Research report

Early stages in the development of bipolar disorder

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ABSTRACT

Background: Numerous studies have observed that offspring of bipolar parents manifest a broad spectrum of psychiatric disorders. We tested the hypothesis that in high risk offspring, bipolar disorder evolves in a predictable clinical sequence from non-specific (non-mood) to specific (mood) psychopathology.
Methods: Offspring from well-characterized families with one bipolar parent (high risk) or two well parents (controls) were assessed annually or at anytime symptoms developed using KSADS-PL interviews for up to 15 years. DSM-IV diagnoses were made on blind consensus review using all available clinical material. We compared the age-adjusted risks of lifetime psychopathology between high risk and control subjects and assessed the conditional probability of developing a mood disorder given a history of non-mood disorders. In subjects meeting full DSM-IV criteria for bipolar disorder, we assessed the sequence of psychopathology against a clinical staging model.
Results: High risk offspring manifest higher rates of anxiety and sleep disorders, as well as major mood and substance use disorders compared to controls. Antecedent anxiety increased the age-adjusted risk of mood disorder from 40 to 85% (hazard ratio of 2.6). High risk subjects who developed a mood disorder had an increased risk of a substance use disorder (hazard ratio of 2.4), typically meeting diagnostic criteria during or after the first major mood episode. The evolution of psychopathology leading to bipolar disorder generally followed the proposed sequence, although not all subjects manifest all stages.
Limitations: Larger numbers of high risk offspring prospectively assessed over the risk period would allow confirmation of these preliminary findings.
Conclusions: Clinical staging may be a useful approach to refine the early diagnosis and facilitate research into the evolution of bipolar disorder in those at familial risk.

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1. Introduction

From the detailed descriptions at the turn of the last century by Kraepelin (1921), to the more recent long-term observations by Angst (Angst, 1986; Angst and Sellaro, 2000; Angst et al., 2005) and others (Akiskal, 1995; Coryell et al., 1995), we have gained a solid understanding of the course of established bipolar disorder (BD) in adults. However, we do not as yet have comparable data about the pre-morbid course and onset of BD. Most of what is known about the early manifestations of BD derives from retrospective data, which is likely to overlook subtle or sub-threshold disturbances. Recall may also be biased toward the onset of the full-blown disorder, overlooking earlier psychiatric manifestations the subject had either forgotten or not associated with the mood disorder itself. A thorough understanding of the early course is important for timely accurate diagnosis and intervention, as well as for the prevention of substantial burden of illness effects (Judd and Akiskal, 2003; MacQueen et al., 2001) and suicide associated with untreated illness (Angst et al., 1990; Muller-Oerlinghausen et al., 1994).

Given the strong genetic contribution to BD (Smoller and Finn, 2003), longitudinal studies of the children of BD parents provide the opportunity for prospective observation and measurement of milder and/or non-specific psychopathological manifestations, which may represent early signs of, or important precursors to, BD. This study design also circumvents diagnostic controversies surrounding the diagnosis of BD in youth, given the specific genetic risk (Duffy, 2007) and the substantial inconsistency of the bipolar diagnosis early in the course in clinical samples unselected for family history (Carlson et al., 2008). A number of cross-sectional high risk studies have consistently reported a broad range of symptoms and disorders among offspring of bipolar parents that cover the spectrum of psychiatric problems (see DelBello and Geller, 2001; Hodgins et al., 2002, for reviews and most recently, Birmaher et al., 2009). However, high risk studies with a longitudinal component have reported that subjects manifesting these non-specific presentations not uncommonly develop mood disorders later in life (Akiskal et al., 1985; Hammen et al., 1990).

In the earliest such study reported by Akiskal et al. (1985), the referred offspring and siblings of bipolar patients were assessed for up to 3 years. The initial psychopathological manifestations among these referred high risk subjects included: anxiety disorders, minor mood disorders and adjustment disorders. Most affective disturbances began during adolescence (mean 15.9 years; mode 15 years) and were depressive in polarity. No manic or mixed or psychotic depressive episodes onset before puberty. Over prospective follow up, the clinical evolution of psychopathology shifted from depressive disturbance to the manifestation of hypomanic episodes and therefore frank bipolarity.

We replicated this finding in a longitudinal prospective study of the offspring of well-characterized bipolar parents (Duffy et al., 2007a, 1998, 2002). Specifically, we observed that in a substantial number of offspring, major mood episodes (major depression, hypomania, mania) were preceded by non-mood disorders in childhood, followed in adolescence by sub-threshold mood disturbances and sensitivity to stress. The observation that subclinical depressive symptoms heralded the onset of major depressive episodes was not surprising based on the same observations in the unipolar (UP) population (Garber, 2006). However, antecedent non-mood disorders were unexpected given that the offspring in our study derived from families with one carefully diagnosed bipolar parent (based on a wealth of longitudinal clinical data), and one psychiatrically healthy parent, thereby minimizing the contribution of assortative mating. It remains open to question whether the early "non-mood psychopathology" represents co-morbid conditions (independent concurrent or sequential disorders), a general vulnerability towards non-specific psychopathology (partially shared diathesis) or the early stages of BD (evolution of one illness over development and time). If the latter, these precursor conditions could identify among those at familial risk who will go on to develop BD.

The importance and utility of a clinical staging model in medicine is well known and has been helpful in schizophrenia research (Phillips et al., 2002) and only recently discussed as a possible approach to refining the diagnosis in BD (Berk et al., 2007). The ability to characterize transitions from well to oligosymptomatic to full-blown illness has important clinical and research implications. BD treated in the early stages may be less treatment refractory with a greater probability of response to monotherapy (Duffy et al., 2009, 2007b). Despite the fact that a positive family history is the single most robust risk factor for BD, the majority of offspring in most families will not develop the illness (Alda and Grof, 2000; Duffy et al., 2000). This makes universal interventions among youth with a positive family history impractical. Reliable clinical precursors of BD in offspring at genetic risk would allow us more specifically to identify subjects at "ultra-high risk" who are appropriate for close surveillance and early intervention. Further, as pointed out by McGorry et al. (2008), research to identify the pathological correlates of clinical stages would assist our understanding of the pathophysiological process underlying illness onset and progression.

