Being a Child of a Bipolar Parent

Psychopathology, Social Functioning and Family Functioning

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Being a Child of a Bipolar Parent

Psychopathology, Social Functioning and Family Functioning

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General introduction

General introduction

"At first everything seemed so easy. I raced about like a crazed weasel, bubbling with plans and enthusiasms, immersed in sports, and staying up all night, night after night, out with friends, reading everything that wasn't nailed down, filling manuscript books with poems and fragments of plays, and making expansive, completely unrealistic, plans for my future. The world was filled with pleasure and promise; I felt great. Not just great, I felt really great. I felt I could do anything, that no task was to difficult. My mind seemed clears and fabulously focused, and able to make intuitive mathematical leaps that had up to that point entirely eluded me. Indeed they elude me still. At the time however, not only did everything make perfect sense, but it all began to fit into a marvellous kind of cosmic relatedness. My sense of enchantment with the laws of the natural world caused me to fizz over, and I found myself buttonholing my friends to tell them how beautiful it all was. They were less than transfixed by the insights into the webbings and beauties of the universe, although considerably impressed by how exhausting it was to be around my enthusiastic ramblings: You're talking to fast, Kay. Slow down, Kay. You're wearing me out, Kay. Slow down, Kay. And those times when they didn't actually come out and say it, I still could see it in their eyes: For God's sake, Kay, slow down.

I did, finally, slow down. In fact I came to a grinding halt. My thinking, far from being clearer than a crystal, was tortuous. I would read the same passage over and over again only to realize that I had no memory at all for what I had just read. Each book or poem I picked up was the same way. Incomprehensible. Nothing made sense. I could not begin to follow the material presented in my classes, and I would find myself staring out the window with no idea of what was going on around me. It was very frightening. My mind was incapable of concentrated thought and turned time and again to the subject of death: I was going to die, what difference did anything make? I was totally exhausted and could scarcely pull myself out of bed in the mornings. I wore the same clothes over and over again, as it was otherwise too much of an effort to make a decision about what to put on. Then a grey, bleak preoccupation with death, dying, decaying, that everything was born but to die, best to die now and save the pain while waiting. I dragged exhausted mind and body around a local cemetery, ruminating about how long each of its inhabitants had lived before the final moment. I sat on the graves

writing long, dreary, morbid poems, convinced that my brain and body were rotting, that everyone knew and know one would say."
(Cited from: An unquiet mind: A memoir of moods and madness, by Kay Redfield Jamison, 1995)

Kay Redfield Jamison, Professor of Psychiatry at the Johns Hopkins University School of Medicine, suffered her first attack of bipolar disorder, a psychiatric illness characterized by severe mood swings, at the age of seventeen. The above mentioned citation is an exquisite example of the bipolar disorder in the early stages: after episodes in which she felt unhappy, this was her first manic episode, tiresome for the surroundings and exhausting for the patient, but not disturbingly over the top. The immediately following depressive episode however was more severe. Next to having a bipolar disorder herself, Kay Redfield Jamison is a child of a bipolar parent. When she was fifteen, her father, a brilliant scientist, suffered very severe depressions, after a period of grandiosity.

Children of parents with a bipolar disorder are the main topic of this thesis. Compared to children from healthy parents, these children have an increased risk to get bipolar disorder and other mood disorders. What are early symptoms of the bipolar disorder? How do they function compared to children in the general population? To find answers to these and other questions we started a study among 140 children of parents with a bipolar disorder.

After describing the overall aim of the study among children of parents with a bipolar disorder, the global aims of this thesis are discussed. Next, an overview of the clinical characteristics of bipolar disorder in adulthood, adolescence and childhood, and the results of previous high risk studies are discussed. Subsequently, the design and the studies included in this thesis are briefly described. Finally, some major previous findings of this study are described.

Overall aim for studying children of parents with bipolar disorder

Many studies have been conducted regarding the phenomenology, biology and treatment of patients with fully developed bipolar disorder. However, not as much attention has been focussed on the early stages of the illness. Theoretically, by intervening before the onset of full-blown bipolar disorder, the disorder may be prevented or at least ameliorated in its severity, necessitating less treatment later in life and preventing high morbidity and poor social and vocational functioning. Therefore one should know how to detect people at risk to develop bipolar disorder: what are the early signs (prodromal features) of the illness? How does the illness develop from these early signs to the full disorder? What are the risk factors? What are the protective factors?

The early development of bipolar disorder is mainly known from retrospective reports obtained from patients already diagnosed with bipolar disorder. A problem in these reports is the often long delay, not only between the onset of first symptoms and the onset of the first (hypo) manic episode, but also from the first (hypo) manic episode to the formal diagnosis made by a clinician. After so many years the recall on what has happened before onset of the illness, may be overshadowed by what has happened later. Therefore, it is very difficult to get a reliable picture.

The most straightforward way to study the development of bipolar disorder would be to follow prospectively a large cohort of children from the general population and to identify new cases with bipolar disorder. However, with an illness with a life time prevalence of 2% such a study would require a very large number of individuals. Therefore it is more practical to study a high risk population. Children of parents with bipolar disorder (heretofore referred to as "bipolar offspring") are at high risk (up to 27%) to develop a bipolar disorder themselves. Therefore, bipolar offspring who have not yet developed bipolar disorder, serve an economic way to demonstrate the early signs and the further progression of bipolar disorder.

Global aims of this thesis

The focus of this thesis is on the functioning and development of children of bipolar parents for two main reasons. First, children of bipolar parents are at genetic risk for developing psychopathology, including bipolar disorder themselves (Alda, 1997;

Gershon et al., 1987; McGuffin & Katz, 1989). Second, children of bipolar parents are subject to environmental stressors partially associated with parental psychopathology and its consequences. These multiple risks may be responsible for multiple types of psychopathology that, in addition, are subject to developmental changes over time. For example, it is possible that the first signs of bipolar disorder are non-specific problems, such as anxiety or mood problems, later followed by the development of a depression that subsequently evolves into a bipolar disorder with also manic episodes. In addition, little is known about the functioning of children of bipolar parents.

Therefore, the global aims of this thesis are:

1. To determine the early symptoms of psychopathology and prevalence and incidence of disorders including mood disorders among the offspring of bipolar parents
2. To determine the prospective course of symptoms
3. To determine at what age these symptoms and disorders start and to test the effects of factors influencing the age at onset
4. To determine the consequences on social functioning and family of being a child of bipolar parents

Definition and epidemiology of bipolar disorder

Beside (unipolar) depressions, bipolar disorder belongs to the mood disorders. In bipolar disorder episodes of mania, hypomania and depression occur in any order over a lifetime. The spectrum of severity ranges from mild cyclothymia to severe bipolar disorder with full blown manic and depressive episodes.

In this thesis we will use the diagnostic criteria as defined by DSM-IV (American Psychiatric Association, 1994). Table 1 shows the DSM-IV definitions of the various episodes as they can occur in patients with bipolar disorder. Based on these episode definitions bipolar disorder can be divided in bipolar I disorder (manic episodes alternating with major depressive episodes or less severe depressions), bipolar II disorder (hypomanic episodes alternating with major depressive episodes) and cyclothymia (recurring hypomanic episodes and mild depressions during more than 2 years).

Together with bipolar disorder not otherwise specified (NOS) (e.g. very rapid alternation (over days) between manic symptoms and depressive symptoms that do not meet minimal duration criteria for a manic or a major depressive episode, or recurrent

hypomanic episodes without intercurrent depressive symptoms) they form what is also called bipolar spectrum disorders.

Table 1: Diagnostic criteria for mood episodes according to DSM-IV (abbreviated)

Major depressive episode *	
Core features	Associated features (4 or more needed)
Depressed mood Loss of Interest	Change of appetite or weight Insomnia or hypersomnia Psychomotor retardation or agitation Fatigue or loss of energy Feelings of worthlessness or guilt Impaired thinking or concentration, or indecisiveness Thoughts of death, or suicidal ideation or plans
Symptoms last at least 2 weeks, and cause significant distress or impairment in social, occupational, or other important areas of functioning	

Manic episode *	
Core features	Associated features (3 or more needed)
Elevated, expansive or irritable mood	Inflated self-esteem or grandiosity Decreased need for sleep More talkative or pressure of speech Flight of ideas or racing thoughts Distractibility Increased activity or psychomotor agitation Involvement in activities with painful consequences
Symptoms last at least 1 week (1 day if hospitalized), and cause significant impairment in social and occupational functioning	

Hypomanic episode *
Core features and associated features as in manic episode.
Symptoms last at least 4 days and are associated with a change in normal functioning, but do not cause marked impairment in social or occupational functioning

Mixed Episode *
Criteria are met for both a manic and a major depressive episode during at least 1 week

* For all episodes the additional requirement must be fulfilled that the symptoms are not due to the direct physiological effects of a substance (drugs of abuse, medication) or a general medical condition

Bipolar disorder in adults

In the Netherlands as in other western countries, both bipolar I disorder and bipolar II disorder have a life time prevalence of around 1 %, while the overall prevalence of bipolar spectrum disorders is estimated to be around 5% (Ten Have et al., 2002.; Regeer et al., 2004). It is more prevalent in persons with a family history of bipolar disorder: among first-degree relatives of a proband with bipolar disorder the risk for bipolar disorder is 6.5% (Kelsoe, 1997) and when this first-degree relative is a parent this risk is even 27% (Gershon et al., 1982). The risk for bipolar disorder among dizygotic twins is 14 % and among monozygotic twins 56% (Torry et al., 1994), indicating that bipolar disorder is at least partially genetically determined. In addition to bipolar disorder, the prevalence of other mood disorders is also increased among first degree relatives (Weissman et al., 1984; Decina et al., 1983; Gershon et al., 1990; Pauls et al., 1992).

The onset of bipolar disorder is often after puberty, with a mean age of 21 years and a median age of 24 years for the first full syndromal episode (Coryell & Winokur, 1982; Depue & Monroe, 1987; Goodwin & Jamison, 1990). In about 60% of the cases the disorder starts with one of more depressive episodes, before the onset of the first hypomanic or manic episode (Werry et al., 1991). It is recognized that many adult patients with a bipolar disorder, with onset during adolescence or later, exhibited symptoms long before they met formal diagnostic criteria of a mood episode. Affective symptoms may predate the onset of illness by average of 10-12 years. In a retrospective study among bipolar patients sampled by mailed questionnaires through the National Depressive and Manic-Depressive Association, 59% of adult patient with bipolar disorder recalled having their first affective symptoms as children or adolescents (Lish et al., 1994). In a more recent retrospective study of 58 adult bipolar patients, the most frequently reported symptoms included episodic changes in mood (Egeland et al., 2000). In a Dutch retrospective study with 55 adult bipolar patients, predictors for diagnostic delay from first symptoms to definitive diagnosis of bipolar disorder were early onset (longer delay), birth cohort (longer in older cohorts) and sexual abuse (Akkerhuis et al., 2000).

Bipolar disorder in adolescents (12-18 years)

It is generally accepted that the classical form of bipolar disorder (Kraepelin, 1929) can be manifested in adolescents and there is consensus that the DSM-IV criteria for bipolar disorder in adults can be applied in this age group as well (Lewinsohn, 2003). In a community sample of high school students in the US, the lifetime prevalence of bipolar disorder was 1%, while 5.7% reported having experienced a distinct period of abnormally and persistently elevated, expansive, or irritable mood (see table 1) even though they never met criteria for bipolar disorder (Lewinsohn et al., 1995). The weighted first incidence of bipolar disorder through age 18 was 1.4%; from ages 19 to 23, it was 0.7%. These rates are comparable to community studies of bipolar disorder in adults in the US (Kessler et al., 1997) and in the Netherlands (Ten Have et al., 2002). The mean age of onset of the first mood disorder for the adolescents was 11.8 years (range 7-15 years) (Lewinsohn et al., 1995). In the majority of cases the first episode was depressed rather than manic. With respect to impaired role functioning, a substantial proportion of adolescents with bipolar disorder exhibited impairment in social (66.7%), family (55.6%), and especially school (83.3%) functioning.

Compared to a control group, adolescents with bipolar disorder have also high prevalence rates of other (comorbid) disorders: anxiety disorder 33% vs. 7% for the controls; ADHD 11% vs. 2.7%; conduct disorder 8.2% vs. 3.0% and substance use 23% vs. 10.4%. These characteristics of adolescents with bipolar disorder, with the exception of comorbid substance use disorder, are strikingly similar to the offspring sample with bipolar disorder described in this thesis (see chapter 8).

Bipolar disorder in children (younger than 12 years)

In contrast to adolescence, there is much more controversy regarding bipolar disorder in children before the age of 12 years, i.e. before puberty. In contrast to most European countries, where child- and adolescent psychiatrists seldom diagnose bipolar disorder in prepubertal children, it is now frequently seen in the United States. However, these children do not fulfil the criteria for bipolar disorder as seen in adults and adolescents and they do not present with the traditional relapsing and remitting illness. According to Geller et al. (1997) childhood-onset bipolar disorder is a non-episodic, chronic, rapid-

cycling, mixed-manic state. There are no community data on the prevalence of bipolar disorder in children. However, according to US colleagues (Wozniak et al. 1995; Biederman et al., 1997) bipolar disorder is relatively common in clinically referred children.

After careful consideration of the evidence, a consensus conference organised in 2004 by the British National Institute for Clinical Excellence (NICE) came to the conclusion that it is possible to establish a diagnosis of bipolar disorder in prepubescent children. However, the conference took the position that the diagnosis should be limited to a narrow phenotype (i.e. bipolar I disorder with even tighter criteria than for adults), and that this is rare in prepubescent children. Although children can present with many features of bipolar disorder and presentation tends to be atypical compared with adults, the conference was not convinced that evidence exists to support the use of diagnoses of bipolar II disorder or bipolar disorder NOS for prepubescent children.

In contrast to multiple studies of the naturalistic course of adolescence- and adulthood-onset bipolar disorder, little is known about the longitudinal outcome of childhood-onset bipolar disorder. We are aware of only one 4-year follow-up study by Geller et al. (2004). Of the 91 subjects with childhood-onset bipolar disorder, 77% continued to show a continuous, rapid cycling picture.

Definition and epidemiology of unipolar depressive disorder

Patients who have major depressive episodes without hypomanic or manic episodes are considered suffering from (so called unipolar) depressive disorder. The criteria for a major depressive episode are the same as in bipolar disorder (see table 1).

The lifetime prevalence of major depression in the Netherlands is 14-15.4% (Alonso et al., 2004, Bijl et al., 1998) which is comparable to the prevalence in the US of 11.5 percent (Jonas et al., 2003). There are clear gender differences in the overall prevalence of unipolar depressive disorders. These disorders are almost twice as common amongst women as amongst men: prevalence of major depression for females 20.1% and for males 10.9% (Bijl et al., 1998).

Previous high risk samples to study the prevalence of psychopathology in bipolar offspring

Table 2 summarizes the lifetime prevalences of bipolar disorder, major depressive disorder and any mood disorder for published studies from 1981 up till 2005 among adolescents and young adults who are children of a parent with bipolar disorder. We only included studies that used (semi-)structured diagnostic interviews resulting in psychiatric diagnoses according to formal classification systems such as the various versions of the DSM (DSM-III, DSM-III-R and DSM-IV). In addition, we only included the studies that at least partially covered the same age group as our study (12-26 years).

Table 2: Life time prevalences of mood disorders in studies among the adolescent and young adult offspring of parents with bipolar disorder

Study	Number of children	Age in years	Any mental disorder	Any mood disorder	Major depressive disorder	Bipolar disorder	Type of bipolar disorder in parent	Treatment setting of parent
Decina et al., 1983	31	7-14	52%	26%	?	0%	I + II	Outpatients
Gershon et al., 1985	29	6-17	72%	41%	10%	3%	I	In- and outpatients
Kashani et al., 1985	9	7-17	52%	22%	?	0%	?	Inpatients
Klein et al., 1985	37	15-21	43%	38%	3%	35%	I	Inpatients
Nurnberger et al., 1985	38	15-25	74%	53%	13%	3%	?	?
LaRoche et al., 1987	37	8-25	24%	16%	3%	0%	?	Outpatients
Hammen et al., 1990	18	8-16	72%	61%	22%	0%	I + II	In- and outpatients
Grigoroiu-Serbanescu et al., 1989	72	10-17	61%	9%	?	1%	I	Inpatients
Todd et al., 1996	16	6-17	44%	44%	13%	25%	I + II	Outpatients
Duffy et al., 1998	36	10-25	53%	33%	14%	14%	I	?
Chang et al., 2000	60	6-18	51%	30%	?	13%	I + II	Outpatients
This study, 2004	129	15-26	59%	40%	10%	10%	I + II	Outpatients

Only five studies reported on life time diagnoses (Klein et al., 1986; Hammen et al., 1990; Todd et al., 1996; Duffy et al., 1998; Chang et al., 2000). We did not include the well known and often reported study by Akiskal et al. (1985) as in this study subjects were a selected sample of subjects who were referred because of already existing symptomatology.

Prevalences of mood disorders reported in the studies varied greatly. In the studies which reported on life time prevalences of any mood disorders, these varied between 30% and 61% with a mean of 37%. Life time prevalences of bipolar disorders varied between 0% and 35% with a mean of 10% and of major depressive disorder between 3% and 22% with a mean of 13%. These percentages for any mood disorder are much higher than what has been reported for adolescents in the general population: there are no European data on the lifetime prevalence of mood disorders in the adolescent age range, but in a US study the lifetime prevalence was 20% (Lewinsohn et al. 1995). Therefore, we can conclude that the adolescent offspring of bipolar parents has indeed a substantially increased risk of developing mood disorders compared to adolescents of the general population.

