits or early stages of BD development. Currently, however, there are no reliable biological markers correlated with risk for development of BD.

EARLY INTERVENTION STUDIES

Researchers have begun to investigate pharmacologic interventions in bipolar offspring who have subsyndromal and therefore possibly prodromal forms of BD. Seventy-eight percent of a cohort of 23 bipolar offspring with mood or behavioral disorders and at least mild affective symptoms were reported to improve clinically after a 12-week open trial of divalproex [Chang et al., 2003c]. In a placebo-controlled study, researchers are investigating the efficacy of divalproex in bipolar offspring with

cyclothymia or BD NOS [Findling et al., 2000]. This study of 60 bipolar offspring has recently been completed and data analysis is pending.

These two studies represent the possibility of early intervention in children at high risk for BD. However, nonpharmacologic intervention strategies could also prove useful. For example, group cognitive therapy was more effective than no specific intervention in reducing depressive symptoms of adolescent offspring of depressed parents [Clarke et al., 2001]. Similarly, psychoeducation sessions for families with a depressed parent may be effective in reducing problematic behaviors of the children in the household [Beardslee and Gladstone, 2001]. These novel approaches to prevention of depression could be similarly applied to bipolar offspring.

It remains to be definitively seen whether these intervention strategies can treat bipolar offspring more effectively than conventional treatment strategies, or whether BD development can be halted by these interventions. Further

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studies, perhaps better informed by using yet to be discovered biological markers, and incorporating placebo arms and longitudinal assessments, will help to identify the appropriate treatments for individuals at high risk for BD development.

GENETICS

The genetic basis of BD has been well established through pedigree analysis,

familial incidence, twin, and adoption studies [for review, see Craddock and Jones, 1999]. However, linkage studies have implicated different chromosomal regions and association studies have been equivocal. The heterogeneity of BD may be partially responsible for this difficulty in isolating consistent gene regions associated with BD and replicating positive findings. Therefore, genetic factors that contribute to BD development may be better identified through more homogenous cohorts within the bipolar spectrum. Bipolar offspring who already exhibit early or fully developed BD would represent such a cohort. However, most genetic studies have targeted bipolar adult probands and their families; there are currently no published genetic studies that have concentrated on affected bipolar offspring in this manner.

Genetic anticipation has also been reported in BD cohorts. Anticipation refers to the phenomenon of a disease state occurring in successive generations with earlier ages of onset and/or higher severity. In other neurological disorders with anticipation, trinucleotide repeat sequences have been found to expand in number of repeats with each generation [for review, see Goossens et al., 2001]. An increase in mean CAG repeat length was associated with a diagnosis of BD [Lindblad et al., 1995; O'Donovan et al., 1996] and with anticipation of BD in a few studies of families with BD [Mendlewicz et al., 1997; Lindblad et al., 1998]. However, there have been no replications of these studies and several negative reports [Craddock et al., 1997; Li et al., 1998; Zander et al., 1998; Meira-Lima et al., 2001]. Furthermore, these repeat sequences have not been successfully linked to meaningful gene regions. Families with reported anticipation from affected parent to affected offspring are a natural choice for investigation for the presence of such repeat sequences. Prospective studies in offspring cohorts that combine genetic analyses with phenomenological assessment would help decrease ascertainment and recall biases and possibly clarify the genetic influences on anticipation in BD.

CONCLUSIONS

Bipolar offspring have been well established as at high risk for the development of BD and other mood disorders. It appears likely that family environment and psychosocial stressors interact with genetic predisposition for affective illness to create such disorders in bipolar offspring. Temperament characteristics of high motor activity, low frustration tolerance, and emotional sensitivity may reflect inborn characteristics in bipolar offspring that may predispose them to BD development. Behavioral disorders in this population such as ADHD may also be early indicators of later development of mood disorders. Delineation of the nature of interaction between environment and genetics needs to be accomplished. Future neurobiological data, from neuroimaging, neuroendocrine, or similar studies of bipolar offspring, will help identify markers that may signal higher risk for or describe etiological factors of BD development. Such studies of bipolar offspring should ideally be longitudinal, in order to fully capture the process of bipolar development in at-risk individuals. Finally, studies combining these biological findings with genetic data acquired from bipolar offspring with full or prodromal BD are needed. The application of modern techniques of DNA analysis and neuroimaging to populations at high risk for BD development may help to eventually reveal the genetic and neurobiological underpinnings of BD.

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