From our repeated longitudinal clinical assessments of high risk subjects over 15 years, we hypothesized a sequence of clinical stages (see Fig. 1) and owing to the prospective nature of the study, we were able to estimate the morbid risk and ages of onset free from recall bias or bias inherent in obtaining information only from parents. We predicted that the majority of subjects would follow this sequence, but could enter the sequence at any point; that is, not all subjects would manifest all clinical stages. Also, we addressed the question of prognostic value of non-mood disorders (anxiety, sleep, attention (ADHD), learning disabilities (LD) and substance use disorders) for the development of major mood episodes in subjects at familial risk of BD. To our knowledge, no study has yet evaluated the conditional probability of developing BD if a child of an affected parent develops a particular non-mood psychiatric disorder early in life.

2. Methods

The high risk and control offspring entered into this analysis were recruited as part of an ongoing longitudinal
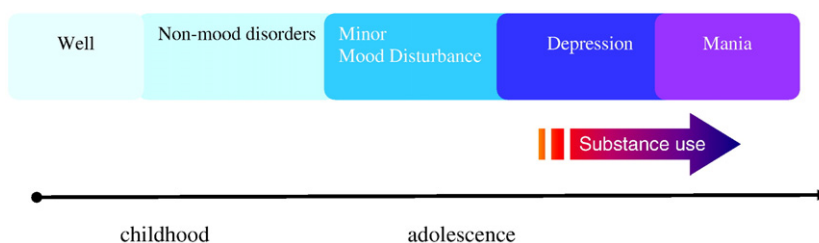

Fig. 1. Proposed staging sequence.

high risk study in accordance with a research protocol described in detail elsewhere (Duffy et al., 2007a). Briefly, high risk families were identified through a parent diagnosed with BD. Parents completed SADS-L (Endicott and Spitzer, 1978) research interviews conducted by a research psychiatrist and met DSM-IV diagnostic criteria for BD (I or II) based on blind consensus review involving at least two additional research psychiatrists using all available clinical material. For inclusion in the high risk study, the other biological parent was determined to have no lifetime history of a major psychiatric disorder on the basis of SADS-L interviews.

Control families were identified through local schools of comparable socioeconomic background to the high risk families. The schools mailed out demographic screening questionnaires to all families with children in grades 3–12 which inquired about family composition and the emotional and physical health of the parents. Interested families mailed back these questionnaires to the research team and those indicating no major psychiatric or acute or chronic medical illness in the parents were invited to a research diagnostic interview. Parents were confirmed to have no lifetime history of a major psychiatric disorder on the basis of SADS-L interviews conducted by a research psychiatrist and confirmed on blind consensus review including at least two additional research psychiatrists.

As a part of this research, all offspring consented and signed forms approved by the responsible research ethics board. Assent was obtained from all under age subjects along with written consent from their parent(s). All consenting/assenting children age 8–25 years from eligible families were assessed in accordance with KSADS-PL/SADS-L format interviews conducted by a child and adolescent psychiatrist. These offspring were then reassessed annually or at anytime symptoms developed, up until the age of 30 years. This was possible because we have ongoing contact with these families either because the adult relatives are patients and/or are involved in other research including genetic studies. We have less than 5% drop-out rate for high risk families and 10% for control families over the duration of the study. In the event of family moves or subjects studying or working at a distance, we would either travel to reassess these subjects or see them when they returned home for holidays or visits. With permission of the families, we also notified the responsible family doctor of study involvement.

Final DSM-IV diagnoses in the offspring were made on the basis of blind consensus review using all available clinical information by at least two additional research psychiatrists, one being a child and adolescent psychiatrist. Age of onset was defined as the earliest age at which the full diagnostic criteria were met, with the exception that for ADHD/LD the age of onset assigned was 5 years. This reflects the fact that these conditions were present throughout early development and were diagnosed at the beginning of elementary school for all subjects.

2.1. Statistical analyses

Survival analysis (product-limit method, with Mantel–Cox test statistics) was used to calculate the rates of Axis I disorders in high risk and control subjects in order to adjust for variable age at onset and for differences in age at last observation. The outcome variable was a specific diagnosis (anxiety disorder, sleep disorder, substance use disorder, mood disorder). The time variable was age of onset for the analyzed Axis I disorders or current age for censored observations. The prevalence rates are reported as an age-adjusted prevalence ± standard error. These analyses were conducted using the BMDP software, module 1L. In order to compare age at last observation and duration of follow up between high and low risk groups, we performed t tests. To compare the sex ratios we used chi-square tests.

A Cox proportional hazard analysis was used to derive the contribution of a number of independent variables to the age-corrected risks of major mood disorders among high risk subjects The independent variables tested included the presence of anxiety, sleep, substance use disorders and ADHD and/or LD. In case of a significant association, we investigated whether the non-mood disorder preceded the onset of mood disorder using the sign test. When the non-mood psychopathology preceded the mood disorder, we also calculated the morbid risk of mood disorder contingent on the presence or absence of a lifetime history of the particular non-mood disorder. When the non-mood psychopathology followed the onset of mood disorder, we calculated the morbid risk of non-mood disorder contingent on the presence or absence of a lifetime history of mood disorder. For these analyses, we included all subjects meeting diagnostic criteria for at least one lifetime major mood episode (major depression, hypomania or mania). As a measure of effect size, we calculated hazard ratios using the Cox proportional hazard model.

To test the staging hypothesis, we plotted the sequence of psychopathology for all subjects affected with BD. The main question was whether subjects progressed through the staging model in the proposed sequence regardless of where they entered the model (Fig. 1). It should be noted that not all stages had to be present; the critical factor was that, of those stages that were present, the proposed order was followed. For each subject, this was coded as "yes, progressed in order" or "no, did not progress in order". We also tested whether other Axis I disorders (ADHD/LD, anxiety, sleep disorders) preceded the onset of mood disorders within subjects using the sign test. We adopted a significance level of $p \leq 0.05$ two-tailed for all analyses.