The above mentioned prevalence studies, with the exception of the studies by Chang et al. and Duffy et al., all have a cross-sectional design. Up till now, there are no data published on follow-up measurements of these last two studies. To evaluate the development of psychopathology, including bipolar disorder, among the bipolar offspring, information on prevalence and incidence of psychopathology is needed. This information can only be obtained in a study with a prospective design as the study in this thesis.

Background and outline of this thesis

In the present studies of this thesis we investigated the course of psychopathology in the bipolar offspring, their social functioning, and the functioning of their families.

In a previous paper from of the same study we assessed the life time and the current (2 months) prevalence of psychopathology at the first measurement (Wals et al.,2001). To further determine the development of the psychopathology, we assessed the prevalence and especially the 14-months incidence of psychopathology at the second measurement (*chapter 2*).

The rationale for studying the incidence of psychopathology, and especially mood disorders, in the adolescent offspring is that up till now there is only cross-sectional or retrospective data available on the prevalence of mood disorders. In addition, recently obtained normative data based on self-report rating scales enabled us to more accurately determine the level of psychopathology in our sample than we previously could (by comparing it with the sixth follow-up measurement in 1997 of the Zuid-Holland sample, Hofstra et al., 2000). On the level of DSM-IV defined disorders however, there are, with the exception of the study by Verhulst et al. (1997) on the six month prevalence of psychiatric disorders during adolescence, no Dutch normative data for this age group.

Although changes in life time prevalence across time can give us information on the incidence of disorders, this kind of diagnostic information does not tell us about the course of illness and especially changes in symptomatology over time. From a developmental perspective it is important to obtain a picture of changes across the whole range of symptom severity, including changes that occur below the threshold of a formal diagnosis. We therefore determined the developmental course of self-reported mood symptoms scored on continuous scales in our sample over the whole study period up till the third measurement (*chapter 3*).

For our questions concerning the development of mood symptomatology in the bipolar offspring, we wanted to know whether individuals who were in the early versus late onset affective symptoms trajectories differed in age at onset of bipolar disorder and in the presence of a number of risk factors, including in the age at onset of bipolar disorder in the parents. A distinction between early versus late onset bipolar disorder may potentially be important for understanding heterogeneity within bipolar disorder. Age at onset for any illness may be a marker of etiologic and genetic heterogeneity and can be used to define homogeneous disorder subtypes, which can be used to identify vulnerability genes (Biederman et al., 2000; Faraone et al., 2003).

A different way for the early detection of mood disorders and especially bipolar disorder in bipolar offspring is the use of a specific diagnostic instrument. In two studies we investigated the validity of the General Behavior Inventory (GBI; Depue et al., 1983) an instrument developed to identify bipolar and unipolar mood disorders across the full spectrum of severity, including full blown major depression and bipolar disorder as well as their minor variants such as minor depression and cyclothymia (*chapter 4*), as well its predictive value for the early detection of bipolar disorder in the bipolar offspring group (*chapter 5*).

Adult bipolar patients have impaired social functioning compared to people in the general population. In 2001, the World Health Organization identified bipolar disorder as the ninth leading cause of years lived with disability in the world among people aged 15 to 44 years. Therefore, growing up in a family with a bipolar parent must have great impact on the functioning of bipolar offspring. However, research to address this hypothesis is scarce.

Most studies on social functioning and bipolar disorder are conducted with adult patients. The few previous high risk studies that reported on social functioning and family functioning (Hammen et al., 1990; Chang et al., 2000) concerned bipolar offspring in the school-aged years (8-18 years). Not much is known about individuals' social functioning prior to or shortly after the onset of bipolar disorder. It may be that individuals with future bipolar disorder are already impaired in social functioning before the onset of the disorder. If, for instance, their social functioning during childhood or adolescence is impaired, this may have negative effects on their adult functioning over and above the effects of the bipolar disorder itself. If, on the other hand, individuals with bipolar disorder showed unimpaired social functioning prior and/or shortly after the onset of the disorder, this may have important implications for treatment which then should not be restricted to alleviating symptoms but should also include a focus on preserving adequate social functioning.

To study these questions we compared social functioning of the offspring at the third measurement (age between 16 and 26 years) with social functioning of adolescents and young adults in the general population (*chapter 6*).

Bipolar disorder does not only affect individuals who have the disorder but also their environment, including family members. With bipolar disorder, there is a mutual influence between the affected individual's functioning and the family. Family attitudes can affect the illness course while the illness has a great impact on family distress and functioning (Reinares et al., 2004). There is no information on the perception of offspring themselves about their upbringing in a family with a parent with bipolar disorder.

We studied how offspring living in a family with a bipolar parent perceived their families compared to adolescents and young adults from the general population, and we determined the impact of parental psychopathology versus offspring psychopathology on parental rearing practices (*chapter 7*).

Main research questions of this thesis

In the various studies we addressed the following research questions:

1. What is the prevalence and incidence of psychopathology, especially mood disorders among the offspring of bipolar parents? (chapter 2)
2. What is the course of affective symptomatology and what are determinants for the age of onset of bipolar disorder in the bipolar offspring? (chapter 3)
3. Is it possible to use the General Behavior Inventory (GBI), an instrument to identify bipolar and unipolar mood disorders across the full spectrum of severity, in a population of adolescent offspring of parents with a bipolar disorder? (chapter 4)
4. Is it possible to use of the GBI as a predictor of bipolar disorder in a population of adolescent offspring of parents with a bipolar disorder? (chapter 5)
5. How is the social functioning of the bipolar offspring? (chapter 6)
6. What is the experience of parental rearing of the bipolar offspring? (chapter 7)

KBO-project

By the end of 1997 the "Kinderen van Bipolaire Ouders" study (Dutch for "Children of Bipolar Parents"; KBO-project) was launched.

Inclusion criteria for the study

One of the parents has a bipolar I or II disorder, with children in the age between 12 and 21 years. A family was included into the study only if all adolescents of the family aged 12 to 21 years agreed to participate. Only adolescents without a severe physical disease or handicap and with an IQ of at least 70 were included. After initial contact all consenting adolescents fulfilled these criteria. Children and parents had to give, written informed consent.

Recruitment

The recruitment of the sample is shown in figure 1.

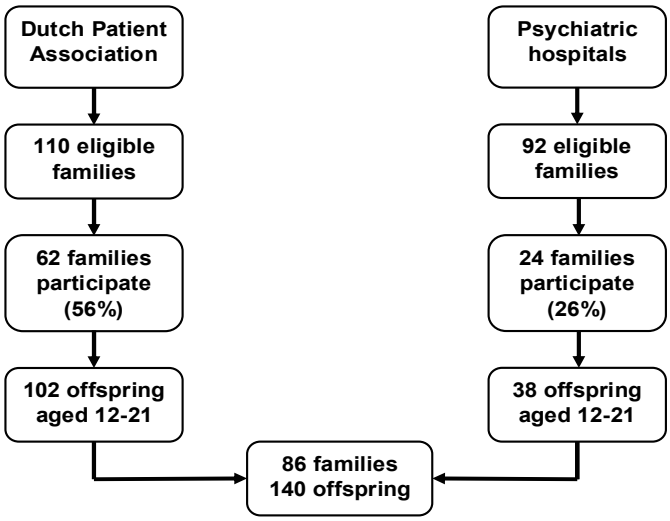

Figure 1: Recruitment of the sample

By the end of 1997 we sent a survey to all 1961 members of the Dutch Association for Manic-Depressives and Relatives (Nederlandse Vereniging voor Manisch-Depressieven en Betrokkenen (VMDB)). This survey explained the aims of the study and included questions concerning the illness of the subjects, family composition and age of the offspring. Of the 712 (36%) who returned the survey, 110 reported that they had one or more children in the age range of 12-21 years. Eventually, 62 out of the eligible 110 parents, so 56% of the bipolar parents who reported to have children in the age range of 12-21 years, agreed to participate with a total of 102 children. In addition, we contacted 9 psychiatric hospitals with an assigned outpatient clinic for patients with bipolar disorder in different regions widely spread over the Netherlands. These 9 psychiatric hospitals identified 91 bipolar patients with children aged 11 to 21 years. Eventually, 24 (26%) of these patients, with a total of 38 children, agreed to participate. All parents were outpatients at the moment of recruitment.

Subjects were enrolled in the study between November 1997 and April 1999. A sample of 140 children, aged 12-21 years, was included in the study. At the second measurement, 14 months after T1, 132 offspring (94% of the original sample) and at the third measurement 129 offspring (92%) agreed to participate again (see figure 2). This thesis is based on results obtained in all three measurements.

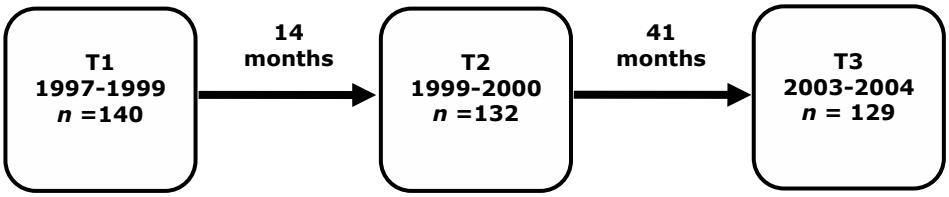

Figure 2: Assessment scheme
T1 = first measurement, T2 = second measurement; T3 = third measurement

Table 3: Demographics characteristics of the KBO-cohort

	n	%	Mean	SD	p
Bipolar fathers	34	40			
Bipolar I disorder	24				
Bipolar II disorder	10				
Divorced	7	20			
Age (years)			46.5	4.7	
Age first episode (years)			25.9	10.7	
Age first manic episode (years)			32	9.8	
Number of hospitalizations			1.9	2.1	
Bipolar mothers	52	60			.06
Bipolar I disorder	40				
Bipolar II disorder	12				
Divorced	12	23			
Age (years)			44.7	4.7	
Age first episode (years)			26.1	9.2	
Age first manic episode (years)			30.4	9.6	
Number of hospitalizations			2.3	2.1	
Non bipolar parents	86				
Age (years)			46.2	5.2	
No psychiatric disorder	59	70			
Mood disorder	21	24			
Other psychiatric disorder	6	6			
Boys	72	51			
Age			16.0	2.72	
IQ			115.0	16.0	
Girls	68	49			.80
Age			16.3	2.72	
IQ			110.7	15.5	
Boys and girls	140				
IQ			113	16	
SES			4.8	2.1	

Description of the sample

The characteristics of the sample at the first measurement are shown in table 3. There were 52 bipolar mothers and 34 bipolar fathers. The majority of them had a bipolar I disorder. Almost a quarter of the parents was divorced. The number of participating boys and girls was almost equal. Boys and girls did not differ in mean age or IQ.

Measures

In order to assess psychopathology and functioning of the offspring, we used three informants: the offspring themselves, their parents and their teachers (Table 4).

Table 4: Sources of information and instruments used in the KBO-study

Offspring	Parents	Teachers
Youth Self-Report (YSR) [4]	Child Behavior Checklist (CBCL) [3]	Teacher's Report Form (TRF) [5]
Young Adult Self-Report (YASR) [6]	Young Adult Behavior Checklist (YABCL) [7]	
Schedule for Affective Disorders and Schizophrenia for School Age Children (K-SADS) [1]	Schedule for Affective Disorders and Schizophrenia for School Age Children (K-SADS) [1]	
Structured Clinical Interview for DSM-IV Axis I Disorders (SCID I) [2]	International Diagnostic Checklist (IDCL)[10]	
General Behavior Inventory (GBI) [8]		
Egna Minnen Beträffande Uppfostran (EMBU) [9]		

To assess and confirm psychopathology in the parents we used the parents themselves and their treating physician.

Bipolar offspring and their parents were interviewed at the first and second measurement by one of the researchers or an intensively trained psychologist using the Schedule for Affective Disorders and Schizophrenia for School Age Children Present and Lifetime Version[1] (K-SADS-PL; Kaufman et al., 1997). The K-SADS is designed to assess current and lifetime DSM-IV diagnoses in children and adolescents, by interviewing the parent(s) and child separately. Because of increasing age of our sample we could not use the K-SADS at the third measurement. Therefore, the Structured Clinical Interview for DSM-IV Axis I Disorders[2] (SCID I, First et al., 1997) was used to determine current

(last month) and past (as of second measurement) psychiatric diagnoses according to DSM-IV.

The Child Behavior Checklist[3] (CBCL; Achenbach, 1991a,b) is a questionnaire to be completed by parents for assessing behavioral/emotional problems for 4- to 18-year-old children. The Youth Self-Report[4] (YSR; Achenbach, 1991a,d) has the same format as the CBCL but has to be completed by 11-18-year-olds themselves.

The Teacher's Report Form[5] (TRF; Achenbach, 1991a,c) can be completed by teachers of 5-18-year-olds. Good reliability and validity of the CBCL, YSR, and TRF have been replicated for the Dutch translations (Verhulst et al., 1996; 1997b,c).

The Young Adult Self-Report[6] (YASR) and Young Adult Behavior Checklist[7] (YABCL) (Achenbach, 1997a,b) are upward extensions of the YSR and CBCL for ages 18 years and older. The YASR is filled out by young adults and the YABCL by parents. The YASR and YABCL can be scored on similar scales as those of the CBCL.

The General Behavior Inventory[8] (GBI; Depue and Klein, 1987) was developed to identify symptoms reflecting a trait-based (i.e. lifetime) measure of unipolar and bipolar affective conditions.

The offspring's perceptions of their parent's rearing behavior was assessed with the Egna Minnen Beträffande Uppfostran[9] (Swedish for "My memories of upbringing"; EMBU), a questionnaire of 81 items answered by the subject on a four point-scale, separately for the mother and the father. We used a short form of the EMBU that contains 23 items and consists of three scales: Rejection, Emotional Warmth and Protection (Arrindel et al., 1999)

The parents were interviewed with the International Diagnostic Checklist[10] (IDCL; Hiller, 1993) in order to check their diagnosis of bipolar disorder.

Results of previous studies of the KBO-study

In order to better understand the various studies of this thesis, it is useful to place them in the context of other studies of the KBO study that have already been published (or are accepted for publication) elsewhere.

The first thesis on this project was by Marjolein Wals (in 2004) concerning the first and second measurement. She addressed the following questions:

1. What is the prevalence of psychopathology at the first measurement? (Wals et al., 2001)
2. What are determinants of mood disorders in children of bipolar parents? The following determinants were examined: familial loading of mood disorders and substance abuse, birth weight, family problems and stressful life events (Wals et al., 2003; Wals et al., 2004)
3. What are determinants of change in level of psychopathology between the first and second measurement, i.e. during a follow-up period of 14 months? (Wals et al., submitted)
4. What is the association between stressful life events and first or recurrent onset of mood disorders during this follow-up of 14 months? (Wals et al., submitted)

Furthermore Manon Hillegers, in the preparation of her thesis, so far completed three papers. The first two of them addressed the following questions:

1. What is the impact of stressful life events, familial loading and their interaction on the onset of mood disorders? (Hillegers et al., 2004)
2. What is the five-year prospective outcome of psychopathology in the adolescent offspring of bipolar parents? (Hillegers et al., 2005)

Regarding the psychopathology at the first measurement, the prevalence of problem behavior and DSM-IV diagnoses among the bipolar offspring, that time aged 12-21 years, was not highly elevated (Wals et al., 2001). On the problem behavior scales, the offspring scored lower than the general population, while the parents scored their offspring more problematic than the general population. The current (= 2 months) prevalence of DSM-IV diagnoses in the offspring was 29%, and the lifetime prevalence was 44%. As far as known, because little research is done in that area, this is comparable to the general population. An exception was the current prevalence of 14% for mood disorders, which was considerable higher than the 6-months prevalence of 7.2% found for the Dutch general population (Verhulst et al., 1997).

All determinants contributed in a different way in the development of psychopathology in the offspring. Familial loading for unipolar disorder and substance use disorder were strong and independent predictors for lifetime mood disorders in the offspring. Familial loading for unipolar disorder was also a strong predictor of increase in

behavioral and emotional problems across the 14-month follow-up interval among the bipolar offspring (Wals et al., submitted). Low birth weight was associated with the development of mood as well as non-mood disorders in the offspring, it did not predict however increase in behavioral and emotional problems. Also family problems did not predict increase in behavioral and emotional problems.

Regarding the experience of stressful life events it was found that these increase the lifetime risk of the onset of a mood disorder and that the impact of life events principally accumulates but at the same time gradually decays as time goes by 25% per year (Hillegers et al., 2004). Furthermore, it was found that this effect was independent of the level of familial loading for unipolar disorders. During follow up, i.e. between the first and second measurement, stressful life events also triggered the onset of a major depressive disorder (Wals et al., 2003). However, prior depressive symptoms also influenced the onset of major depressive disorder. The conclusion was that prior depressive symptoms seem to increase the risk of the occurrence of serious life events as well as a major depressive episode.

The final study regarded the prevalence of psychopathology of the sample at the third measurement (n= 129) (Hillegers et al., 2005). It was found that, compared to the first measurement, the lifetime prevalence of bipolar disorder had increased from 3% to 10%; of overall mood disorders from 27% to 40% and of overall psychopathology from 44% to 59%

In summary, the previous studies showed an increasing level of psychopathology in the bipolar offspring, especially for mood disorders. Important determinants for the development of mood disorders were familial loading with unipolar disorder and substance use disorder, low birth weight and stressful life events.

Chapter 2

Psychopathology in the adolescent offspring of bipolar parents

Psychopathology in the adolescent offspring of bipolar parents

Catrien G. Reichart, Marjolein Wals, Manon H. J. Hillegers, Johan Ormel, Willem A. Nolen and Frank C. Verhulst

Abstract

Background: The aim of this study was to determine the prevalence and 14-months incidence of psychopathology in adolescent offspring of a bipolar parent. *Method:* Parent, teacher and self-report rating scales and Kiddie-SADS were used to assess 132 13–23-year-old offspring of bipolar parents.

Results: Compared to the general population, there were few differences between rating scale scores for bipolar offspring and problem scores for normative adolescents. Of the sample 49% had a lifetime psychiatric disorder, most commonly (33%) a mood disorder.

Limitations: There was no suitable control group and there are no comparison data for psychiatric diagnoses (DSM-IV), based on semi-structured interviews in the adolescent age group in the Netherlands.

Conclusions: The overall level of psychopathology of bipolar offspring was not particularly elevated, but when there were more problems, they tended to be mood disorders.

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Introduction

Bipolar disorder is more prevalent in individuals with a family history of bipolar disorder (Gershon and Cloninger, 1994). In the majority of cases, the disorder starts after puberty with affective symptoms or depressive episodes (Goodwin and Jamison, 1990 and Werry et al., 1991). Because little is known about the onset of bipolar disorder, study of the development of children of bipolar parents is important. In an earlier paper, we reported on the prevalence of psychopathology among 140 children aged 12–21 years of a parent with a bipolar disorder (Wals et al., 2001). We found lower levels of psychopathology than most comparable studies, although the prevalence of mood disorders in our sample was higher than that in adolescents from the general population (Verhulst et al., 1997a). The present study reports on the second measurement of the sample, 14 months after the first. The prevalence and the 14-months incidence of psychopathology was determined.

Method

Population and procedure

A sample of 140 children, aged 12–21 years, of 86 parents with a bipolar I or II disorder was recruited. The recruitment procedure was described in detail by Wals et al. (2001). At 14 months after the first measurement (T1), 132 subjects, aged 13–23 years, were reassessed. Dropouts (n=8; seven girls, one boy) and remainers (n=132) did not differ significantly in age distribution (mean age dropouts 15.8 vs. remainers 17.2; t=1.57, df 138, P=0.12), T1 Child Behavior Checklist (CBCL), Total Problem Scores (mean dropouts 38.67 vs. remainers 25.69; t=1.484, df 100, P=0.141), parental age at onset of bipolar symptoms (mean age dropouts 23.2 vs. remainers 26.4; t=0.76, df 82, P=0.45), and socioeconomic status (mean SES dropouts 3.75 vs. remainers 4.95; t=1.55, df 138, P=0.123).

Instruments

The Child Behavior Checklist (CBCL; Achenbach, 1991a and Achenbach, 1991b), Teacher's Report Form (TRF; Achenbach, 1991a and Achenbach, 1991c) and Youth Self-Report (YSR; Achenbach, 1991a and Achenbach, 1991d) are questionnaires to be

completed, respectively, by parents, teachers and adolescents themselves and can be scored on eight syndrome scales (Withdrawn, Somatic Complaints, Anxious/Depressed, Social Problems, Thought Problems, Attention Problems, Delinquent Behavior and Aggressive Behavior), and two broad-band groupings of syndromes: Internalizing (consisting of the first three scales), and Externalizing (consisting of the last two scales). A total problem score is derived by summing the individual item scores. The good reliability and validity of the CBCL, YSR, and TRF have been replicated for the Dutch translations (Verhulst et al., 1996, Verhulst et al., 1997b and Verhulst et al., 1997c).

The Young Adult Behavior Checklist (YABCL) and Young Adult Self-Report (YASR) are upward extensions of the CBCL and YSR for ages 18 years and older (Achenbach, 1997).

For the comparisons with the parent, teacher and self-report rating scales we selected data from a longitudinal study of an epidemiological sample of Dutch children and adolescents (Verhulst et al., 1985a, Verhulst et al., 1985b, Verhulst et al., 1996, Verhulst et al., 1997a and Hofstra et al., 2000).

The K-SADS-present (2 months) and lifetime version (K-SADS-PL; Kaufman et al., 1997), a semi-structured interviewer oriented diagnostic interview designed to assess current (2 months) and past DSM-IV symptomatology, was used to derive DSM-IV diagnoses. The interviews were performed by three of the investigators (M.W., M.H. and C.R.) and five interviewers with graduate degrees in psychology. All interviewers were intensively trained, and most interviews were discussed with a child/adolescent psychiatrist (C.R.), in order to guarantee consistency between the interviews.

Socioeconomic status (SES) was scored on a 9-point scale of parental occupational level with 1=lowest and 9=highest. If both parents worked, the highest score was used. For the normative sample SES was assessed using a 6-point scale of parental occupation (Van Westerlaak et al., 1975). To make SES scores compatible, we transformed SES scores in both samples into a 3-point scale (1=low, 2=middle; 3=high).

Results

Problem behavior

Analyses of covariance (ANCOVAs) were performed in a 2 group (bipolar vs. comparison) × 2 gender (girls vs. boys) factorial design with age (13–18) and SES (1–3) as covariates to test differences in mean problem scores. To aid readers in judging the practical importance of statistically significant effects, we report effect sizes (ES) evaluated according to the criteria of Cohen (1988), with 1–5.9% of variance indicating small, 5.9–13.8% indicating median and 13.8% or more indicating large effect sizes.

Table 1 shows the mean problem scores as reported by mothers for adolescents aged <19 years on the CBCL, and for adolescents aged ≥19 years on the YABCL; by the adolescents aged <19 years on the YSR and aged ≥19 years on the YASR; and by the teachers for adolescents aged 11–19 years on the TRF.

DSM-IV diagnoses

Table 2 shows the prevalence of the current and the lifetime K-SADS/DSM-IV diagnoses in the adolescents at T1 and at T2 in our sample as well as the 14-months incidence. At T2 65 adolescents (49%) met criteria for any lifetime disorder and 43 (33%) for any lifetime mood disorder, including five (4%) with a bipolar disorder. Of the adolescents with a lifetime disorder, 66% had a mood disorder. The last column shows the 14 months incidences of the lifetime K-SADS/DSM-IV diagnosis. The 14 months incidence for any disorder was 5% and for any mood disorder 6%, indicating that in some adolescents the mood disorder was preceded by another disorder.

Table 1: Mean problem scale scores for children of bipolar parents versus comparison samples on the YSR, CBCL, TRF, YASR and YABCL and results of comparisons between both groups in ANCOVAs with age and SES as covariates and sex and case source as fixed factors

Scale	Total problems	Internalizing	Externalizing	Withdrawn	Somatic complaints	Anxious/ depressed	Social problems/ Intrusive	Thought problems	Attention problems	Delinquent behavior	Aggressive behavior
CBCL (n=2)	22.73-18.08	7.56-5.83	7.91-5.66	2.66-2.08	1.51-1.16	3.74-2.75	1.18-1.09	0.54-0.42	3.60-3.05	2.10-1.33	5.82-4.33
p Value	0.006	0.009	0.001*	0.046	0.042	0.008	0.629	0.241	0.113	0.001*	0.005
YABCL (n=6)	19.24-15.65	5.35-3.99	5.74-4.39	1.20-1.13	1.52-1.31	4.15-2.87	1.57-1.55	0.35-0.27	3.02-2.86	1.09-0.71	3.09-2.13
p Value	0.150	0.058	0.123	0.937	0.602	0.015	0.781	0.601	0.886	0.056	0.060
YSR (n=81)	27.15-33.49	7.64-9.59	9.48-10.49	2.31-2.51	2.12-2.52	3.41-4.74	1.64-2.46	0.85-1.22	3.77-4.70	3.19-3.29	6.30-7.20
p Value	0.001*	0.010	0.064	0.250	0.229	0.003	0.002	0.044	0.001*	0.244	0.057
YASR (n=47)	28.57-29.07	8.28-7.41	5.62-6.28	1.98-2.34	2.26-2.25	6.30-5.07	2.34-2.61	0.21-0.19	2.40-2.60	1.23-1.16	2.04-2.50
p Value	0.532	0.495	0.140	0.207	0.911	0.146	0.199	0.907	0.240	0.998	0.076
TRF (n=55)	15.53-17.61	5.09-5.56	4.09-4.59	2.31-2.09	0.16-0.36	2.76-3.23	1.49-1.64	0.22-0.30	5.24-6.17	0.82-0.73	3.27-3.85
p Value	0.396	0.625	0.677	0.629	0.175	0.476	0.816	0.488	0.226	0.839	0.601

* Small ES (1% of variance); all the other effect sizes< 1%
The left score is for the children of bipolar parents and the right score is for the comparison sample. In all cases the information was provided by the mother, except for one CBCL which was completed by the father.

Table 2: Number and percentages of adolescents with DSM-IV diagnosis at T1 (age 12–22) and T2 (age 13–23)

	Current diagnoses T2 (n=132)		Lifetime diagnoses T1 (n=132)		Lifetime diagnoses T2 (n=132)		Incidence T1-T2	
	n	%	n	%	n	%	n	%
Any mood disorder	21	14	36	27	43	33	7	6
Major depressive disorder	3	2	8	6	10	8	2	2
Dysthymic disorder	5	4	8	6	10	7	2	2
Depressive disorder NOS	5	4	13	11	19	14	6	5
Bipolar disorder	5	4	4	3	5	4	1	1
Cyclothymic disorder	2	1	2	1	2	1	-	-
Mood disorder NOS	1	1	2	1	3	2	1	1
Adjustment disorder with depressed mood	0	0	1	1	1	1	-	-
Anxiety disorders	6	4	15	11	15	11	-	-
Disruptive behavioral disorders	5	4	7	6	9	7	2	2
Attention deficit disorder	4	3	6	5	6	5	-	-
Substance abuse disorder	11	8	8	6	13	9	5	4
Other disorders *	9	7	22	16	23	17	1	1
Any Disorder	39	28	58	44	65	49	7	5

* The "other disorders"-category consists of enuresis, encopresis, pervasive developmental disorder, tic and eating disorders

Discussion

A major limitation of our study was that we did not have a control group of children from parents with other psychiatric disorders. Instead, we compared our findings on parent, teacher and self-report rating scales with those derived from the Dutch general population. Compared to these normative data the offspring of bipolar parents showed only few differences. These findings are roughly similar to the findings of the first measurement and they do not support the notion that the level of psychopathology in children aged 13–23 years of bipolar parents is highly elevated. It should be stressed that the Anxious/Depressed scale was among the few problem scales that were scored significantly higher by parents of bipolar offspring than those of normative subjects. This indicates that among parent reported problems, problems of anxiety and depression were salient.

It is unclear whether the prevalences of K-SADS/DSM-IV diagnoses found in the present sample differ significantly from those in the general population, since no K-SADS/DSM-IV diagnoses are available for the Dutch general population. Verhulst et al. (1997a) assessed 6-months prevalences of DSM-III-R diagnoses resulting from combining parent and child information on a structured interview: the Diagnostic Interview Schedule for Children (DISC; Shaffer et al., 1996) for a sample of 13–18-year-olds from the Dutch general population. In this study a 6-months prevalence of mood disorders of 7.2% was found, while 35.5% had any psychiatric disorder. This means that 20% of adolescents with a disorder had a mood disorder. In our study the current (2 months) prevalence of K-SADS/DSM-IV mood disorders at the second measurement was 14%, and the current prevalence of any disorder 28%, indicating that 50% of adolescents with a current disorder had a mood disorder.

The lifetime prevalence of 33% of K-SADS mood disorders, is high when compared to lifetime K-SADS diagnoses of mood disorders found for community samples (8.0% according to Kashani et al. (1987) and in the middle range of other high risk studies among bipolar offspring in the adolescent age range (Klein et al., 1985, LaRoche et al., 1987, Nurnberger et al., 1988, Hammen et al., 1990, Todd et al., 1996 and Chang et al., 2000).

In our sample the lifetime prevalence of bipolar disorder was still relatively low: five subjects (4%) had a lifetime bipolar disorder and two subjects (2%) a cyclothymic disorder compared to 36 subjects with a non-bipolar mood disorder. Studies that focus on the adult offspring of parents with a mood disorder (MDD) indicate that almost one in two will develop a major mood disorder by early adulthood (Weissman et al., 1997).

Our sample is in the age range of 13–23 years with a mean age of 17 years. Therefore, it seems reasonable to anticipate that in our sample over the next few years the lifetime prevalence not only of mood disorders will further increase, but probably also of bipolar disorders. To what extent this will happen and whether it will be possible to predict such development will be the subject of future measurements.

Chapter 3

Development of affective problems in children of parents with bipolar disorder

Development of affective problems in children of parents with bipolar disorder

Catrien G. Reichart, Manon H.J. Hillegers, Marjolein Wals, Ilja L. Bongers, Willem A. Nolen, Johan Ormel and Frank C. Verhulst

Abstract

Objective: To determine the presence of different developmental trajectories of self-reported affective problems in offspring of parents with bipolar disorder and to test whether trajectories with early versus late onset were differentially associated with clinical diagnoses and with a number of risk factors.

Method: Offspring from bipolar parents were assessed 3 times with respectively 2 and 3 year intervals. Developmental trajectories for YSR/YASR affective problems that were computed for a general population sample were used to classify developmental trajectories of YSR/YASR problems in the offspring group.

Results: A group with early onset of increasing levels of affective problems and a group with adolescence onset of affective problems that tended to decrease in young adulthood could be distinguished; besides these two trajectories three other developmental trajectories were distinguished. Significantly more bipolar offspring were classified into these more problematic trajectory groups than individuals from the general population. More individuals in the problematic trajectory groups had lifetime mood disorders than individuals who were classified in the less problematic trajectory groups. Offspring with early onset affective problems and bipolar disorder themselves, had parents with early onset of manic episodes. No other specific risk factors could be identified for the offspring with early onset of affective problems.

Conclusions: Bipolar offspring are indeed at risk for the development of affective problems, including DSM-IV defined mood disorders.

Key words: Bipolar, adolescents, age at onset

Submitted

Introduction

In the majority of patients with bipolar disorder, the illness starts with one or more depressive episodes before the onset of the first hypomanic or manic episode (Werry, 1991). In adults with depression a change from unipolar depression to bipolar disorder has been reported to occur in about 1% of the patients per year (Angst et al., 2005; Coryell et al., 1995). In addition, early age at onset of mood disorders is associated with increased risk of developing bipolar disorder later in life. Strober et al. (1993) found that unipolar mood disorder with psychotic features and onset between 12 and 18 years predicted bipolar disorder in young adulthood in 28% of the cases. Weissman et al. (1999) found that prepubertal onset of depression is associated with a high risk to develop bipolar disorder. In a study by Geller et al. (2001), 33% of the children with prepubertal onset of major depression had developed bipolar I disorder by the age of 20.

First degree relatives of probands with a bipolar disorder with juvenile age at onset have an increased lifetime prevalence of bipolar disorder compared to probands with a later age at onset (Pauls et al., 1992; Rice et al., 1987; Strober et al., 1988). In a study among 6- to 18-year old children of parents with bipolar disorder, Chang et al. (2000) found that an earlier parental symptom onset tended to be associated with increased risk of bipolar disorders in their offspring.

To study the role of age at onset on the development of mood disorders, we investigated the development of psychopathology in a high risk sample of children of bipolar parents. The present study involves a follow-up of a cohort of 140 children of parents with a bipolar disorder who were assessed three times with respectively 2 and 3 year intervals (Wals et al., 2001; Reichart et al., 2004; Hillegers et al., in press). At initial assessment when the sample was between 12 and 21 years, the lifetime prevalence of DSM-IV mood disorder was 27% and of bipolar disorder 4% (Wals et al., 2001). Five years later, the lifetime prevalence had increased to 40% for mood disorders and to 10% for bipolar disorders. Although changes in lifetime prevalence across time can give us information on the incidence of disorders, this kind of diagnostic information does not tell us about changes in symptomatology occurring below the diagnostic threshold. From a developmental perspective it is important to obtain a picture of changes in symptomatology across time and across the whole range of symptom severity, including changes that occur at a diagnostic subthreshold level. We therefore determined the developmental course of self-reported mood symptoms scored

on a continuous scale in this sample of bipolar offspring. Recent advances in statistical techniques have improved the ability to analyze longitudinal data to address questions about change over time. In an earlier study, Bongers et al. (submitted) determined group-based developmental trajectories of the Youth Self-Report (YSR; Achenbach, 1991) and Young Adult Self-Report (YASR; Achenbach, 1997) Affective Problems scale assessed in a general population sample of adolescents and young adults initially aged 11 to 18 years and assessed at 4 times with 2 year and 6 year intervals. The authors reported 5 distinct developmental trajectories for the Affective Problems scale.

In the present study, the YSR or YASR Affective Problems scale sores obtained at the 3 measurements across time in the bipolar offspring sample were classified according to the group-based developmental trajectories as determined in the general population sample. The objectives of the present study were: (1) to test similarities in developmental trajectories of self-reported affective problems in offspring of parents with bipolar disorder versus individuals from the general population; (2) to test whether different trajectories of self-reported affective problems were differentially associated with clinical diagnoses; and (3) to test whether different trajectories of self-reported affective problems were differentially associated with a number of risk factors. In particular, we wanted to know whether individuals who were in the early versus late onset affective symptoms trajectories differed in the presence of a number of risk factors, including in the age at onset of bipolar disorder in the parents.

Method

Subjects

The sample consisted of children of parents with a bipolar I or bipolar II disorder assessed at three times with respectively 2 and 3 year intervals. Subjects recruited for the first measurement (T1) were aged 12 to 21 years and came from 86 families (52 bipolar mothers and 34 bipolar fathers). Of the bipolar parents 64 had a bipolar I disorder and 22 a bipolar II disorder**.** If a family had two or more adolescents in that age group, all of them participated. All bipolar parents were treated as outpatients at the moment of recruitment.

The recruitment procedure was described by Wals et al. (2001). Only adolescents without a severe physical illness or handicap and with an IQ of at least 70 were included. Initially 140 adolescents (72 boys, 68 girls) participated. At T2, 132 subjects (71 boys, 61 girls), aged 13 to 23 years from 83 families, and at T3 129 subjects (69 boys, 60 girls), aged 15 to 26 years from 80 families participated. Six families with a total of 11 adolescents (8 girls, 3 boys) who participated at T1 refused to participate at T3.