3. Results

3.1. Description of the study cohort

Table 1 displays descriptive statistics and compares diagnostic information for the high risk and control offspring. This analysis included 207 high risk and 87 control subjects. The sex ratio was comparable between the groups (approximately 60% females). The mean age at enrolment occurred in mid-adolescence, and on average the control subjects were somewhat younger than the high risk subjects. It is important to note that the majority (64%) of major mood episodes in this analysis were prospectively captured and that the clinical course is largely naturalistic as medication played a minimal role in the early course of mood disorder (Duffy et al., 2009).

Table 1
Descriptive information for high risk and control subjects.

	High risk	Control	p
Number	207	87	–
Sex: % female	59	59	NS
Mean age at enrolment (SD)	16.5 (5.2)	14.7 (2.2)	<.001
Mean age at analysis (SD)	20.2 (6.4)	16.1 (2.3)	<.001
Prevalence ADHD/LD %[a]	8.3	5.8	NS
Age-adjusted prevalence — anxiety disorders % (SE)	23.2 (3.4)	7.8 (3.1)	≤.01
Mean age of onset (SD)	9.4 (4.8)	12.3 (1.6)	
Age-adjusted prevalence — sleep disorders % (SE)	18.0 (3.1)	0 (0.0)	<.001
Mean age of onset (SD)	9.9 (5.7)	–	
Age-adjusted prevalence — minor mood disorders % (SE)	31.8 (7.7)	8.1 (3.2)	NS
Mean age of onset (SD)	14.5 (6.2)	11.2 (4.4)	
Age-adjusted prevalence — major mood disorders % (SE)	52.8 (5.2)	1.3 (1.2)	<.001
Mean age of onset (SD)	16.8 (3.6)	12.3 (–)	
Age-adjusted prevalence — substance use disorders % (SE)	25.7 (4.1)	1.6 (1.6)	≤.05
Mean age of onset (SD)	17.0 (2.8)	15.0 (–)	

[a] ADHD/LD not age-adjusted as the age of onset for all subjects was taken as age 5 years.

3.2. Lifetime psychopathology — high risk versus control offspring

As indicated in Table 1, high risk subjects manifested a significantly higher age-adjusted prevalence of major mood, anxiety, sleep and substance use disorders compared to control subjects. There was no statistically significant difference in the rate of minor mood disorders, ADHD and/or LD between the high risk and control groups; although the prevalence of minor mood/adjustment disorders was several fold higher in high risk compared to control subjects. With the exception of substance use disorder, all non-mood lifetime diagnoses had an earlier onset than major mood disorder. From earliest to latest, the mean age of onset for non-mood diagnoses in the high risk subjects affected for a major mood disorder were: sleep disorders, anxiety disorders, adjustment and/or minor mood disorders, major mood disorders and finally substance use disorders.

3.3. Major mood disorders

Of the total sample, 67 high risk (8 BD I, 12 BD II, 1 Schizoaffective BP, 17 BD NOS and 29 UP) and 1 control subject (UP) had met lifetime DSM-IV diagnostic criteria for a major mood disorder at the time of this analysis. Among those high risk subjects affected with a major mood disorder, 67% were females with a mean age of onset of mid-adolescence. In 97% (65/67) of these high risk subjects, the first mood episode was either minor or major depression. When including only major mood episodes, 90% (60/67) of subjects had major depression as their first mood episode. No subject manifested hypomania or mania prior to age 14, with an average latency of 3.5 ± 2.6 years following the index depressive episode. The mean age of onset of the first hypomanic or manic episode was 19 ± 3.8 years.

3.4. Age corrected risk of major mood disorder given other non-mood lifetime diagnoses

In the Cox proportional hazard model, the presence of anxiety and substance use disorders independently and significantly contributed to the risk of major mood disorder among high risk subjects (see below), whereas there was no statistically significant association between sleep disorders or ADHD/LD and major mood disorders (Table 2).

At the time of the last observation, 41 high risk subjects had met lifetime DSM-IV criteria for at least one anxiety disorder (generalized, social, simple phobia, panic disorder); however, no cases of post traumatic stress or obsessive compulsive disorder were observed. Among subjects with both an anxiety and a mood disorder ($n = 27$), in all cases the anxiety disorder preceded the onset of the index major mood episode (sign test, $p < 0.0001$) by an average of $8 ± 5.1$ years. The mean age of onset of anxiety disorders in the group with both mood and anxiety disorders was $9 ± 4.5$ years, while the mean age of onset of mood disorder was $17 ± 4.3$ years.

In the majority of subjects with a lifetime history of both anxiety and mood disorders (20/27), the onset of anxiety was prior to 10 years of age and the onset of mood disorder was after age 10. Only 6 of the 27 subjects had onset of anxiety disorder after 10 years of age and all of these subjects had an onset of mood disorder after age 10 years as well.

Since anxiety disorder preceded mood disorder, we calculated the morbid risk for the development of mood disorder in high risk subjects with versus without an anxiety disorder. The age-adjusted morbid risk of mood disorder among subjects with an anxiety disorder was 85% compared to 40% in those without a history of anxiety disorder, with a hazard ratio of 2.6; 95%CI = 1.59–4.25 (Table 2, Fig. 2).

At the time of the last observation, 34 high risk subjects had met lifetime DSM-IV criteria for a substance use disorder. Among the high risk subjects with both substance use and mood disorders ($n = 21$), in 7 out of 21 cases substance use preceded the onset of the index major mood episode, whereas in all other subjects (14/21) substance use started during or after the onset of the index major mood episode. Among subjects with both a mood and substance use disorder, the mean age of onset was $16.9 ± 3.5$ and $16.9 ± 2.4$ years, respectively. Since substance use disorders in most instances onset during or following the first major mood episode, we calculated the morbid risk for the development of substance use disorders in high risk subjects with versus without a mood disorder. High risk subjects without a history of mood disorder had 18% age-adjusted morbid risk of substance use disorder. Among those high risk subjects with a history of

Table 2
Results of Cox proportional hazard model analysis.