To investigate selective attrition, we compared "dropouts" and "remainers" with respect to YSR (Youth Self-Report; Achenbach, 1991) and YASR (Young Adult Self-Report; Achenbach, 1997) total problems scores. Differences in T1 YSR mean total problems scores for dropouts (n= 8) and remainers (n= 97) who were 18 years or younger at T1 were not significant (mean for dropouts 26.0 versus remainers 31.3; t=-.772, df= 100, p=.44). Also differences in T1 YASR total problems scores for dropouts (n=3) and remainers (n=32) who were older than 18 years at T1 were not significant (mean for dropouts 50.0 versus remainers 34.4; t= 1.144, df= 33, p=.26).

The study was approved by the Medical Ethical Review Committee of the University Medical Center Utrecht. After a complete description of the study was given, written informed consent from the bipolar parents, their spouses and their offspring was obtained.

Instruments

The Youth Self-Report (YSR, Achenbach, 1991) is a rating scale to be completed for ages 11 to 18 years. Good reliability and validity of the YSR have been replicated for the Dutch translation (Verhulst et al., 1997).

The Young Adult Self-Report (YASR, Achenbach, 1997) is an upward extension of the YSR for ages 18 years and older. Both the YSR and YASR contain emotional and behavioral problem items that can be scored 0= not true, 1= somewhat or sometimes true, and 2= very true or often true. The YSR and the YASR problem items can be scored on DSM-Oriented Scales.

For the present study, we only used the scale designated as Affective Problems (Achenbach & Rescola, 2003). Because the YSR and YASR do not have exactly the same items, we excluded the items "enjoys little","apathetic" and "sleeps less" from the Affective problems scale. Table 1 shows the items that we used in this study.

Table 1: Items of the YSR and YASR included in the developmental trajectories

Affective problems		
Cries	Guilty	Sleep problems
Harms self	Tired	Lacks energy
Doesn't eat	Sleeps more	Sad
Worthless	Thinks suicide	

The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID I, First et al., 1997) was used to determine psychiatric diagnoses according to DSM IV at T3 from the bipolar offspring. Since the SCID did not include all DSM IV diagnoses, an appendix for attention deficit hyperactivity disorder, oppositional defiant disorder, conduct disorder and tic disorders originating from the K-SADS-PL (Kaufman et al., 1997) was added to the SCID.

The Family History Research Diagnostic Criteria (FH-RDC, Andreasen et al., 1977) interview was used to interview parents and to calculate a continuous familial loading score for unipolar mood disorder and bipolar disorder (see Wals et al., 2004).

Life Events and Difficulties Schedule (LEDS; Brown and Harris, 1978) is a semi-structured interview for assessing stressful life events (SLEs) and long term difficulties in adults, including loss, danger, humiliation, entrapment and required adjustment. It guarantees a relatively objective measurement of the meaning of events and difficulties, and its reliability and validity are satisfactory (Brown and Harris, 1989; Wals et al., 2004).

Data Analysis

First, as described in detail by Bongers et al. (submitted), we estimated group-based developmental trajectories of the YSR/YASR Affective Problems scale for the general population using a semiparametric mixture model fitting procedure as proposed by Nagin et al. (1999) Briefly, in a sample of 1,886 subjects from the general population (Hofstra et al., 2000; Verhulst et al., 1985) we computed developmental trajectories from the YSR/YASR Affective Problems scale obtained at four measurements at respectively 2-,2-,2-, and 6-year intervals. Using a semiparametric mixture model fitting procedure, we estimated group based developmental trajectories.

Using this procedure, affective problems scores in the general population sample was best described by 5 trajectories designated as near zero, low, medium persisters, adolescence onset, and early onset.

Figure 1 shows the trajectories. The subjects included in each trajectory have in common that they follow trajectories with similar patterns of variation and levels of problems between the ages of 11 and 26. The vertical axis indicates the level of problem behavior. Higher scores mean more problems.

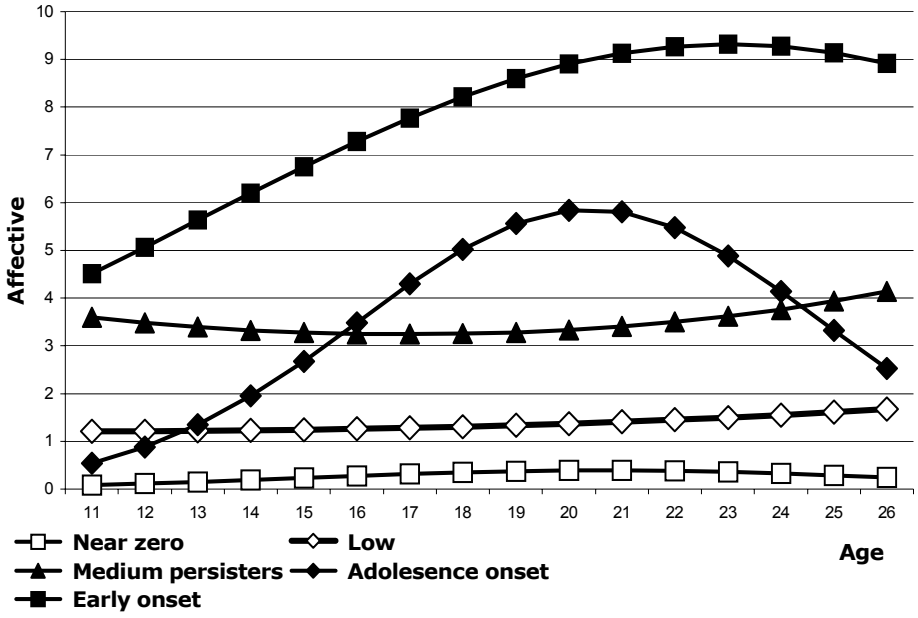

Figure 1: Developmental trajectories of affective symptoms during the adolescent and young adult years of general population subjects (n=1886)

Next, we used these group-based developmental trajectories to classify individuals from the bipolar offspring sample based on their scores obtained at the three measurements. For each subject in the bipolar offspring sample, the posterior probability of group membership for each of the developmental trajectories that were determined for the general population was estimated. Individuals where assigned to the group with the largest posterior probability estimate. These group membership designations form the point of departure for testing differences between the general population and the offspring sample in the distribution across the trajectories and to test differences in the distribution of the DSM-IV lifetime diagnoses across the trajectories. To test differences

between the early onset and adolescence onset trajectories, we used a two sample t test (for continuous data) and chi-square test (for the categorical data). Findings with $p<0.05$ were considered statistically significant.

Results

Distribution across developmental trajectories

Based on the three measurements, it was possible to classify individuals in the bipolar offspring sample into the affective problems trajectories that were determined in the general population sample (mean posterior probability of group membership for the general population sample 0.75 and for the bipolar offspring sample 0.74, t-test = 0.89, p=0.374, no significant differences between the general population and the bipolar offspring sample).

Table 2 gives the distribution of subjects in the offspring sample and in the general population sample across the five affective problems trajectories.

Table 2: Classification individual trajectories of affective problems

		General population			Offspring		
		Total (n=1886)	Boys (n=900)	Girls (n=986)	Total (n=140)	Boys (n=72)	Girls (n=68)
		%	%	%	%	%	%
1.	Near zero	20.7	27.2	14.7	13.5	16.9	10.1
2.	Low	43.9	49.2	39.0	44.0	50.7	37.7
3.	Medium persisters	21.2	16.9	25.2	18.4	18.3	18.8
4.	Adolescence onset	9.9	5.1	14.3	14.9	9.9	18.8
5.	Early onset	4.3	1.6	6.8	9.2	4.2	14.5

Distribution of general population and offspring across the trajectories (Chi-Square= 13.88, df 4, p= .008)
Gender distribution offspring group (Chi-Square= 8.47, df 4, p= .07)
Gender distribution general population (Chi-Square= 132.04, df 4, p <.00)

As can be seen, more subjects in the bipolar offspring sample were assigned to the two trajectories (adolescence onset and early onset) reflecting a more problematic

developmental course than subjects from the general population. This difference in the distribution of the individuals across the trajectories in the offspring versus general population samples was significant (Chi-Square= 13.88, df 4, p= .008). The two trajectories representing the most problematic development in affective problems differed in age at onset of affective problems and in their course over time, with an early onset trajectory showing increasingly high levels of affective problems and an adolescence onset trajectory with an increase in affective problems until the age of 20-21 years and a gradual decrease up to age 26.

The gender distribution for the offspring sample across the trajectories was not significantly different for boys versus girls (Chi-Square= 8.47, df 4, p= .07). In the general population sample (Chi-Square= 132.04, df 4, p <.00) significantly more boys were in the near zero and low trajectories and more girls in the medium persisters, adolescence onset and early onset trajectories**.**

DSM-IV disorders

Table 3 shows the distribution of T3 lifetime DSM-IV diagnoses across the 5 Affective Problems trajectories.

Table 3: Number and percentages of lifetime DSM-IV disorders in 129 adolescents and young adults and their distribution over trajectories of affective symptoms at the third measurement

	DSM-IV disorders				
Affective trajectories	Total	No Disorder	Non-mood disorder	Unipolar disorder	Bipolar disorder
1. Near zero	15	8 (54%)	2 (13%)	3 (20%)	2 (13%)
2. Low	58	34 (58%)	12 (21%)	11 (19%)	1 (2%)
3. Medium persisters	23	7 (31%)	6 (26%)	9 (39%)	1 (4%)
4. Adolescence onset	20	4 (20%)	4 (20%)	8 (40%)	4 (20%)
5. Early onset	13	0	1 (8%)	7 (54%)	5 (38%)
Total	129	53 (41%)	25 (19%)	38 (29%)	13 (10%)

Distribution of DSM-IV disorders across the trajectories (Chi-Square= 38.820, df 12, p= .000, Fisher´s exact T=2.75, p= .007)

Bipolar disorders in offspring were overrepresented in the adolescence onset and early onset trajectories in comparison with the other trajectories (9/33 versus 4/92,

significant difference, Chi-Square=14.47, p= .0004). In the early onset trajectory, even 92% had a DSM-IV mood disorder and there was a significant difference in number of mood disorders between the early onset and adolescence onset trajectory (12/13 versus 12/20, Chi-Square=4.15, p=.04).

Early onset versus adolescence onset of affective problems

We tested differences between early onset and adolescence onset affective problems trajectories for the following variables: current diagnoses, current bipolar diagnoses, lifetime mood diagnoses, number of severe life events before the age of 12 years, family load for bipolar disorder and unipolar disorder, birth weight in offspring, and age first manic episode and severity of bipolar disorder in bipolar parents (table 4).

Table 4: Early onset versus adolescence onset of affective problems

	All subjects				Subjects with bipolar disorder			
	Early onset trajectory (n=13)	Adolescence onset trajectory (n=20)			Early onset trajectory (n=5)	Adolescence onset trajectory (n=4)		
Adolescents								
statistics			χ^2	*p*			χ^2	*p*
Lifetime mood diagnosis	12 (92%)	12 (60%)	4.15	.04	5 (100%)	4 (100%)	n.a.	n.a.
Lifetime bipolar diagnosis	5 (38%)	4 (20%)	1.74	ns	5 (100%)	4 (100%)	n.a.	n.a.
Current mood diagnosis	7 (54%)	9 (45%)	.53	ns	4 (80%)	1 (20%)	2.72	ns
statistics			*t*	*P*			*t*	*p*
Number severe life events before 12 years	3.2	2.3	-1.26	ns	3.2	1.5	-1.26	ns
Family load for bipolar disorder	1.4	1.5	.09	ns	1.9	1.2	-.75	ns
Family load for unipolar disorder	.096	-.075	-.43	ns	-.23	-.23	-.00	ns
Birth weight (pounds)	6.9	6.6	-.81	ns	6.8	6.3	-.70	ns
Parents								
Age first manic episode	30.3	29.6	-.18	ns	25.4	37.2	2.70	.03
Severity bipolar disorder	3.5	3.4	-.33	ns	2.8	3.5	.99	ns

ns= nonsignificant; n.a.= not applicable

Lifetime mood diagnoses were significantly more prevalent in offspring with early onset than with adolescence onset of trajectories. There was no significant difference in the presence of current diagnoses across the two trajectories. When we looked at the distribution of the 5 subjects with bipolar diagnoses across the two trajectories, we found that 4 in the early onset trajectory had a current diagnosis versus 1 in the adolescence onset trajectory. This difference was not significant, however.

The difference in age at onset of first manic episode of the bipolar parents across the two trajectories was not significant. When we looked at offspring who met criteria for lifetime bipolar disorder themselves, parents of offspring in the early onset trajectory affective problems had their first manic episode at a mean age of 25 years versus a mean age of 37 years for parents of offspring with adolescence onset affective problems. This difference was significant.

We also determined the ages at onset of the DSM-IV mood disorders of the offspring. The mean age at onset of the first mood disorder for the offspring in the early onset Affective Problems trajectory was 15.1 years and 17.4 years in the adolescence onset Affective Problems trajectory. For the 13 offspring with a bipolar disorder the mean age at onset of the first mood disorder was 13.1 years.

Discussion

The objectives of the present study were to test similarities in developmental trajectories of self-reported affective problems in offspring of parents with bipolar disorder versus individuals from the general population and to test whether trajectories of self-reported affective problems were differentially associated with clinical diagnoses and with a number of risk factors.

Based on the affective problems scores each of the individuals in the bipolar offspring sample could be classified into one of the five trajectories that were identified in the general population sample. Compared with the distribution in the general population sample a larger proportion of individuals in the offspring sample were assigned to trajectories indicating a more problematic development. Especially in the adolescence onset and in the early onset trajectories, bipolar offspring were overrepresented compared to individuals from the general population sample. This finding that bipolar offspring clearly showed a more problematic development in the

area of self-reported affective functioning than same aged individuals in the general population contrasts somewhat with earlier findings based on cross-sectional comparisons of self-reported problems in the same offspring sample (Wals et al., 2001; Reichart et al., 2004), stressing the importance of longitudinal information for identifying high risk individuals who show a deviant development.

The majority of offspring who met criteria for DSM-IV bipolar disorder were assigned to one of the two trajectories reflecting the most problematic development (adolescence onset and early onset). If we consider the trajectory designated as medium persisters as also reflecting a problematic development, then 34 of the 51 individuals with a lifetime DSM-IV mood disorder (both unipolar and bipolar) could be regarded as showing a problematic development. These findings indicate that in bipolar offspring, information captured by developmental trajectories of affective problems based on prospective self-report information, converged with lifetime DSM-IV diagnoses based on retrospective interview information.

The two affective problems trajectories reflecting problematic functioning, early onset and adolescence onset, differed in three important aspects. The first is the age at onset, with high levels of affective problems prior to the age of 12 in the early onset group and low levels of affective problems at age 12 that tended to increase from ages 12 to 19 in the adolescence onset group. The second difference is the course of problems over time with increasingly high levels of affective problems across adolescence that tended to persist in young adulthood in the early onset group and a gradual decrease of affective problems after age 20/21 in the adolescence onset group. The third difference is the overall level of problems with much higher levels in the early onset versus the adolescence onset trajectory. The early onset trajectory thus by far reflected more problematic functioning with an earlier onset, and a higher and more persistent level of affective problems. These findings support the idea that there is an early-onset pathway for unipolar and bipolar disorder in a subgroup of offspring of parents with bipolar disorder. This finding is in line with the study by Hammen et al. (1990) who assessed school-aged children of bipolar women. Offspring of bipolar women experienced higher rates of mood disorder and it appeared that most children with mood diagnoses had an onset in preadolescence and, moreover, they continued a chronic or intermittent course.

We have looked for differences between offspring with early onset affective problems versus adolescence onset problems. As expected, compared to offspring with adolescence onset affective problems, offspring with early onset affective problems had

more current (54% versus 45%), and more lifetime mood disorders (92% versus 60%) and the age at onset for the first mood disorder was more than two years earlier. Except for the difference in lifetime mood diagnoses, none of the differences were significant, probably due to the small number of subjects.

Another finding was that the age of the first manic episode of the parents of the offspring with a bipolar disorder with early onset affective problems was significantly younger than for parents of offspring with a bipolar disorder with adolescence onset affective problems. Offspring with bipolar disorder themselves who had an onset of affective problems in childhood, have parents with an earlier onset of bipolar disorder. This finding is in line with Chang et al. (2000) who found a possible association of age at onset of bipolar disorder in parents and offspring. Our finding is also in line with a study by Leboyer et al. (1998) who reported a high intrafamilial correlation for age at onset among bipolar siblings (Leboyer et al., 1998), suggesting that the age at onset of bipolar disorder "runs in families". In addition, age at onset of bipolar disorder has been considered as a potentially useful variable for constructing homogeneous subgroups of patients (Faraone et al., 2003), which may be useful in unraveling some of the clinical heterogeneity among individuals with bipolar disorder.

Age at onset of bipolar disorder is associated with several clinical features such as illness chronicity (more mood episodes and a greater proportion of days depressed), suicidality and concomitant substance abuse (Perlis et al., 2004). Early age at onset of bipolar disorder was found to be associated with a chronic course (Sax et al., 1997, Carlson et al., 2002). This is in line with the identification of an early onset developmental trajectory of affective symptoms in the present study also showing that an early onset apparently goes together with a chronic and more severe course of affective problems.

Various authors have noted a significant effect of family history of bipolar disorder (Grigoroiu-Serbanescu et al., 2005; Chang et al., 2000) and stressful life events (Kessing et al., 2004, Petti et al., 2004) on the early development of bipolar disorder. We also found more serious life events in the early onset versus the adolescence onset group. However, probably due the limited number of cases, this difference was not significant. In the present study we did not find significant differences in family load for unipolar and bipolar disorder for early versus adolescence onset trajectories.