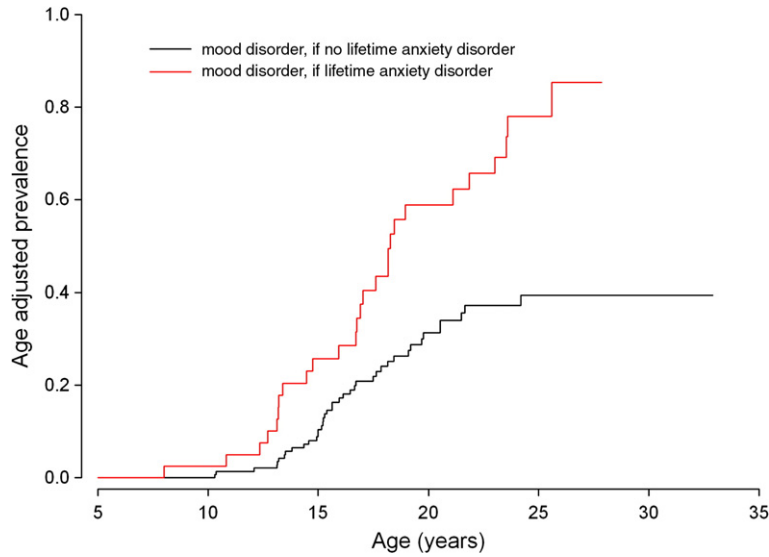| Outcome (dependent variable)	Independent variable	β	SE β	Hazard ratio (95% CI)	p
Presence of major mood disorder	Anxiety disorder	0.96	0.25	2.60 (1.59–4.25)	0.0003
	Substance use disorder	0.75	0.26	2.12 (1.26–3.58)	0.007
Presence of substance use disorder	Major mood disorder	0.87	0.35	2.4 (1.20–4.76)	0.01

Fig. 2. Risk of mood disorders in subjects with and without a history of anxiety disorders.

major mood disorder, the age-adjusted morbid risk of substance use disorder was 35%, with a hazard ratio of 2.4; 95%CI = 1.20–4.76 (Table 2).

3.5. Clinical stages of bipolar disorder among high risk offspring

As a test of the proposed staging model, we plotted the temporal sequence of psychopathology for all high risk offspring meeting lifetime diagnostic criteria for BD of which there were 21 subjects, see Fig. 3.

In Table 3, we report the mean age of onset for lifetime psychiatric diagnoses for these same 21 subjects meeting DSM-IV lifetime criteria for BD. Although not all subjects manifested all clinical stages, the sequence (non-mood → minor mood/adjustment → major depression → hypomania/mania) was followed by 15/21 subjects (71%). Nineteen out of 21 subjects

(90%) followed the progression from non-mood → minor mood/adjustment disorders → major mood disorders.

Nine of the 21 subjects (43%) with a diagnosis of BD experienced ADHD, anxiety or sleep disorders. In all of these cases the anxiety or sleep disorder preceded the onset of first major mood episode (sign test, $p = 0.008$). Eight of the 21 subjects (38%) experienced a minor mood disturbance as defined by either a depression NOS, mood disorder NOS or an adjustment disorder with depressed and/or anxious symptoms. In all but one subject, the onset of the minor mood disorder preceded the first major mood episode (sign test, $p = 0.07$).

In 16 out of 21 (76%) subjects who met diagnostic criteria for BD, the first major mood episode was depressive ($p = 0.01$). When taking minor mood episodes (depression NOS) into account, 18 out of 21 subjects (86%) had either a major or minor depression as the first episode (sign test
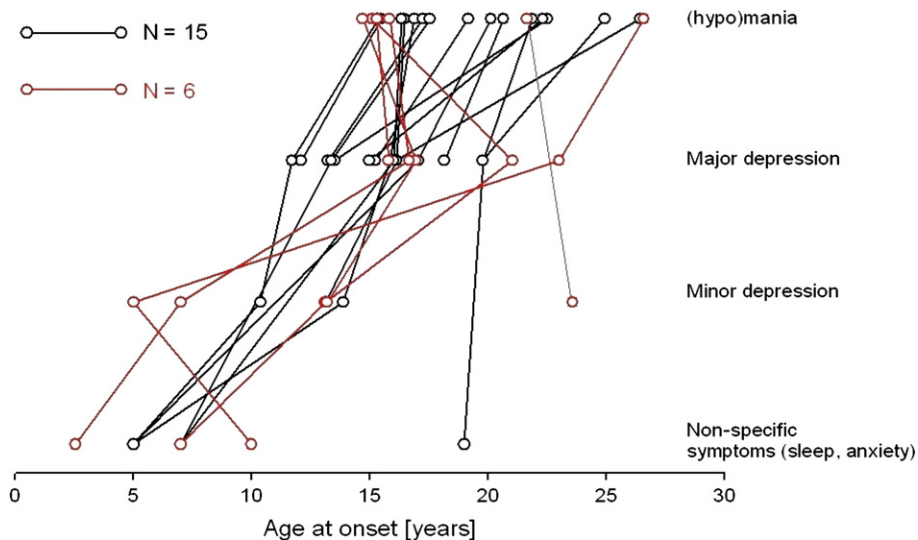

Fig. 3. Age of onset of diagnosable disorders in high risk subjects with bipolar disorder.

Table 3
Lifetime diagnoses in high risk offspring meeting DSM-IV diagnostic criteria for bipolar disorder.