The present study illustrates that a distinction between adolescent versus childhood onset of mood symptomatology can be made. This distinction may potentially be important for understanding the heterogeneity within bipolar disorder.

Limitations

Statistical power was limited by relatively small sample sizes, particularly in the subgroup of offspring with bipolar disorder. The assessment of age at onset of the first mood episode in the bipolar parents relied on retrospective reporting of past episodes and may have been vulnerable to recall bias.

Notwithstanding the above limitations, a few strengths are noteworthy. The prospective design of our study made it possible to determine the onset and course of affective problems as well as the age at onset of the first DSM-IV mood episode in the offspring sample with great precision. A fourth measurement, when probably more offspring will have developed a bipolar disorder, will increase the statistical power of the equations in this cohort.

Clinical implications

The early detection of serious mood disorders, such as bipolar disorder in adolescents and young adults, is of major importance. This is especially so for individuals who run a high risk for developing a mood disorder, such as children of parents with a bipolar disorder. This study shows that bipolar offspring with affective problems starting before the age of 12 years show a chronic course of these problems across adolescence and into young adulthood. Moreover, offspring with increasing levels of affective problems in childhood or adolescence run a substantial risk of developing a bipolar disorder themselves. Therefore this subgroup with an early start and chronic course of affective problems, as well as the subgroup with increasing affective problems in adolescence should receive special attention in order to detect bipolar disorder as soon as possible.

By intervening before the onset of full-blown bipolar disorder, the disorder may be prevented or at least ameliorated in its severity, preventing poor social and vocational functioning.

Chapter 4

The use of the GBI in a population of adolescent offspring of parents with a bipolar disorder

The use of the GBI in a population of adolescent offspring of parents with a bipolar disorder

Catrien G. Reichart, Jan van der Ende, Marjolein Wals, Manon H. J. Hillegers, Johan Ormel, Willem A. Nolen and Frank C. Verhulst

Abstract

Objective: To assess the psychometric properties and the usefulness of the General Behavior Inventory (GBI) in the adolescent age range.
Method: The GBI, the Schedule for Affective Disorders and Schizophrenia for School Age Children, Kiddie-SADS-Present and Lifetime Version (K-SADS-PL) and the Youth Self-Report (YSR) were used to assess 117 adolescents of a bipolar parent twice with an interval of 14 months. Based on the K-SADS results, the bipolar offspring were assigned to one of three groups: with mood disorders, with non-mood disorders, and with no disorders.
Results: Principal component analyses resulted in the same two-factor solution as reported for adults. The Depression scale of the GBI discriminated between adolescents with a DSM-IV mood disorder, a non-mood disorder and no disorder on Axis I. Significant correlations between GBI scales and the corresponding Internalizing and Externalizing scales of the YSR showed convergent validity.
Conclusions: The GBI can be used in the adolescent age range as a self-report to discriminate mood disorders from non-mood disorders or no disorders.

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Introduction

To aid the assessment of affective problems in adolescents, standardized diagnostic procedures that result in quantitative measures of psychopathology can be used to complement diagnostic approaches that result in categories of predefined disorders exemplified by the approach of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association, 1994).

The General Behavior Inventory (GBI; Depue et al., 1981) is a self-report that was designed to quantify affective problems in adults. The instrument consists of two scales, designated as depression and biphasic/hypomania, that were constructed on an a priori, clinical basis. Two studies in adolescents (Klein et al., 1985 and Findling et al., 2002) and several studies in adults have indicated that the GBI has high specificity and adequate sensitivity to accurately identify the full range of subsyndromal to syndromal affective conditions (Depue et al., 1981; Depue et al., 1989; Depue and Klein, 1988; Klein et al., 1985 and Klein et al., 1986).

In the present study, we tested the usefulness of the GBI by: (i) testing the two-factor structure of the GBI (depressive and hypomanic/biphasic) in the adolescent offspring of a bipolar parent; (ii) comparing GBI ratings with diagnoses derived from the Schedule for Affective Disorders and Schizophrenia for School Age Children, Kiddie-SADS-Present and Lifetime Version (K-SADS-PL) (Kaufman et al., 1997) and with Youth Self-Report (YSR; Achenbach, 1991) ratings; (iii) computing the correlations between GBI and YSR scores; and (iv) computing the 14-month stability of the GBI.

Method

A total of 140 adolescents aged 12–21 years of a parent with a bipolar I or II disorder were assessed between 1997 and 1998 (T1) and again after 14 months (T2). Recruitment was done via nine specialized outpatient clinics for bipolar patients and via the Dutch patient association; the procedure is more extensively described by Wals et al. (2001). The study was approved by the Medical Ethical Review Board of the University Medical Centre Utrecht. After a complete description of the study was given, written informed consent from the bipolar parents, their spouses, and their offspring, was obtained. To test the usefulness of the GBI in the adolescent age range we included

for this study only adolescents aged 18 years or younger at T1, leaving 117 adolescents (53% males and 47% females), with a mean age of 15.4 years.

Instruments

The GBI was developed by Depue (1987) to identify symptoms reflecting a trait-based (i.e. lifetime) measure of unipolar and bipolar affective conditions. It has 73 questions reflecting intensity and duration of symptoms that can be understood by adolescents from age 12 years onwards. The GBI is composed of three sets of items which can be scored on two scales, a Depression scale with 46 items and a Hypomania/Biphasic scale with 21 hypomanic and seven biphasic items. Each item is rated on a four-point scale of intensity: 0='hardly ever', 1='sometimes', 2='often' and 3='very often'. In scoring the items, we retained the original four-point scoring, because this will preserve more information, increase the variability in observed scores, and increase the reliability (Pedhazar and Schmelkin, 1991), all of which are desirable features in both research and clinical settings (Wiggins, 1973).

The K-SADS-PL (Kaufman et al., 1997) is an interviewer oriented diagnostic interview designed to assess current (2 months) and past DSM-IV symptomatology resulting in diagnoses in children and adolescents, by interviewing the parents and children separately.

The YSR (Achenbach, 1991) is a questionnaire to be completed by 11–18-year-old adolescents and can be scored on eight syndrome scales (Withdrawn, Somatic Complaints, Anxious/Depressed, Social Problems, Thought Problems, Attention Problems, Delinquent Behavior and Aggressive Behavior, and two broad-band groupings of syndromes: Internalizing (consisting of the first three scales), and Externalizing (consisting of the last two scales). A total problems score is derived by summing the individual item scores. Good reliability and validity of the YSR have been replicated for the Dutch translations (Verhulst et al., 1997).

Procedure

Adolescents completed the GBI and the YSR in the week prior to the psychiatric interview with the adolescent. The K-SADS-PL was conducted by three of the authors (M.W., M.H., and C.R.), and by five intensively trained interviewers with graduate degrees in psychology, who did not have access to other information.

Results

DSM-IV diagnoses

Table 1 shows the prevalence of the lifetime K-SADS/DSM-IV diagnoses at T1. Of the 117 adolescents, 50 (43%) met criteria for any disorder. Subjects were classified into three groups: no disorder (*n*=67), any mood disorder (*n*=32, including two with a bipolar disorder and two with cyclothymia) and any non-mood disorder (*n*=18). The mood disorder group included 19 subjects with comorbid non-mood disorders.

Table 1: Number and percentages of adolescents with DSM-IV diagnosis at T1 (age 12–18)

	Lifetime diagnoses at T1 (n=117)	
	n	%
Any Mood Disorder	32	27
Bipolar disorder	2	2
Major depressive disorder	7	6
Other mood disorder	25	21
Any Non-Mood Disorder *	37	32
Anxiety Disorders	15	11
Disruptive Behavioral Disorders	6	5
Attention Deficit Disorder	5	4
Substance Abuse Disorder	4	3
Other Disorders **	19	16
Any Disorder	50	43

* Nineteen of the adolescents with a non-mood disorder have a comorbid mood disorder
** The "other disorders"-category consists of enuresis, encopresis, pervasive developmental disorder, tic and eating disorders

Factor analyses

Factor analysis was used to test the two-factor structure according to Depue and Klein (1988). To maintain a reasonable subject-to-variable-ratio a similar procedure was used as in Youngstrom et al. (2001). By summing three to four items into one score, 20 item parcels were computed. These 20 item parcels were subjected to a principal components analysis, followed by a Varimax rotation.

All factor loadings, except one of the item parcels on the target factor, were higher than the loading on the other factor (Table 2).

Table 2: Principal components analysis with Varimax rotation of 20 item parcels of the GBI (n=117)

			Factor Loadings	
	Parcel	Items	Depression	Hypomanic/Biphasic
Biphasic	1	2, 24,35, 48	.53	.63
	2	19, 40, 53	.52	.66
Hypomanic	3	4, 7, 15	.39	.84
	4	22, 30, 31, 66	.34	.81
	5	11, 17, 42, 51	.14	.71
	6	27, 44, 54	.57	.64
	7	8, 57, 64	.46	.68
	8	38, 43, 46, 61	.18	.87
Depression	9	3, 23, 45, 63	.88	.35
	10	47, 56, 62, 73	.88	.02
	11	9, 10, 13, 70	.39	.75
	12	21, 33, 49,59	.57	.54
	13	1, 12, 41	.66	.50
	14	5, 25, 37, 52	.69	.41
	15	14, 39, 55	.78	.43
	16	29, 36, 50, 71	.77	.45
	17	16, 60, 65, 67	.79	.49
	18	20, 32, 34, 72	.87	.32
	19	18, 26, 58, 68	.75	.43
	20	6, 28, 69	.80	.42

Parcel 11 had a loading of 0.39 on the target factor and a loading of 0.75 on the other factor. Many differences between loadings of item parcels on target factors and other factors were small. This indicates a high correlation between scales based on this factor structure. The correlation between the Depression and Hypomanic/Biphasic scales was 0.82.

Group differences on GBI scales

Table 3 presents the mean GBI scores for each of the three diagnostic groups and the results of the comparisons between the mean scores in ANOVAs with disorder (any mood disorder, any non-mood disorder, no disorder) and sex (boys vs. girls) as factors. The three group disorder factor showed significant differences on the Depression scale. On the Hypomanic/Biphasic scale the differences between non-mood disorder and no disorder were not significant in the post hoc tests. There was, however, a significant difference between any mood disorder and any non-mood disorder or no disorder.

Table 3: Mean GBI scores for adolescent boys and girls with any mood disorder, non-mood disorder or no disorder and results of comparisons between the 3 groups in ANOVAs and L.S.D. post hoc test.[1]

	Any mood disorder (n=32)	Any non-mood disorder (n=18)	No disorder (n=67)	F	p
Depression	31.75[ab]	19.26[ac]	8.46[bc]	24.6[d,e]	<0.001
Hypomania and biphasic	16.60[ab]	10.78[a]	5.96[b]	13.0	<0.001

[1] Equal superscript across rows indicate pairwise significant differences according to the LSD post hoc test.
[d] Girls obtain higher scores than boys (F= 18.2; p<0.001)
[e] Significant interaction between disorder and sex (F=5.8; p<0.01), indicating higher scores for girls versus boys for any mood and any non-mood disorder, but no significant difference for no disorder

Correlations between GBI and YSR

In order to test the convergent validity of the GBI we computed Pearson correlations between the YSR Internalizing and Externalizing scales and the Depression and the Hypomanic/Biphasic scales on the GBI (Table 4).

Table 4: Pearson correlations between GBI and YSR scales

GBI Scales / YSR Scales	Depression	Hypomanic/biphasic
Internalizing	0.76	0.58
Externalizing	0.35	0.42

All correlations significant at P<0.05.

The GBI Depression scale scores were more strongly correlated with the Internalizing scale on the YSR (r=0.76) than with the Externalizing scale on the YSR (r=0.35). This was a significant difference (z=5.49, P<0.05; test for dependent correlations; Steiger, 1980).

The correlations between the GBI Hypomanic/Biphasic scale and the Externalizing scale on the YSR (r=0.42) were lower than those with the Internalizing scale on the YSR (r=0.58). This difference was not significant (z=1.92; test for dependent correlations; Steiger, 1980).

The 14-month stability of the GBI

The correlation between T1 and T2 for the Depression scale was 0.58 and for the Hypomania/Biphasic scale 0.62.

Discussion

In adult populations the GBI has demonstrated excellent validity as a self-report measure for mood disorders. This study examined the usefulness of the GBI in the evaluation of adolescent mood disorders. Principal component analyses of the GBI resulted in the same two-factor structure, with a Depression scale and a Hypomanic/Biphasic scale, as in adults.

The Depression scale of the GBI discriminated well between adolescents with a DSM-IV mood disorder, non-mood disorder or no disorder (good criterion-related validity). Significant correlations between the GBI scales Depression and Hypomanic/Biphasic and the Internalizing and Externalizing scales of the YSR showed convergent validity. The correlation of 0.58 for the Depression scale at T1 and T2 and of 0.62 for the Hypomanic/Biphasic scale reflects the continuity of symptoms across time. However, it may also reflect the inability of the lifetime version of this instrument to capture change in symptoms over time.

The present findings demonstrate that the GBI is a useful instrument in research among adolescents with (possible) mood disorders, while its use as an adjunct for the diagnosis of mood disorders among adolescents in general deserves further study. In addition it would be of clinical importance to investigate its sensitivity to change, for which purpose a ‘current’ version of the GBI may be developed.

Chapter 5

The use of the GBI as predictor of bipolar disorder in a population of adolescent offspring of parents with a bipolar disorder

The use of the GBI as predictor of bipolar disorder in a population of adolescent offspring of parents with a bipolar disorder

Catrien G. Reichart, Jan van der Ende, Marjolein Wals, Manon H.J. Hillegers, Willem A. Nolen, Johan Ormel and Frank C. Verhulst

Abstract

Objective: To assess the usefulness of the General Behavior Inventory (GBI) to predict the development of mood disorders in the offspring of parents with bipolar disorder.
Method: The GBI and the K-SADS (first measurement) and the SCID (last measurement) were used to assess psychopathology among 129 adolescent and young adult children of a bipolar parent with an interval of 5 years. Based on the SCID results at the last measurement, the offspring were assigned to one of four groups: with bipolar mood disorder, with unipolar mood disorders, with non-mood disorders and without disorders and GBI-scores at the first measurement were compared across the four groups.
Results: The scores on the Depression scale of the GBI for the offspring who later developed a bipolar or any mood disorder were significantly higher than for the offspring who did not develop a mood disorder across a 5-year interval. For the offspring with a unipolar mood disorder at the first measurement the scores on the Depression scale were significantly lower for those who switched to bipolar disorder versus those who remained unipolar.
Limitations: The predictive validity of the GBI was tested in a population of children with a high risk to develop bipolar disorder. The findings of this study can not be generalized to the general population.
Conclusions: The GBI can be used in a high risk sample of children of parents with bipolar disorder as a self-report measure as an aid to detect those who will develop bipolar disorder across a 5-year interval.

Submitted

Introduction

In the majority of cases, bipolar disorder starts after puberty with affective symptoms or depressive episodes (Werry et al., 1991; Goodwin & Jamison, 1990, Hillegers et al., 2005). The disorder is more prevalent among individuals with a family history of bipolar disorder than among individuals in the general population (Gershon & Cloninger, 1994). Therefore, the study of children of parents with bipolar disorder (offspring study) presents a good opportunity for determining the early signs of bipolar disorder. Studies have shown that children of bipolar parents are at increased risk to develop psychopathology, especially mood disorders (Duffy et al., 1998; Chang et al., 2000; Wals et al., 2001; Reichart et al., 2004a). For targeting early interventions it is important to identify those children who run the highest risk for developing a bipolar disorder as early as possible. Up till now no markers for bipolar disorders have been identified.

The General Behavior Inventory (GBI; Depue, 1981) was developed with the purpose to identify bipolar and unipolar mood disorders across the full spectrum of severity, including full blown major depression and bipolar disorder as well as their minor variants such as minor depression and cyclothymia. The GBI thus can be used in community samples of adolescents and young adults for the early identification of individuals who are at increased risk for developing major depressive disorder or bipolar disorder (Akiskal et al., 1979). In a sample of adolescents from the community (n=1507) 40% of individuals with affective problems designated by the authors as subsyndromal, developed a major depressive disorder in young adulthood while the rate of switching from initial major depressive disorder to bipolar disorder was 1% (Lewinsohn et al., 2000).

Several studies among adults have indicated that the GBI has high specificity and adequate sensitivity to accurately identify the full range of affective conditions (Depue et al., 1981; 1988; 1989; Klein et al., 1985; 1986). Five studies among adolescents (Klein et al., 1985; Youngstrom et al., 2001; Findling et al., 2002; Danielson et al., 2003; Reichart et al., 2004b) have shown that GBI subscales are a useful adjunct to assess mood disorders in youth and to discriminate between bipolar versus unipolar disorder or other DSM-IV disorders. Danielson et al. (2003) found that the GBI assigned patients to the appropriate diagnostic groups (bipolar disorder, unipolar mood disorder and disruptive behavior disorder) with better than 74% accuracy.

All these studies supported the convergent validity of the GBI by demonstrating high concordance with interview-derived diagnoses. There are, however, few data on the predictive validity of the GBI. Klein and Depue (1984) reported that college students with elevated GBI scores continued to exhibit high levels of impairment in a 19-month follow-up. It was not clear from this study whether GBI scores predicted mood disorders. Klein et al. (1989) explored the predictive validity of the GBI over a 6-7 month follow-up period in adult outpatients with unipolar depression. They found that the Hypomanic/Biphasic scale predicted the development of hypomanic episodes during the follow-up period. Patients who reported episodes of hypomania scored significantly higher on the Hypomanic/Biphasic scale than patients who did not experience hypomanic episodes during the follow-up period. Nobody in this study, however, developed manic episodes. Lewinsohn et al. (2003) reported that elevated GBI scores were associated with a significantly increased risk of developing a first-onset bipolar disorder or cyclothymia across a 4-year period in a community sample of adolescents and young adults. Less than 1% of adolescents with a unipolar mood disorder switched to bipolar disorder in this 4 year period (Lewinsohn et al., 2000).