Subject	Diagnosis [a]	Sex	Age of onset of non-mood disorder	Non-mood disorder diagnosis	Age of onset of minor mood disorder	Minor mood disorder diagnosis	Age of onset of index major depressive episode	Age of onset index hypomanic/manic, episode
1	BD I	M	19.0	Anxiety	–	–	19.8	21.9
2	BD I	M	–	–	–	–	12.1	15.5
3	BD I	M	5.0	ADHD [b]	13.9	Mood NOS [c]	15.9	16.9
4	BD I	M	–	–	–	–	13.2	17.2
5	BD I	F	–	–	23.6	Dep NOS		21.7
6	BD I	F	–	–	–	–	18.2	20.7
7	BD I	F	–	–	–	–	19.8	24.9
8	BD I	F	10.0	Anxiety	5.0	Adjustment	23.0	26.6
9	BD II	M	–	–	–	–	13.5	22.5
10	BD II	F	7.0	Anxiety	13.1	Dep NOS	21.0	15.1
11	BD II	M	–	–	–	–	16.1	26.4
12	BD II	F	–	–	13.2	Dep NOS	16.9	14.7
13	BD II	F	–	–	13.1	Dep NOS	16.1	16.5
14	BD II	M	–	–	–	–	15.8	15.3
15	BD II	F	7.0	Anxiety	–	–	13.4	17.5
16	BD II	F	–	–	–	–	15.2	19.2
17	BD II	F	2.5	Sleep	7.0	Adjustment	16.7	15.8
18	BD II	M	5.0	Anxiety	–	–	17.0	20.1
19	BD II	F	7.0	Anxiety	–	–	16.0	16.3
20	BD II	F	–	–	–	–	15.0	22.3
21	Sch-BD	F	5.0	ADHD	10.4	Dep NOS	11.7	15.4

[a] BD I, bipolar disorder I; BD II, bipolar disorder II; Sch-BD, schizoaffective-bipolar disorder.
[b] Attention deficit/hyperactivity disorder.
[c] Not otherwise specified.

$p = 0.002$). Finally, 48% of the BD subjects would have met diagnostic criteria for BD NOS at an earlier stage of illness on the basis of at least one major depressive episode and full-threshold hypomanic symptoms falling short of the one week DSM-IV duration criterion.

4. Discussion

There was a significantly increased risk of both mood and non-mood disorders including sleep, anxiety and substance use disorders, but not ADHD, among the offspring of parents with well-characterized BD compared to offspring of well parents. The first major mood episode in the overwhelming majority of high risk offspring was depression, occurring in mid-adolescence. The presence of anxiety disorders among the high risk offspring more than doubled the risk of developing a major mood disorder, on average 8 years after meeting full diagnostic criteria for the anxiety disorder. Moreover, having a mood disorder was associated with almost double the risk for developing a substance use disorder. In the majority of cases, subjects diagnosed with BD followed a predictable sequence of evolving psychopathology. Specifically, a number of children developed sleep and anxiety disorders, then around puberty minor depressive symptoms and sensitivity to stress. Subsequently, in mid-adolescence, recurrent major depressive episodes onset followed several years later by activated mood episodes. These observations collectively support the utility of a clinical staging model in BD.

The evolution from non-mood antecedents to mood disorders represents a departure from the findings reported in classical studies of adult patients with established illness. Specifically, earlier observations in adults suggested an abrupt onset of major mood episodes starting in late adolescence and early adulthood, which in some patients followed milder attenuated mood disturbances (Angst, 1986; Kraepelin, 1921). These studies did not report an elevated risk of non-mood psychopathological antecedents in childhood. This may reflect the fact that both Kraepelin and Angst described patients identified through hospitalization, and had to rely on retrospective information in order to reconstruct the onset and pre-hospitalization course of illness. Further, biases associated with retrospective recall may have been amplified by the effects of psychosis, medication and duration of illness.

The increased risk of non-mood psychopathology in those developing mood disorders is congruent with several other studies. The Dunedin study reported on heterotypic associations between childhood psychiatric disorders and subsequent psychopathological manifestations in early adulthood (Kim-Cohen et al., 2003). Genetic studies have shown that childhood anxiety disorders, but not childhood depressive disorders, share a genetic predisposition with adolescent depression (Eaves et al., 2003). Finally other high risk studies have reported an evolution of psychopathology over development in keeping with our own observations (Akiskal et al., 1985; Hammen et al., 1990; Shaw et al., 2005).

Ours is the first study to report on the prognostic impact of non-mood psychopathology for the later development of BD among longitudinally assessed high risk offspring. This observation has important clinical and research implications. A positive family history of BD is the strongest single risk factor for the development of related mood disorders. Previous studies have estimated the relative risk of BD among the offspring of affected parents at around 10 to 15 fold that of the general population risk (Duffy et al., 2000; Hodgins et al., 2002; Lapalme et al., 1997). However, the majority of first degree relatives of bipolar probands do not develop the illness (Rice et al., 1987). Currently we lack

clinical or biological markers which would allow us to identify among those at familial risk who will become ill.

From our observations over almost 15 years, we have preliminary evidence that anxiety disorders manifesting in individuals at familial risk for BD represent an early stage of BD and thus may assist in the early identification of "ultra-high risk" individuals who will go on to develop BD. Combining familial risk with the presence of an anxiety disorder elevated the age-adjusted risk of a major mood disorder in our cohort to over 80%. In other words, whereas the majority of offspring of bipolar parents will remain unaffected, the majority of offspring of bipolar parents who manifest anxiety disorders, will develop a major mood disorder later in life. It is also remarkable that this harbinger of future mood disorder in high risk subjects appears on average 8 years prior to the index major mood episode. This time interval may become greater as more high risk subjects go on to develop a mood disorder with further longitudinal observation.

The developmental trajectory of mood disorder in the high risk offspring, from depression in mid-adolescence to the first activated episode (hypomanic/manic) on average 3 years later (in all cases after the age of 14), stands in contradiction to recent descriptions of mania in very young children. That is, some researchers have proposed that very young children manifesting a syndrome characterized by ADHD, behavioral problems, chronic irritability and rapid mood cycling are suffering from an early severe form of BD usually referred to as pediatric-BD (Biederman et al., 1999; Geller et al., 2008). Others contend that this clinical presentation is more likely a non-specific predictor of variable psychiatric outcomes and not an early form of BD (Dubicka et al., 2007; Harrington and Myatt, 2003; Klein et al., 1998). Our observations from prospective follow up of offspring of carefully diagnosed parents with BD support the latter view.

There are fundamental differences between the early clinical stages of BD described in our high risk subjects compared to the presentations of pediatric-BD described in clinically referred children unselected for family history. In our study, over 60% of the subjects affected for a mood disorder were female, and the early childhood disturbances tended to be sleep and/or anxiety disorders, not behavioral or conduct disorders. In addition, we did not find an increased rate of ADHD or LD among the high risk offspring compared to controls. Further, diagnosable mood disorders began to manifest only in early adolescence and there were no diagnosable hypomanic or manic episodes in childhood. Last but not the least, the depressive and hypomanic/manic episodes we did observe were generally typical, characterized by a refractory depressed or euphoric mood, respectively; as opposed to chronic irritability and/or ultra-rapid cycling.

High risk studies starting with more homogenous carefully diagnosed bipolar parents and including prospective repeated assessments of the offspring are congruent with our observations. Specifically, these studies support the finding that hypomanic and manic episodes with relatively classical features do not manifest until at least mid-adolescence, although sub-threshold mood symptoms and non-mood disorders (anxiety, sleep) may be antecedents (Akiskal et al., 1985; Hillegers et al., 2005; Shaw et al., 2005). While prospective observations of clinical populations of children diagnosed with BD report much earlier onsets and atypical clinical presentations (Birmaher and Axelson, 2006; Leibenluft et al., 2003a, b), the consistency of the bipolar diagnosis is very low in longitudinal follow up, especially in youth with psychotic symptoms and in those with a history of early childhood psychopathology (Carlson et al., 2008; Hazell et al., 2003; Meyer and Carlson, 2003).

Overall, we did not find an elevated rate of ADHD in our high risk sample compared to controls, as reported in some other high risk studies (Chang et al., 2000). In a recent study involving a large heterogeneous sample of bipolar families, the significantly increased rate of ADHD in high risk compared to control offspring became non-significant after adjusting for possible confounding variables, including socio-economic status and non-bipolar psychopathology in the control parents (Birmaher et al., 2009). In a prior report, we found an elevated rate of ADHD and/or LD among the offspring of lithium non-responders compared to the offspring of lithium responders and to controls (Duffy et al., 2007a). We did not have sufficient numbers to compare between high risk subgroups in this analysis, although our data suggests that cognitive difficulties may be present in some high risk offspring as part of a specific subgroup characterized by neurodevelopmental antecedents (cluster A traits, ADHD, LD), non-completely remitting mood disorders and parents whose BD does not respond to prophylactic lithium.

The staging sequence supported by our high risk data has direct implications for treatment. The current DSM diagnostic approach lends itself to polypharmacy as there is the embedded assumption that different diagnoses represent independent disorders, each requiring a separate treatment. As discussed by Reichart and others (DelBello et al., 2001; Reichart and Nolen, 2004) there is a risk of unmasking latent BD by treating high risk children with psychostimulants. Similarly, without considering the familial risk or the developmental course of illness, early manifestations of latent BD may often be treated with some form of psychotherapy and/or antidepressants. In symptomatic offspring at genetic risk for BD, the recommended treatments for anxiety or depression may be unhelpful and potentially harmful considering the high risk of suicide associated with untreated BD (Muller-Oerlinghausen et al., 1992) and the risk of paradoxical worsening associated with antidepressants (Duffy, 2006; O'Donovan et al., 2008). It is not known but worthwhile studying, if by treating anxious or depressed patients at genetic risk for BD with mood stabilizers, we might positively influence the future illness course. Furthermore, the observation that substance use disorder is a major complication of mood disorder in the high risk population provides an opportunity for studying specific risk factors and testing early and possibly preventive interventions.

In terms of limitations, it should be noted that the observations described in this report relate only to youths at familial risk of BD and not to community based or referred populations unselected for family history. Therefore, in populations not at familial risk for BD, childhood anxiety, sleep and/or minor mood disturbances should not be viewed as early stages of BD; a point made earlier by Carlson (Carlson and Weintraub, 1993) among others. The conclusions are also limited in this report by the small numbers of subjects meeting full diagnostic criteria for BD ($n = 21$). In the initial analyses we included all high risk subjects meeting diagnostic

criteria for at least one major mood episode ($n = 67$) given the high likelihood that UP disorders represent latent BD in these families (Blacker and Tsuang, 1993). We would like to raise the point that BD in offspring at genetic risk appears to present in clinical stages and starts for many in childhood; however, we are not suggesting that in all individuals BD evolves in this way. Finally, we require longer observation of larger numbers of high risk offspring developing BD to confirm the findings reported here.

The findings from this analysis raise questions as to why BD manifests in a sequence of non-specific psychopathological presentations. Speculations would have to include the possibility that central nervous system maturation plays an important role in mediating the nature of the clinical manifestations of the underlying genetic inheritance. As well, we would have to take into consideration important aspects including the interaction of genetic risk with other mediating and moderating influences. Finally, we agree with McGorry et al. (2006) that mapping the pathological correlates associated with clinical stages would increase the validity and utility of staging in BD and would shed light on mechanisms that explain, or factors that intensify, illness progression. For now, it is clear that we need to incorporate the family history and the nature of the longitudinal course in diagnostic assessments of young patients manifesting psychiatric symptoms in order to put these relatively non-specific early presentations in a clinically meaningful context.

References

Akiskal, H.S., 1995. Developmental pathways to bipolarity: are juvenile-onset depressions pre-bipolar? Journal of the American Academy of Child and Adolescent Psychiatry 34 (6), 754–763.

Akiskal, H.S., Downs, J., Jordan, P., Watson, S., Daugherty, D., Pruitt, D.B., 1985. Affective disorders in referred children and younger siblings of manic-depressives. Mode of onset and prospective course. Archives of General Psychiatry 42 (10), 996–1003.

Alda, M., Grof, P., 2000. Genetics and lithium response in bipolar disorders. In: Soares, J.C., Gershon, S. (Eds.), Basic Mechanisms and Therapeutic Implications of Bipolar Disorder. InMarcel Dekker, New York, pp. 529–543.

Angst, J., 1986. The course of affective disorders. Psychopathology 19 (Suppl 2), 47–52.