The relevance of testing the predictive validity of the GBI lies in the potential of this instrument to detect those individuals who run a high risk for developing serious mood disorders as early as possible. Therefore it is important to test the effectiveness of the GBI in samples of children and adolescents. Previous studies which tested the predictive validity of the GBI in children or adolescents pertained samples of individuals from the community who run a relatively low risk for developing bipolar disorder. Therefore we tested the usefulness of the GBI as a predictor of the development of unipolar and bipolar disorder in a sample of 129 offspring of bipolar parents aged 11-21 years during a follow-up period of five years.

We studied the following questions:

1. Does the GBI predict the development of mood disorders in individuals who run a high risk for developing a mood disorder?
2. Does the GBI predict the switch from unipolar mood disorder to bipolar disorder?

Method

The present study concerns the results of the first and third measurement in a prospective study among children of a parent with a bipolar I or bipolar II disorder in the Netherlands. The 140 subjects recruited for the first measurement (T1) were aged 11 to 21 years and came from 86 families who agreed to participate. All bipolar parents were treated as outpatients at the moment of recruitment. The recruitment procedure was described by Wals et al. (2001). Adolescents with a severe physical disease or handicap and with an IQ below 70 were excluded. The study was approved by the Medical Ethical Review Committee of the University Medical Center Utrecht. After a complete description of the study was given, written informed consent from the bipolar parents, their spouses and their offspring was obtained. The third measurement (T3) was performed after 5 years and included 129 subjects (60 girls and 69 boys), aged 15 to 26 years from 80 families (48 bipolar mothers and 32 bipolar fathers). Of the bipolar parents 59 had a bipolar I disorder and 21 a bipolar II disorder. We selected all 129 subjects who participated both at T1 and T3 for our analyses.

Instruments

The GBI was developed by Depue and Klein *(*1987) to identify symptoms reflecting a trait-based (i.e. lifetime) measure of unipolar and bipolar affective conditions. It has 73 questions reflecting intensity and duration of symptoms that can be understood by adolescents from age 12 years onwards. The GBI is composed of three sets of items which can be scored on two scales, a Depression scale with 46 items and a Hypomania/Biphasic scale with 21 hypomanic and 7 biphasic items. Each item is rated on a four-point scale of intensity, 0= "hardly ever", 1="sometimes", 2="often" and 3= "very often". In scoring the items, we retained the original four-point scoring, because this will preserve more information, increase the variability in observed scores, and increase the reliability (Pedhazar & Schmelkin, 1991). For this study group principal component analyses of the GBI resulted in the same two-factor structure, with a Depression scale and a Hypomanic/biphasic scale as in adults (Reichart et al., 2004b). Higher scores on the Depression scale or Hypomanic/Biphasic scale indicate more symptoms.

At T1 we used the present and lifetime version (K-SADS-PL, Kaufman et al., 1997), an interviewer oriented diagnostic interview designed to assess current (2 months) and

past DSM-IV symptomatology resulting in diagnoses in children and adolescents, by interviewing the parent(s) and child separately. If parents and child disagreed on the presence of a symptom, greater weight was typically given to parents' reports of observable behavior and children's reports of subjective experiences (Herjanic & Reich, 1982). The K-SADS-PL was conducted by three of the authors (MW, MH, and CR) and by five intensively trained interviewers with graduate degrees in psychology. In addition to the K-SADS derived diagnoses, we also screened for DSM-IV pervasive developmental disorders.

At T3 we used the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID I, First et al., 1997) to determine current (last month) and past psychiatric diagnoses according to DSM-IV in adults. We decided to switch to the SCID at T3 as most of the offspring were 18 years or older. Since the SCID does not include all DSM-IV diagnoses, a questionnaire for Attention Deficit Hyperactivity Disorder, Oppositional Defiant Disorder, Conduct Disorder and Tic Disorders originating from the K-SADS-PL was added. The SCID interview was conducted by two of the authors (MH and MW) and 3 trained interviewers with graduate degrees in psychology (Hillegers et al., in press). All interviewers were intensively trained, and all interview outcomes were discussed with a child and adolescent psychiatrist (CR).

Lifetime DSM-IV diagnoses at T3 were based on the psychiatric interviews that took place during all three measurements (T1, T2, T3) adding up the incidence of psychopathology between T2 and T3 to the incidence of psychopathology between T1 and T2 and the lifetime T1 diagnoses. At the same time the hierarchical rules of DSM-IV were taken into account. For example, a subject with a lifetime major depressive disorder at T1, who developed a manic episode between T2 and T3, counted lifetime only for a bipolar disorder at T3.

Procedure

The offspring of bipolar parents completed the GBI in the week prior to their first psychiatric interview in 1997 and 1998 (Reichart et al., 2004a). The interviewers who performed the K-SADS or SCID interviews did not have access to the scores on the GBI.

Logistic regression analyses were used to calculate the odds ratios per unit increase of the scores on the Depression and Hypomanic/Biphasic scale of the GBI at T1 associated with diagnoses at T3. We considered results with p values <0.05 as statistically significant.

Results

DSM-IV diagnoses

Figure 1 shows the development of lifetime DSM-IV diagnoses between T1 and T3. At T1 58 of the 129 adolescents (45%) and at T3 76 of the 129 adolescents and young adults (59%) met criteria for any disorder. Subjects were classified into four groups according to their T3 diagnoses: no disorder, bipolar disorder, unipolar mood disorder and other disorder. In the bipolar group 70% had a comorbid disorder and in the unipolar group 71%. Seven adolescents with a unipolar disorder, one with an anxiety disorder and one without a disorder at T1 developed a bipolar disorder during the 5 year follow-up interval. Ten adolescents without a disorder and 4 adolescents with a non-mood disorder developed a unipolar mood disorder during the follow-up interval.

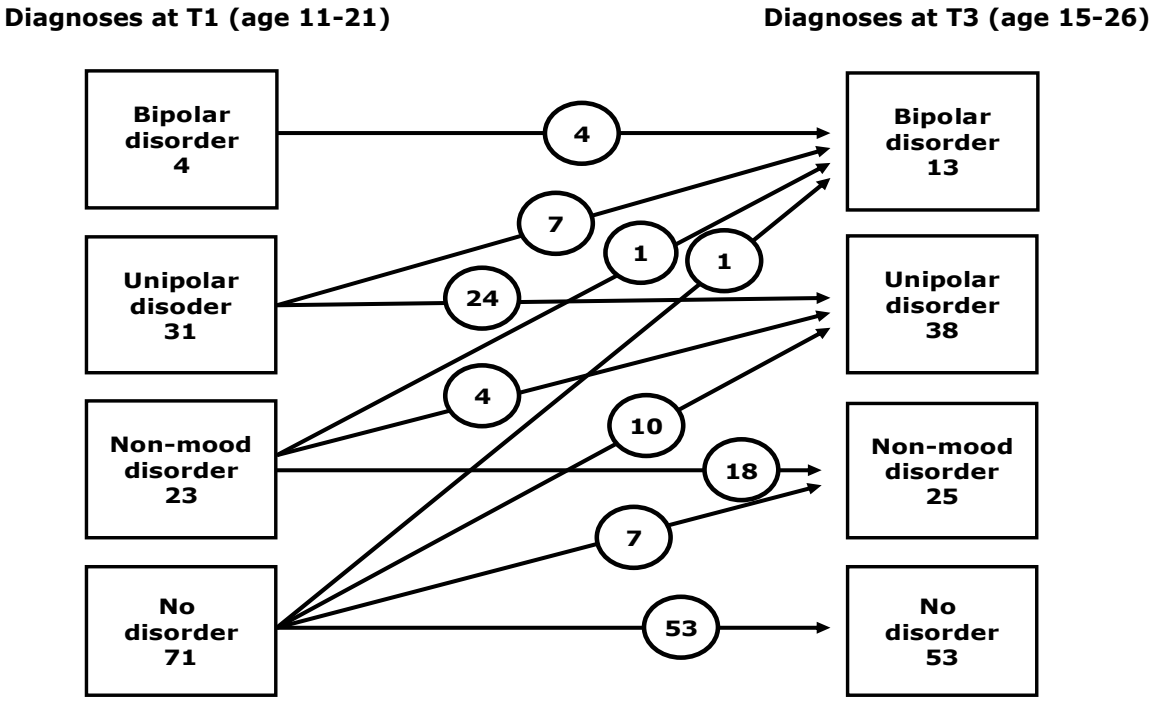

Figure 1: Development of Lifetime DSM-IV diagnoses among 129 children of parents with bipolar disorder over a 5-year follow-up period. The "non-mood disorder" category consists of enuresis, encopresis, pervasive developmental disorder, tic and eating disorders, anxiety disorders, disruptive behavioral disorders, attention deficit disorder or substance abuse disorder

Prediction of DSM-IV diagnoses

The first step was to test the prediction of new cases of bipolar disorder (9) and new cases of unipolar mood disorder (14) across the 5-year follow-up interval from T1 GBI scores. Table 1 presents the odds ratios per unit increase on the Depression and Hypomanic/Biphasic scale of the GBI at T1 associated with diagnoses (new bipolar disorder, new unipolar disorder or any new mood disorder versus no disorder or non-mood disorder) at T3. For example the risk for a new bipolar disorder versus no disorder increases by 1.12 for each unit increase on the Depression scale.

Table 1 shows that on the Depression scale it is possible to differentiate between new bipolar disorder and no disorder or non-mood disorder. The odds ratios for the Hypomanic/Biphasic scale were not significant. It was also possible to differentiate between the whole group of new mood disorders (unipolar and bipolar) and the group with non-mood disorders and the group without disorders on the Depression scale.

Table 1: Logistic regression analyses using Depression and Hypomanic/Biphasic scales from the General Behavior Inventory at T1 for 129 offspring aged 11-21 year to predict new bipolar disorders and new unipolar disorders across the 5-year follow-up

		Odds ratios and 95% confidence intervals for each unit increase on the GBI scales			
		Depression scale		Hypomanic/ Biphasic scale	
Prediction of new diagnoses at T3	n	OR	95% CI	OR	95% CI
New bipolar disorder					
vs. unipolar disorder	9 vs. 14	1.13*	1.02-1.25	0.83*	0.69-0.99
vs. non-mood diagnosis	9 vs. 53	1.12*	1.04-1.22	1.00	0.84-1.19
vs. no diagnosis	9 vs. 25	1.96*	1.00-3.85	0.44	0.18-1.05
New unipolar disorder					
vs. No diagnosis	14 vs. 53	1.03	0.97-1.10	1.08	0.96-1.22
vs. non-mood disorder	14 vs. 25	1.08	0.97-1.20	0.95	0.80-1.13
Any new mood disorder					
vs. no diagnosis	23 vs. 53	1.07*	1.01-1.14	1.02	0.91-1.15
vs. non-mood disorder	23 vs. 25	1.14*	1.02-1.26	0.89	0.75-1.04

* $p<.05$

Prediction of switch from unipolar mood disorder to bipolar disorder

The next step was to explore if the GBI scales at T1 predict a switch from unipolar to bipolar disorder between T1 and T3 among the 31 offspring with a unipolar mood

disorder at T1. Seven of them switched to bipolar disorder versus 24 individuals who remained unipolar. The odds ratio for this switch was significant for the Depression scale (odds ratio 1.13, 95% confidence interval 1.02-1.24, p=0.019), but not for the Hypomanic/Biphasic scale (odds ratio 0.85, confidence interval 0.71-1.41, p=1.03). Thus, only elevated scores on the Depression scale predicted a switch from unipolar to bipolar disorder.

Discussion

The purpose of this study was to test the usefulness of the GBI as an instrument to predict the development of bipolar disorder in a sample of adolescent children of parents with bipolar disorder over a follow up period of five years. In adult and adolescent populations the GBI has demonstrated to be a valid self-report measure for mood disorders (Depue et al., 1988; Findling et al., 2002) and a valid instrument to discriminate between mood disorders and behavioral disorders (Danielson et al., 2003).

Unlike the other studies, we found that especially the Depression scale and not the Hypomanic/Biphasic scale of the GBI discriminated well between the emergence of a new bipolar disorder versus unipolar disorder, non-mood disorder or no disorder across the 5-year follow-up interval. For the offspring with a unipolar mood disorder at T1 the Depression scale discriminated well between those who switched to bipolar disorders versus those who remained unipolar across the 5-year follow-up interval. The score on the Depression scale at T1 for offspring with a unipolar disorder who later developed a bipolar disorder was significantly higher than for offspring who persistently showed a unipolar mood disorder across the five year interval.A higher score on the Depression scale predicted the development of a new bipolar disorder. Our findings indicate that in the offspring of parents with bipolar disorder prior to the development of any mood disorder a higher number of depressive symptoms but not of (hypo)manic symptoms predict the eventual bipolar disorder. And, when the disorder has started with a depression, a higher level of depressive symptoms predict the switch to bipolar disorder.

According to Depue et al. (1981) it is to be expected that on the GBI, the hypomanic/biphasic symptoms and not the depressive symptoms discriminate between bipolar versus unipolar disorders. Bipolar disorder starts, however, in more than 80% of the cases with a unipolar mood disorder (Werry, 1991) which was also found in our study (Hillegers et al., in press). High scores on the Depression scale in the early phase

of bipolar disorder are in conformity with this course. Therefore, taking the developmental pathway of bipolar disorder into account, high scores on the Depression scale are to be expected prior to onset of the illness.

This finding also shows that the clinical-diagnostic (DSM-IV) approach and the empirical-quantitative (GBI) approach generate supplementary information. For example, at the first measurement, 31 adolescent offspring had a unipolar mood disorder according to the DSM-IV classification. With the supplementary information on the GBI it was possible to discriminate between those subjects who switched to bipolar disorder across the five year interval versus those who did not.

It should be noted that we tested the predictive validity of the GBI in a population of children with a high risk to develop bipolar disorder. It is not possible to draw conclusions from this study about the usefulness of the GBI as a predictor of bipolar disorder in adolescents from the general population as the estimated overall incidence of bipolar I or II disorder of less than 0.1% per year (Bebbington and Ramana 1995) is much lower than the incidence of 2% per year in our sample.

Clinical consequences

Children of parents with a bipolar disorder are at high risk for developing a mood disorder. Offspring who developed a unipolar mood disorder have a high chance to develop a bipolar disorder themselves (Hillegers et al., in press). In this sample, children still without a disorder but with high scores on the Depression scale of the GBI have an increased probability of a later mood disorder and especially a later bipolar disorder. We would like to suggest to monitor children of parents with a bipolar disorder for the development of mood symptoms, for instance with the GBI. When they develop depressive symptoms, it is important to follow them closely to be able to detect and possibly treat a first (hypo)manic episode, in order to prevent the deterioration of social functioning that can occur after the recurrence of one or more episodes of bipolar disorder (Calabrese et al., 2003).

Conclusion

The present findings demonstrate that the GBI may be used for early detection of bipolar disorders in adolescent offspring of parents with a bipolar disorder.

Chapter 6

Social functioning of bipolar offspring

Social functioning of bipolar offspring

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Abstract

Objective: Bipolar patients have impaired social functioning compared to people in the general population. It has been suggested that children of bipolar patients also have impaired social functioning. The objective of this study was to compare social functioning of adolescent and young adult offspring of bipolar parents with social functioning of adolescents and young adults in the general population.

Method: Subjects were 140 offspring of bipolar parents and 1,122 adolescents and 1,175 young adults from the general population. Parent, teacher and self-report ratings were used to asses social functioning.

Results: Analyses revealed no differences in scores on social functioning for offspring aged 11 to 18 years, and few differences for ages 18 to 26 years compared to same aged individuals from the general population. Offspring with a DSM-IV disorder showed a lower level of social functioning compared to Dutch subjects from the general population in the same age range.

Conclusions: Bipolar offspring in the adolescent age range have good overall level of social functioning. Social functioning in offspring aged 18 years or older with a bipolar or other mood disorder is impaired, and especially in the domain of family functioning. For all other domains no significant differences in social functioning between bipolar offspring and individuals from the general population could be found.

Submitted

Introduction

Bipolar disorder is an illness with substantial impact on social functioning. In 2001, the World Health Organization identified bipolar disorder as the ninth leading cause of years lived with disability in the world among people aged 15 to 44 years (World Health Organisation, 2001). A number of studies on the impact of bipolar disorder reported more difficulties with social functioning in individuals with bipolar disorder versus those without (Calabrese et al., 2003; Coryell et al., 1993; Dean et al., 2004). MacQueen et al. (2001) reviewed 17 studies on psychosocial outcome in bipolar disorder over the last 25 years and concluded that 30 to 60% of individuals with this disorder fail to regain full functioning in occupational and social domains. These studies pertained to the social functioning of adults who had been subjected to the negative consequences of the disorder over an extended period. Several studies found that functional impairment often persists after syndromal recovery (Winokur et al., 1995; Keck PE et al., 1995; Tohen et al., 2003).

To our knowledge there is much less known about individuals' social functioning prior to or shortly after the onset of bipolar disorder. It may be that individuals with future bipolar disorder are already impaired in social functioning before the onset of the disorder. If, for instance, their social functioning during childhood or adolescence is impaired this may have negative effects on their adult functioning over and above the effects of the bipolar disorder itself. If, on the other hand, individuals with bipolar disorder showed unimpaired social functioning prior and/or shortly after the onset of the disorder this may have important implications for treatment which then should not be restricted to alleviating symptoms but should also include a focus on preserving adequate social functioning.

Several studies reported retrospectively on premorbid social functioning of bipolar patients. Two studies looked retrospectively at premorbid social functioning in adolescent onset bipolar patients. Kutcher et al. (1998) reported on premorbid academic and peer functioning and premorbid psychiatric illness in 28 adolescent onset bipolar I patients. The authors reported good to excellent peer and academic functioning prior to illness onset, while rates of premorbid psychiatric illnesses were similar to that described in epidemiologic samples. Cannon et al. (1997) found that prior to onset of their illness adolescent patients with bipolar disorder (N= 28) functioned well at school but exhibited more social impairment in adolescence than comparison subjects, though

to a lesser degree than schizophrenic subjects (N= 70). Retrospective studies reporting on the premorbid adjustment of schizophrenic patients, that used adult bipolar patients and healthy subjects as controls, found that premorbid adjustment in bipolar patients was less than in healthy controls, but better than among patients with schizophrenia (Bailer et al., 1996; Gureja et al., 1994; Kolakowska et al., 1985; Mueser et al., 1990). Another way to study social functioning of bipolar patients before and shortly after the onset of the disorder is to study children at risk for developing bipolar disorder such as children of bipolar parents. However, in addition to the genetic risk, these children are also subjected to the risks associated with growing up in a family with a bipolar parent.

Two studies looked at social functioning of children of bipolar mothers. Anderson & Hammen (1993) compared four groups: children of unipolar depressed, bipolar, medically ill, and psychiatrically normal women. In total 69 children, aged 8-16 years, were assessed over a 2-year period at 6-month intervals on social competence, academic performance and behavior problems with the Child Behavior Checklist (Achenbach & Edelbrock, 1983). Children of unipolar depressed mothers showed significantly poorer functioning on all measures when compared to the other three groups of children, including bipolar offspring. A greater proportion of children in the unipolar group had relatively chronic, clinically significant problems in social functioning. Children of bipolar women did not differ from children of psychiatrically normal women. In the study by Petti et al. (2004) a significant difference in social functioning between offspring (aged 7-16 years) with (N= 23) or without (N= 27) a bipolar parent was found. The offspring with a bipolar parent had lower self-reported scores on supportive class-mates and on teachers' and parents' ratings on the Harter scale (1988), compared to offspring with an unaffected parent.

In conclusion, except for the study by Cannon et al. !1997) who reported poor premorbid social functioning among bipolar adolescents and the study by Petti et al. (2004) who reported poor social functioning in children of bipolar parents, the other studies on the social functioning of bipolar adolescents or offspring of bipolar parents did not find impaired social functioning in these groups. However, the study samples were highly selected hampering the generalizability of findings.

In the present study we determined the social functioning of 140 children (age range 11 to 26 years) of a bipolar parent enrolled in a high risk study with three assessment points: at baseline (T1), after one year (T2) and after five years (T3). In previous papers (Wals et al., 2001; Reichart et al., 2004; Hillegers et al., in press) we described that self- and parent-reported problem scores for this bipolar offspring showed few

differences compared with problem scores for normative samples at T1 and T2 while the prevalence of DSM-IV life time bipolar disorder and other mood disorders in this group had increased from 3% and 24% respectively at T1 to 10% and 30% at T3, respectively.

The aims of this study were:

1. To compare the social functioning in adolescent and young adult offspring of bipolar parents with that in individuals of the same age from the general population
2. To compare the social functioning of offspring with bipolar disorder, unipolar mood disorder, other disorders or without disorder

Material and methods

Bipolar offspring

The present study concerns the results of the first and third measurement in a prospective study among 140 children of a parent with a bipolar I or bipolar II disorder in the Netherlands. Subjects recruited for the first measurement (T1) were aged 11 to 21 years and came from 86 families who agreed to participate. All bipolar parents were treated as outpatients at the moment of recruitment, but in the past 70% had been hospitalized several times (14 parents once, 16 parents twice, 10 parents 3 times, 4 parents 4 times, 7 parents 5 times, 7 parents 6 times, one parent 7 times and one parent 8 times). Of the non-bipolar parent 21 (24%) had a mood disorder and 7 (8(%) an other DSM-IV disorder. The recruitment procedure and the results of T1 are described by Wals et al. (2001). Only adolescents without a severe physical disease or handicap and with an IQ of at least 70 were included. The study was approved by the Medical Ethical Review Committee of the University Medical Center Utrecht. After a complete description of the study was given, written informed consent from the bipolar parents and their spouses, and their offspring, was obtained.

The third measurement (T3) was performed after 5 years and included 129 subjects (60 girls and 69 boys), aged 15 to 26 years from 80 families (48 bipolar mothers and 32 bipolar fathers). Of the bipolar parents 59 had a bipolar I disorder and 21 a bipolar II disorder. Six families with a total of 11 adolescents (8 girls, 3 boys) who participated at T1 refused to participate at T3.

Adolescents from the general population

For the comparisons in the age range of 11 to 18 years we used a representative sample of 2227 children and adolescents from the Dutch general population (Verhulst et al., 1997). For our comparisons we only used adolescents aged 11 to 18 years, leaving us with 1122 subjects.

For the comparisons in the age range of 18 to 26 years we used data from a longitudinal study of a random sample of 2,076 children and adolescents aged 4 to 16 years from the Dutch general population. For details on the initial data collection, see Verhulst et al. 1997, Verhulst et al., 1985). The last measurement was in 1997 (Hofstra et al., 2000). For our comparisons we only used young adults aged 18 to 26 years, leaving us with 1175 subjects.

Instruments

The Child Behavior Checklist (CBCL; Achenbach 1991-a) is a questionnaire to be completed by parents of 4- to 18-year-olds on their child's behavioral and emotional problems and competence. In this study we report on the competence part. The 20 competence items of the CBCL obtain parents' reports of the amount and quality of their child's participation in sports, hobbies, games, activities, jobs and chores, and friendships; how well the child gets along with others and plays alone; and school functioning. Competence items can be scored on four scales: Activities, Social, School and Total Competence. Total Competence comprises the sum of the three specific scale scores. The CBCL was used to assess subjects from the general population and the bipolar offspring.

The Youth Self-Report (YSR; Achenbach 1991-ba) has the same response format as the CBCL but has to be completed by 11-18-year-olds themselves. It consists of 17 competence items that can be scored on the same scales as the CBCL competence scales. The YSR was used to assess subjects from the general population and the bipolar offspring

The Teacher's Report Form (TRF; Achenbach 1991-c) can be completed by teachers of 5-18-year-olds who have known a pupil in a school setting for at least two months. It consists of ratings for academic performance, four adaptive functioning scales (Working Hard, Behaving Appropriately, Learning and Happy), and the sum of the four scales. The TRF was used to assess subjects from the general population and the bipolar offspring.

Good reliability and validity of the CBCL, YSR, and TRF have been replicated for the Dutch translations (Verhulst et al., 1996; Verhulst et al., 1997-a; Verhulst et al.,1997-b).

The Young Adult Self-Report (YASR; Achenbach 1997) is an upward extension of the YSR for ages 18 years and older. The YASR is filled out by young adults. The adaptive functioning scales of the YASR consist of Friends, Spouse/Partner, Family, Job, Education and the Mean Adaptive Scale. The Friends and Family scales are scored for all respondents. The Spouse/Partner, Job and Education scales are scored only for respondents for whom the items were relevant at any time the preceding 6 months. The Mean Adaptive Scale provides a summary score based on whatever combination of adaptive scales the subject completes. Examples of questions are: how well do you get along with your close friends; my spouse or partner and I enjoy similar activities; compared to others, how well do you get along with your father; I achieve what I am capable of. The YASR also contains three Substance Use scales, Tobacco ("In the past six months, about how many times per day did you use tobacco?"), Alcohol ("In the past six months, on how many days were you drunk?") and Drugs ("In the past six months, on how many days did you use drugs for nonmedical purposes, including marijuana, cocaine, and other drugs, except alcohol and nicotine?"). The YASR was used to assess subjects from the general population and the bipolar offspring.

Higher scores on CBCL, YSR, TRF and YASR competence scales indicate more favorable functioning. Higher scores on YASR Substance Use scales indicate more use.
The K-SADS-present and lifetime version (K-SADS-PL, Kaufman et al., 1997) was used to derive DSM-IV diagnoses at T1 (Wals et al. 2001) from the bipolar offspring. The SCID (First et al., 1997) was used to derive DSM-IV diagnoses at T3 (Hillegers et al., submitted) from the bipolar offspring.

Statistical Methods

For the comparisons at T1 we only used the youngest adolescents (11-17 years, n=102) in our cohort and at T3 only the oldest adolescents (18-26 years, n=106), as these subjects were assessed with CBCL/YSR or YASR, respectively (table 1).

Table 1: Available scoring lists

	Time 1		Time 3	
Age adolescents	11-17	18-21	15-17	18-26
CBCL/YSR				
Offspring	102		23	
General population	1122		566	
YASR				
Offspring		38		106
General population		441		1175

Of the cohort, 37 adolescents were included in both comparisons. The remaining 38 adolescents at T1 (assessed with YASR) and 23 adolescents at T3 (assessed with CBCL/YSR) were analyzed separately.

For the comparison on social functioning between the bipolar offspring at T1 the 140 subjects were classified into four groups according to their primary DSM-IV lifetime diagnoses at T1: bipolar disorder (n=4), unipolar mood disorder (n=34), other disorder (n=23) and no disorder (n= 79) (see table 2).

Table 2: Available offspring

	Lifetime diagnoses at T1			Lifetime diagnoses at T3	
	Offspring n=140	Offspring with CBCL/YSR (n=102)	Offspring with TRF (n=77)	Offspring (n=129)	Offspring with YASR (n=106)
Mood disorder		30	21		
Bipolar disorder	4			13	10
Unipolar disorder	34			38	35
Other disorder	23	14	12	25	21
No disorder	79	58	44	53	40

Comorbid diagnoses were not taken into account. For 102 of the 140 adolescents in the age range of 11-17 years at T1 CBCLs and YSRs were available. Because this left us

with only 2 subjects with a bipolar disorder in this group the 102 subjects were classified into three groups: mood disorder (n=30), other disorder (n=14) and no disorder (n=58). For 77 of the 140 adolescents TRFs were available at T1. For the comparisons the 77 subjects were also classified into three groups: mood disorder (n=21), other disorder (n=12) and no disorder (n=44).

For the comparison on social functioning between the bipolar offspring at T3 the 129 subjects were classified into four groups according to their primary DSM-IV diagnosis at T3: bipolar disorder (n=13), unipolar mood disorder (n=38), other disorder (n=25) and no disorder (n=53). Comorbid diagnoses were not taken into account. For 106 of the 129 adolescents in the age range of 18 to 26 years at T3 YASRs were available: bipolar disorder (n=10), unipolar disorder (n=35), other disorder (n=21) and no disorder (n=40).

Analyses of variance (ANOVAs) were performed in a 5 group (bipolar, unipolar, other, no disorder, general population) $\times$ 2 gender (girls versus boys) factorial design to test differences in social functioning. Differences significant at a level of $p < .05$ are indicated. ANOVAs were followed by a LSD post hoc test and a test for the contrast of bipolar offspring versus general population subjects.

To aid readers in judging the practical importance of statistically significant effects, we report effect sizes (ES) evaluated according to Cohen´s criteria (Cohen, 1988), with 1% to 5.9% of variance indicating small, 5.9% to 13.8% indicating median and 13.8% or more indicating large effect sizes.

Results

Table 3 shows the results of the ANOVAs of social functioning of adolescents, aged 11-18 years, as reported by mothers, teachers and adolescents themselves at T1. Only for self-reported Activities a significant effect was found, indicating higher (more favorable) scores for the bipolar offspring than adolescents in the general population. Pair wise comparisons indicated that offspring with mood disorder and without disorder had higher scores than adolescents from the general population. The academic performance and total social functioning scores reported by teachers yielded no significant differences between the different groups and the general population subjects.

Table 3: Mean Scores on the social functioning scales on the CBCL, YSR and TRF at T1 for adolescent aged bipolar offspring with a lifetime bipolar disorder, an unipolar mood disorder, an other disorder or no disorder at T1 versus general population subjects and results of comparisonsbetween the groups in ANOVA's with group and gender as fixed factors and followed by LSD post hoc test

Bipolar offspring with:	Parent Report				Self-Report				Teacher Report					
	Total competence	School	Social	Activities	Total competence	School	Social	Activities	Total adaptive	Working hard	Behaving appropriately	Learning	Happy	Academic performance
Mood disorder (n=30)	14.8	4.3	5.6	5.0	12.9	2.2	6.2	4.5[ab]	18.3	4.4	4.7	4.7	4.3	369
Other disorder (n-14)	14.6	4.5	5.8	4.3	13.1	2.4	6.7	3.5[a]	18.1	5.2	4.0[j]	4.4	4.5	348
No disorder (n=58)	15.3	4.9	5.7	4.9	13.1	2.3	6.5	4.3[c]	18.2	4.7	4.7[j]	4.6	4.4	365
General population subjects (n=1122)	15.4	4.7	5.9	4.7	12.6	2.3	6.4	3.9[bc]	18.2	4.5	4.5	4.4	4.8	351
F	0.50	1.84	0.73	0.65	0.86	1.06	0.29	3.65	0.01	0.67	1.15	0.42	2.36	0.66
p	.68	.14	.53	.58	.46	.36	.83	.01[1]	.99	.57	.33	.74	.07	.57

[a-c] Equal superscript across columns indicate pair wise significant differences according to the LSD post hoc test.
[1] Effect size<1%
Note: higher scores means better functioning

Table 4: Mean Scores on the social functioning scales and substance use on the YASR for adolescent aged Bipolar Offspring with a lifetime bipolar disorder an unipolar mood disorder, an other disorder or no disorder at T3 versus general population subjects and results of comparisons between groups in ANOVAs with group and gender as fixed factors and followed by a LSD post hoc test

	n	Friends	Education	Job	Family	Spouse	Mean adaptive functioning	Tobacco	Alcohol	Drugs
Bipolar offspring with:										
Bipolar disorder	10	6.9	3.7	3.9	10.4[a]	5.7	44.5[abc]	6.2	3.9[a]	4.2
Unipolar disorder	35	7.3	3.9	4.4	12.0[b]	6.3	46.7[d]	6.0[a]	4.9[b]	24.1[ab]
Other disorder	21	7.8	4.0	4.8	12.1[c]	7.2	47.9[a]	4.0	8.2[abcd]	19.1[cd]
No disorder	40	7.4	4,4	4.7	13.3	7.4	48.2[b]	0.9[ab]	2.4[c]	0.4[ac]
General population Subjects	1175	7.6	3.7	4.7	14.3[abc]	6.4	48.5[cd]	5.5[b]	3.2[d]	4.8[bd]
F		1.08	1.16	0.68	5.77	0.79	4.18	3.26	2.49	5.18
P		.36	.33	.61	.00[1]	.53	.00[1]	.01[1]	.04	.00[1]

[a-d] Equal superscripts across columns indicate pair wise significant differences according to the LSD post hoc test.
Note: higher scores on the social functioning scales means better functioning. Higher scores on the substance use scales mean higher use.
[1] Small ES (1% of variance); all the other effect sizes <1%

Table 4 shows the results of the ANOVAs of self-reported YASR-social functioning and substance use of young adults aged $\geq$ 18 years at T3. Four of the social functioning scales did not show significant differences in scores between the different groups. In contrast, on the Family scale a significant effect was found (ES 1.8%). Pair wise comparisons indicated that offspring with bipolar disorder, unipolar mood disorder and with another disorder had lower Family scale scores than adolescents from the general population. The test for difference between scores for bipolar offspring as a group and young adults in the general population was significant ($p<0.01$). Also on the Mean Adaptive Scale a significant effect was found (ES 1.3%), with pair wise comparisons indicating that offspring with bipolar disorder or unipolar mood disorder had lower scores than adolescents from the general population. The test for difference between scores for bipolar offspring as a group and young adults in the general population was significant ($p <0.01$).

Also for the substance use scales significant differences were found. On the Drugs scale a significant difference was found (ES 1.6%). Pair wise comparisons indicated that offspring with unipolar mood disorder or another disorder had significantly higher scores than adolescents from the general population. The test for difference between offspring as a group and young adults in the general population was significant ($p <0.05$). On the Alcohol scale, only offspring with another disorder had higher scores than adolescents from the general population. The Tobacco scale showed significantly lower scores for offspring without disorder than for adolescents from the general population.

In order to verify findings we also analyzed available CBCL and YSR scores from 23 adolescents who were 18 years or younger at T3 and YASR scores from 38 young adults who were 18 years or older at T1. The comparisons between bipolar offspring and subjects from the general population revealed only one significant difference. Self-reported activities was scored higher by bipolar offspring ($p<0.01$) than by subjects from the general population (data not shown for reasons of brevity).

Discussion

In this study we compared the social functioning of offspring of bipolar parents with that of individuals in the general population divided into two age groups: 11 to 18 years and 18 to 26 years. Comparisons revealed different results for these two age groups. For 11-

to 18-year-olds, mothers scored their offspring on total social functioning in the same range as mothers in the general population. Adolescent offspring scored themselves even as more favorable functioning on the Activities scales than adolescents from the general population.

In contrast, in the age group of 18 to 26 years, offspring with bipolar disorder had significantly lower scores on the Mean Adaptive Functioning Scale than young adults from the general population. Offspring with unipolar mood disorder also had lower Mean Adaptive Functioning scores than young adults from the general population. Offspring without disorder had similar levels of social functioning as adolescents from the general population. As a group offspring aged ≥18 years had lower scores on the Family scale than young adults from the general population. This scale comprises questions on how well the individual gets along with brothers, sisters, father or mother. Pair wise comparisons showed that only for offspring without DSM-IV diagnoses (41% of the sample aged ≥18 years), no differences in Family Scale scores compared to young adults from the general population were found. Having a family with a bipolar father or mother seems to be difficult for young adults with a psychiatric disorder. Problems with family functioning were assessed for the older subjects at T3 only. Their mean age was 21 years and 50% had their own household. Despite the fact that half of the sample did not live with their parents anymore, they reported more problems in their relationship with their original family than individuals of the same age from the general population.