Angst, J., Sellaro, R., 2000. Historical perspectives and natural history of bipolar disorder. Biological Psychiatry 48 (6), 445–457.

Angst, J., Stassen, H.H., Gross, G., et al., 1990. Suicide in affective and schizoaffective disorders. In: Maneros, A., Tsuang, M.T. (Eds.), Affective and Schizoaffective Disorders. InSpringer, Berlin, pp. 168–185.

Angst, J., Gamma, A., Neuenschwander, M., jdacic-Gross, V., Eich, D., Rossler, W., Merikangas, K.R., 2005. Prevalence of mental disorders in the Zurich Cohort Study: a twenty year prospective study. Epidemiologia e psichiatria sociale 14 (2), 68–76.

Berk, M., Hallam, K.T., McGorry, P.D., 2007. The potential utility of a staging model as a course specifier: a bipolar disorder perspective. Journal of Affective Disordorders 100 (1–3), 279–281.

Biederman, J., Mick, E., Prince, J., Bostic, J.Q., Wilens, T.E., Spencer, T., et al., 1999. Systematic chart review of the pharmacologic treatment of comorbid attention deficit hyperactivity disorder in youth with bipolar disorder. Journal of Child and Adolescent Psychopharmacology 9, 247–256.

Birmaher, B., Axelson, D., 2006. Course and outcome of bipolar spectrum disorder in children and adolescents: a review of the existing literature. Development and Psychopathology 18, 1023–1035.

Birmaher, B., Axelson, D., Monk, K., Kalas, C., Goldstein, B., Hickey, M.B., Obreja, M., Ehmann, M., Iyengar, S., Shamseddeen, W., Kupfer, D., Brent, D., 2009. Lifetime psychiatric disorders in school-aged offspring of parents with bipolar disorder: the Pittsburgh Bipolar Offspring study. Archives of General Psychiatry 66 (3), 287–296.

Blacker, D., Tsuang, M.T., 1993. Unipolar relatives in bipolar pedigrees: are they bipolar? Psychiatric Genetics 3, 5–16.

Carlson, G.A., Weintraub, S., 1993. Childhood behavior problems and bipolar disorder — relationship or coincidence? Journal of Affective Disorders 28 (3), 143–153.

Carlson, G., Kotov, R., Bromet, E.J., 2008. Child psychopathology and outcome in psychotic bipolar disorder. American Academy of Child and Adolescent Psychiatry Scientific Proceedings 58 Ref Type: Abstract.

Chang, K.D., Steiner, H., Ketter, T., 2000. Psychiatric phenomenology of child and adolescent bipolar offspring. Journal of the American Academy of Child and Adolescent Psychiatry 39, 453–460.

Coryell, W., Endicott, J., Maser, J.D., Keller, M.B., Leon, A.C., Akiskal, H.S., 1995. Long-term stability of polarity distinctions in the affective disorders. The American Journal of Psychiatry 152 (3), 385–390.

DelBello, M.P., Geller, B., 2001. Review of studies of child and adolescent offspring of bipolar parents. Bipolar Disorders 3, 325–334.

DelBello, M.P., Soutullo, C.A., Hendricks, W., Niemeier, R.T., McElroy, S.L., Strakowski, S.M., 2001. Prior stimulant treatment in adolescents with bipolar disorder: association with age at onset. Bipolar Disorders 3, 53–57.

Dubicka, B., Carlson, G.A., Vail, A., Harrington, R., 2007. Prepubertal mania: diagnostic differences between US and UK clinicians. European Child and Adolescent Psychiatry 649–657.

Duffy, A., 2006. Lithium treatment in children and adolescents: a selected review and integration of research findings. In: Bauer, M., Grof, P., Muller-Oerlinghausen, B. (Eds.), Lithium in Neuropsychiatry: The Comprehensive Guide. InTaylor & Francis Book Ltd, London, UK, pp. 193–206.

Duffy, A., 2007. Does bipolar disorder exist in children? A selected review. Canadian Journal of Psychiatry 52, 409–417.

Duffy, A., Alda, M., Kutcher, S., Fusee, C., Grof, P., 1998. Psychiatric symptoms and syndromes among adolescent children of parents with lithium-responsive or lithium-nonresponsive bipolar disorder. The American Journal of Psychiatry 155, 431–433.

Duffy, A., Grof, P., Robertson, C., Alda, M., 2000. The implications of genetic studies of major mood disorders for clinical practice. Journal of Clinical Psychiatry 61, 630–637.

Duffy, A., Alda, M., Kutcher, S., Cavazzoni, P., Robertson, C., Grof, E., Grof, P., 2002. A prospective study of the offspring of bipolar parents responsive and non-responsive to lithium treatment. Journal of Clinical Psychiatry 63, 1171–1178.

Duffy, A., Alda, M., Crawford, L., Milin, R., Grof, P., 2007a. The early manifestations of bipolar disorder: a longitudinal prospective study of the offspring of bipolar parents. Bipolar Disorders 9, 828–838.

Duffy, A., Alda, M., Milin, R., Grof, P., 2007b. A consecutive series of treated affected offspring of parents with bipolar disorder: is response associated with the clinical profile? The Canadian Journal of Psychiatry 52, 369–375.

Duffy, A., Milin, R., Grof, P., 2009. Maintenance treatment of adolescent bipolar disorder: open study of the effectiveness and tolerability of quetiapine. BioMed Central Psychiatry 9 (4), 1–10.

Duffy, A., Alda, M., Hajek, T., Grof, P., 2009. The early course of bipolar disorder in a prospective study of high-risk offspring. British Journal of Psychiatry 195 (5), 457–458.

Eaves, L., Silberg, J., Erkanli, A., 2003. Resolving multiple epigenetic pathways to adolescent depression. Journal of Child Psychology and Psychiatry 44 (7), 1006–1014.

Endicott, J., Spitzer, R.L., 1978. A diagnostic interview: the schedule for affective disorders and schizophrenia. Archives of General Psychiatry 35 (7), 837–844.

Garber, J., 2006. Depression in children and adolescents: linking risk research and prevention. American Journal of Preventive Medicine 31 (6 Suppl 1), S104–S125.

Geller, B., Tillman, R., Bolhofner, K., Zimerman, B., 2008. Child bipolar I disorder: prospective continuity with adult bipolar I disorder; characteristics of second and third episodes; predictors of 8-year outcome. Archives of General Psychiatry 65, 1125–1133.

Hammen, C., Burge, D., Burney, E., Adrian, C., 1990. Longitudinal study of diagnoses in children of women with unipolar and bipolar affective disorder. Archives of General Psychiatry 47, 1112–1117.

Harrington, R., Myatt, T., 2003. Is pre-adolescent mania the same condition as adult mania? A British perspective. Biological Psychiatry 53, 961–969.

Hazell, P.L., Carr, V., Lewine, T.J., Sly, K., 2003. Manic symptoms in young males with ADHD predict functioning but not diagnosis after 6 years. Journal of the American Academy of Child and Adolescent Psychiatry 42 (5), 552–560.

Hillegers, M.H., Reichart, C.G., Wals, M., Verhulst, F.C., Ormel, J., Nolen, W.A., 2005. Five-year prospective outcome of psychopathology in the adolescent offspring of bipolar parents. Bipolar Disorders 7, 344–350.

Hodgins, S., Faucher, B., Zarac, A., Ellenbogen, M.A., 2002. Children of parents with bipolar disorder: a population at high risk for major affective disorders. Child and Adolescent Psychiatric Clinics of North America 11, 533–554.

Judd, L.L., Akiskal, H.S., 2003. The prevalence and disability of bipolar spectrum disorders in the US population: re-analysis of the ECA database taking into account subthreshold cases. Journal of Affective Disordorders 73 (1–2), 123–131.

Kim-Cohen, J., Caspi, A., Moffitt, T.E., Harrington, H., Milne, B.J., Poulton, R., 2003. Prior juvenile diagnoses in adults with mental disorder: developmental follow-back of a prospective-longitudinal cohort. Archives of General Psychiatry 60 (7), 709–717.

Klein, R.G., Pine, D.S., Klein, D.F., 1998. Resolved: mania is mistaken for ADHD in prepubertal children. Debate forum: negative. Journal of the American Academy of Child and Adolescent Psychiatry 37, 1093–1096.

Kraepelin, E., 1921. Manic-Depressive Insanity and Paranoia. Edinburgh, Livingston.

Lapalme, M., Hodgins, S., Laroche, C., 1997. Children of parents with bipolar disorder: a meta-analysis of risk for mental disorders. The Canadian Journal of Psychiatry 42, 623–631.

Leibenluft, E., Charney, D.S., Towbin, K.E., Bhangoo, R.K., Pine, D.S., 2003a. Defining clinical phenotypes of juvenile mania. The American Journal of Psychiatry 160, 430–437.

Leibenluft, E., James, R., Blair, R., Charney, D.S., Pine, D.S., 2003b. Irritability in pediatric mania and other childhood psychopathology. Annals of the New York Academy of Sciences 1008, 201–218.

MacQueen, G.M., Young, L.T., Joffe, R.T., 2001. A review of psychosocial outcome in patients with bipolar disorder. Acta Psychiatrica Scandinavica 103 (3), 163–170.

McGorry, P., Killackey, E., Yung, A., 2008. Early intervention in psychosis: concepts, evidence and future directions. World Psychiatry 7, 148–156.

McGorry, P.D., Hickie, I.B., Yung, A.R., Pantelis, C., Jackson, H.J., 2006. Clinical staging of psychiatric disorders: a heuristic framework for choosing earlier, safer and more effective interventions. Australia and New Zealand Journal of Psychiatry 40 (8), 616–622.

Meyer, S.E., Carlson, G., 2003. Bipolar disorder in youth: an update. Current Psychosis and Therapeutics Reports 1, 79–84.

Muller-Oerlinghausen, B., Ahrens, B., Grof, E., Grof, P., Lenz, G., Schou, M., Simhandl, C., Thau, K., Volk, J., Wolf, R., 1992. The effect of long-term lithium treatment on the mortality of patients with manic-depressive and schizoaffective illness. Acta Psychiatrica Scandinavica 86 (3), 218–222.

Muller-Oerlinghausen, B., Wolf, T., Ahrens, B., Schou, M., Grof, E., Grof, P., Lenz, G., Simhandl, C., Thau, K., Wolf, R., 1994. Mortality during initial and during later lithium treatment. A collaborative study by the International Group for the Study of Lithium-treated Patients. Acta Psychiatrica Scandinavica 90, 295–297.

O'Donovan, C., Garnham, J.S., Hajek, T., Alda, M., 2008. Antidepressant monotherapy in pre-bipolar depression; predictive value and inherent risk. Journal of Affective Disordorders 107 (1–3), 293–298.

Phillips, L.J., Yung, A.R., Yuen, H.P., Pantelis, C., McGorry, P.D., 2002. Prediction and prevention of transition to psychosis in young people at incipient risk for schizophrenia. American Journal of Medical Genetics 114 (8), 929–937.

Reichart, C.G., Nolen, W.A., 2004. Earlier onset of bipolar disorder in children by antidepressants or stimulants? An hypothesis. Journal of Affective Disordorders 78 (1), 81–84.

Rice, J., Reich, T., Andreasen, N.C., Endicott, J., Van Eerdewegh, M., Fishman, R., Hirschfeld, M.A., Klerman, G.L., 1987. The familial transmission of bipolar illness. Archives of General Psychiatry 44, 441–447.

Shaw, J.A., Egeland, J.A., Endicott, J., Allen, C.R., Hostetter, A.M., 2005. A 10-year prospective study of prodromal patterns for bipolar disorder among Amish youth. Journal of the American Academy of Child and Adolescent Psychiatry 44 (11), 1104–1111.

Smoller, J.W., Finn, C.T., 2003. Family, twin, and adoption studies of bipolar disorder. American Journal of Medical Genetics Part C (Semin. Med. Genet.) 123C, 48–58.