An explanation for the relatively unimpaired social functioning of bipolar offspring that we found, especially for offspring below the age of 18 years, could be that bipolar parents in our sample probably are a selection of rather well-functioning parents. Almost two thirds of them were members of a patient organization, all were under current treatment and the occupational level of our sample was similar to that for the general population. The majority was willing to cooperate in this prospective study across a 5 year period. Nevertheless, the present study's results are in line with results from earlier studies concerning younger bipolar offspring. Anderson & Hammen (1993) found that the overall level of social functioning of bipolar offspring aged 4 to 16 did not differ from that of children and adolescents in the general population. Of course it is possible that this unimpaired social functioning will not last as these children grow older and that in a few years social problems will emerge.

Substance use is an important factor responsible for the deterioration in patients with bipolar disorder. Drug and alcohol use reported on the YASR was high for offspring in our sample between 18 and 26 years with unipolar or other disorders. According to

the SCID 20% (8 out of 38) of the offspring with a unipolar mood disorder and 50% (12 out of 25) of the offspring with another disorder had a comorbid DSM-IV substance use disorder. Surprisingly offspring with a bipolar disorder did not show increased levels of substance use on the YASR and according to the SCID only 7% (1 out of 13) had a comorbid DSM-IV substance use disorder. Offspring without diagnosis used less than individuals from the general population. This may be a chance finding, but it is also possible that in adolescent and early young adult years, children of bipolar parents are aware of the risks of substance abuse, possibly through their parent's experiences with substance abuse (Regier et al., 1990; Strakowski et al., 2000; Winokur et al., 1998).

Many subjects in our sample had life-time disorders but no current disorders: 27 % had any current disorder and 59% a life-time disorder at time 3. When we excluded subjects with current diagnoses form our analyses, the results regarding social functioning remained the same (data not presented). Thus, it seems that having a life-time diagnosis, with or without currently fulfilling criteria for a mood disorder was associated with social impairment. This is in line with Coryell et al. (1993) who found that psychosocial deficits in patients with bipolar or unipolar mood disorder sustain as long as 2 years following recovery from a depressive or manic episode.

In conclusion, the most salient finding in the present study was that the overall level of social functioning of bipolar offspring under the age of 18 years did not differ from that of adolescents from the general population. In contrast, after the age of 18 years subjects with bipolar disorder, another mood disorder or any other DSM-IV disorder had impaired social functioning, especially in the domain of family functioning.

Limitations

A limitation of this study, shared with other studies in offspring of bipolar parents, is the lack of information on the representativeness of the sample. It could be that the more motivated parents participated or that the most impaired parents and/or adolescents refused to participate.

As a consequence of the broad age range in our cohort, we have used different instruments that assessed partly different domains of social functioning for different ages. For ages 11 to 18 years we have assessed social functioning in school and at home according to three different informants (parents, teachers and adolescents). For ages 18 years or older, we have assessed social functioning in school, job, at home and with spouses as well as substance use through self-reports. The use of different

instruments may have contributed to differences in results for the two age groups that we found.

Clinical implications

This study showed that adolescent offspring of bipolar parents do not show signs of impaired social functioning. This is very important because in general one of the predictors for success of treatment is good premorbid social functioning (Emslie et al., 2003).

At the last assessment, 13 individuals (10%) of the 129 bipolar offspring fulfilled the criteria for bipolar disorder. The bipolar offspring are now in the age range of 15 to 26 years. We anticipate that in this sample, because of its high risk for developing bipolar disorder, the prevalence of bipolar disorder will further increase over the next few years. These individuals have probably a better prognosis and a better chance on success with treatment, if there is no prior impaired social functioning.

From studies among adults we know that bipolar and other mood disorders are associated with impaired social functioning. From the present study's findings we concluded that our offspring group with a high risk for developing bipolar disorder (and 10% indeed developed a bipolar disorder up till now) do not show impaired social functioning. Only with those subjects who had a lifetime DSM-IV disorder at T3 we did see increased levels of impairment, especially with regard to family functioning. Our results therefore support the idea that social functioning of bipolar (and also unipolar) patients prior to illness onset is largely unimpaired and that impairment is the result of the disorder. It is therefore that clinicians should extend their interventions beyond mere treatment of mood symptoms. They should also pay attention to restoring or improving social functioning, e.g. via rehabilitative interventions (Kopelowicz & Liberman, 2003).

Chapter 7

Perceived parental rearing of bipolar offspring

Perceived parental rearing of bipolar offspring

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Abstract

Objective: First: to compare parental rearing behavior perceived by young adult offspring of bipolar parents with parental rearing behavior perceived by same aged young adults from the general population. Second: to examine the associations between perceived parental rearing behavior and parental psychopathology and psychopathology in offspring.

Method: Subjects were 129 offspring of 80 bipolar parents and their spouses and 1,122 young adults from the general population. In offspring the SCID was used to assess DSM-IV diagnoses and the EMBU was used to asses perceived parental rearing in both groups.

Results: In general, offspring growing up in a family with a bipolar parent perceived their mothers as less rejecting, more emotionally warm and less overprotecting and their fathers as less emotionally warm and less overprotecting compared to young adults from the general population. Perceived rejection was related to psychopathology in offspring.

Conclusions: Parental rearing in families with a parent with a bipolar disorder is not more dysfunctional, as perceived by their offspring, than in families from the general population. Offspring with a bipolar disorder perceive their parents as more rejecting.

Submitted

Introduction

Bipolar disorder does not only affect individuals who have the disorder but also their environment, including family members. With bipolar disorder, there is a mutual influence between the affected individual's functioning and the family. Family attitudes can affect the illness course while the illness has a great impact on family distress and functioning (Reinares & Vieta, 2004). When living with someone with bipolar disorder, family members have to deal with various aspects of the disorder. Manic episodes during which patients are overactive, aggressive or destructive, and depressive episodes during which patients are inactive, absent, or even suicidal can lead to various reactions in family members such as experiencing painful emotions, anger, anxiety, concern and ambivalence.

Also families with bipolar patients may experience restrictions in social and leisure activities, a drop in family income and strain on marital relations. In the Netherlands Mental Health Survey and Incidence Study (NEMESIS), a study among 7,076 individuals from the general population, respondents with bipolar disorder (n=136) scored as significantly more dysfunctional than respondents with other types of mental disorders. This pertained not only to mental health, but also to role limitations and social functioning scales (Ten Have et al., 2002). In another study, 53% of spouses of patients with bipolar disorder, compared with 5% of the bipolar patients themselves, indicated that they would not have been married, and 47% of spouses, compared with 5% of patients, would not have had children, had they known more about bipolar illness prior to making these decisions (Targum et al., 1981). This study suggests that bipolar patients minimized the seriousness of the effects of the illness. In a more recent study, 62% of the partners of bipolar patients reported that they would probably not have entered into the relationship if they had had more knowledge about the illness and its effects (Dore & Romans, 2001).

Often family relations in families with a bipolar patient are seriously disturbed. Brodie and Leff (1971) found that marital failure rates were significantly higher in bipolar patients, compared with unipolar depressed patients, and suggested the probable incompatibility of manic symptoms with a stable marriage. Chakrabarti et al. (1992) found that the burden of care in families with a bipolar patient was greater than in families with a patient with unipolar depression. The authors suggested that social disruption, due to manic episodes, might explain this difference.

According to these studies it can be concluded that apparently growing up in a family with a father or mother with bipolar disorder must have an enormous negative impact on children. In a study by Chang et al. (2001) on 60 children from 37 families with at least one parent with a bipolar disorder, parents judged their families as less cohesive, less organized and more conflicted.

To our knowledge, there is no information on the perception of children themselves about their upbringing in a family with a parent with bipolar disorder. Parenting is not a unidirectional process, but part of a dyadic relationship, in which the child actively participates (Bell & Chapman, 1986). Attachment research shows that children are influenced by the rearing behavior of their parents through their mental representations of this behavior (Main et al., 1985). Therefore, when investigating the role of parental rearing, it is especially important to capture the children's perception of their upbringing.

The aim of the present study was to compare how adolescent and young adult offspring living in a family with a bipolar parent (bipolar offspring) perceive their families versus the perception of family functioning by adolescents and young adults from the general population, and to determine the association between a number of parent and offspring related factors and the offspring's perception of parental rearing practices.

This leads to the following questions:

1. How do offspring of bipolar parents perceive parental rearing practices compared to subjects from the general population?
2. Do parental characteristics (gender of the bipolar parent, severity of bipolar disorder, number of hospitalizations, age of first episode, socio economic status) and child characteristics (gender, IQ, psychiatric status) explain the differences in parental rearing practices as perceived by bipolar offspring?

Materials and methods

Bipolar offspring

The present study concerns the results of the third measurement in a prospective study among 140 children of a parent with a bipolar I or bipolar II disorder in the Netherlands (see Wals et al. (2001)) for details on the recruitment procedure. At the first measurement, subjects were aged 12 to 21 years and came from 86 families who

agreed to participate. Adolescents with a severe physical disease or handicap or with an IQ below 70 were excluded. All bipolar parents were treated as outpatients at the moment of recruitment, but in the past 70% had been hospitalized (14 parents once, 16 parents twice, 30 parents 3 times or more). The study was approved by the Medical Ethical Review Committee of the University Medical Center Utrecht. After a complete description of the study was given, written informed consent from the bipolar parents, their spouses, and their offspring, was obtained.

The third measurement was performed 5 years after the first measurement and included 129 subjects (60 girls and 69 boys), aged 16 to 26 years from 80 families (48 bipolar mothers and 32 bipolar fathers). Of the bipolar parents 59 had a bipolar I disorder and 21 a bipolar II disorder. Six families with a total of 11 adolescents (8 girls, 3 boys) who participated in the first measurement did not participate anymore. Lifetime diagnoses in the offspring were bipolar disorder (n=13, 10%), unipolar mood disorder (n=38, 30%), other disorder (n=25, 19%) and no disorder (n=53, 41%). Comorbid diagnoses were not taken into account. Detailed information of the parents still participating in the study is presented in table 1.

Table 1: Demographics parents at T3

	n	%	Mean	SD
Bipolar fathers	32	40		
Bipolar I disorder	23			
Bipolar II disorder	9			
Age (years)			46.5	4.7
Age first episode (years)			25.9	10.7
Age first manic episode (years)			32	9.8
Number of hospitalizations			1.9	2.1
Severity of bipolar disorder according to IDCL			3.5	1.0
Bipolar mothers	48	60		
Bipolar I disorder	36			
Bipolar II disorder	12			
Age (years)			44.7	4.7
Age first episode (years)			26.1	9.2
Age first manic episode (years)			30.4	9.6
Number of hospitalizations			2.3	2.1
Severity of bipolar disorder according to IDCL			3.6	1.3
Non bipolar parents	80			
Age (years)			46.2	5.2
No psychiatric disorder	56	70		
Mood disorder	19	24		
Other psychiatric disorder	5	6		

General population

For the comparisons with the general population we used data from a longitudinal study of 2,076 children and adolescents randomly selected from the Dutch general population. For details on the initial data collection, see Verhulst et al. (Verhulst et al., 1985). The last measurement was in 1997 (Hofstra et al., 2000). For our comparisons we used information on 1,122 young adults aged 18 to 26 years.

Instruments

Offspring assessment

Respondents' perceptions of their parents´ rearing behavior was assessed with the EMBU (Swedish acronym for Egna Minnen Beträffande Uppfostran, 'My memories of upbringing'), a questionnaire of 81 items answered by the subject on a four point-scale, separately for the mother and the father (Perris et al., 1980; Arrindell et al., 1983). The scales of the EMBU show strong factorial stability across samples both within and across nations (Arrindell et al., 1994). We used a short form of the EMBU (Arrindell et al., 1999) that contains 23 items and consists of three scales: Rejection, Emotional Warmth and Overprotection.

Psychiatric diagnoses were assessed with the K-SADS-present and -life time version (K-SADS-PL; Kaufman et al., 1997) at the first two measurements and (because the respondents had become older) with the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID I; First et al. (1997)) at the third measurement in order to determine current (last month) and lifetime psychiatric diagnoses according to DSM-IV. Since the SCID did not include all DSM-IV diagnoses, an appendix for Attention Deficit Hyperactivity Disorder, Oppositional Defiant Disorder, Conduct Disorder and Tic Disorders derived from the K-SADS-PL was added to the SCID. The interviews were conducted by two of the authors (MH and MW) and 3 trained interviewers with graduate degrees in psychology. All interviewers were intensively trained, and all interview outcomes were discussed with a child and adolescent psychiatrist (CR). Lifetime DSM-IV diagnoses were based on the psychiatric interviews that took place during all three measurements adding up the lifetime diagnoses at the first measurement with the incidence of psychopathology since then. At the same time the hierarchical rules of DSM-IV were taken into account. For example, a subject with a lifetime major depressive disorder at the first measurement, who subsequently developed a manic episode was counted lifetime only for a bipolar disorder in this study.

Parent assessment

To confirm DSM-IV bipolar I or II diagnoses of the bipolar parent we used the mood disorders section of the International Diagnostic Check List (IDCL, Hiller et al., 1993). Comparisons between IDCL-based diagnoses and DSM-IV diagnoses made by the treating psychiatrist revealed no discrepancies. The severity of the bipolar disorder was scored on a 5-point scale based on the number and severity of episodes and number and duration of the hospitalization, ranging from 0 (= only hypomania) to 5 (= more than 6 manic or depressive episodes and more than 2 hospitalisations and/or a hospitalisation of more than 13 weeks).

Socioeconomic status (SES) was scored on a 9-point scale of parental occupational level with 1 = lowest and 9 = highest. If both parents worked, the highest score was used. The mean SES of the parents in our sample of 4.9 (SD = 2.1) did not differ significantly from the mean of 4.5 (SD = 2.1) from a Dutch general population sample (Netherlands Central Bureau of Statistics, 1993) (t = 1.94, p = .06).

Statistical Analyses

For the comparison on perceived parental rearing among the bipolar offspring, the 129 subjects were classified into four groups according to their primary DSM-IV diagnosis: bipolar disorder, unipolar mood disorder, other disorder or no disorder. Analyses of variance (ANOVAs) were performed in a 5 group (bipolar, unipolar, other, no disorder, general population) × 2 gender (girls versus boys) factorial design to test differences in perceived parental rearing. Differences significant at a level of $p < .05$ are indicated. ANOVAs were followed by a LSD post hoc test and a test for the contrast of bipolar offspring versus general population subjects. To aid readers in judging the practical importance of statistically significant effects, we reported effect sizes (ES) evaluated according to Cohen´s (Cohen, 1988) criteria.

For the analyses of determinants of perceived rearing practices linear regression analyses were performed with the EMBU scales Rejection, Emotional Warmth and Overprotection as dependent variables, separately for father and mother. To control for the impact of the level of social functioning of the families we added parental SES as independent variable in the linear regression analyses and found no significant differences. Therefore we did not include this variable in the rest of the analyses. Then we added as independent variables gender of bipolar parent (0 = mother, 1 = father), gender of offspring (0 = girl, 1 = boy), interaction gender offspring and gender bipolar parent, and psychopathology in offspring (bipolar disorder (1) versus no disorder (0),

unipolar disorder (1) versus no disorder (0), other disorder (1) versus no disorder (0)). After that, we added several variables that reflected the severity of parental psychopathology: number of hospitalizations of the bipolar parent (0= fewer than 2 hospitalizations, 1 = 2 or more hospitalizations), age of onset first episode of the bipolar parent, number of manic episodes of the bipolar parent, psychiatric disorder of the non-bipolar parent.

Results

Compared to young adults in the general population, offspring growing up in a family with a bipolar parent perceived their mothers as significantly less rejecting, more emotionally warm and less overprotecting, and their fathers as significantly less emotionally warm and less overprotecting (table 2).

Table 2: Mean Scores on the EMBU for bipolar offspring versus general population subjects and results of comparisons between groups in ANOVAs with group and gender as fixed factors

Scale	Rejection		Emotional warmth		Overprotection	
	Father	Mother	Father	Mother	Father	Mother
General population subjects (n=1122)	8.85^{de}	8.77^{1ab}	17.08^{1bd}	16.78^{1abc}	17.37^{1abc}	18.74^{1ab}
Bipolar offspring with						
Bipolar disorder (n=13)	10.73^{abcd}	9.08	15.95	17.80	16.27	18.03
Unipolar mood disorder (n=38)	8.74^{b}	7.95^{a}	15.24^{ab}	17.71^{a}	15.10^{a}	17.45^{a}
Another disorder (n=25)	8.34^{c}	8.08	14.91^{cd}	18.82^{b}	15.24^{b}	18.01
No disorder (n=53)	8.09^{ae}	7.85^{b}	17.65^{ac}	18.65^{c}	16.15^{c}	17.03^{b}
F	3.35	3.87	3.92	9.00	6.49	3.73
P Value	.01	.00	.00	.00	.00	.00
ES	1.1%	1.2%	1.2%	2.7%	2.0%	1.2%

No significant differences in EMBU scores for boys versus girls
[a-e] Equal superscripts across columns indicate pair wise significant differences according to the LSD post hoc test.
[1] Indicates significant difference between general population and bipolar offspring (p value contrast .00)
ES= Effect Size (1%-5.9% of variance is small effect size according to Cohen´s criteria)

When offspring were divided into subgroups of those with a lifetime bipolar disorder, unipolar disorder, other disorder or no disorder, there were a few significant differences in perceived parental rearing compared to subjects from the general population. Compared to young adults from the general population, offspring without DSM-IV diagnoses perceived their fathers and their mothers as significantly less rejecting and less overprotecting, and their mothers as more emotionally warm. Offspring with a lifetime bipolar disorder themselves perceived their fathers as significantly more rejecting. Offspring with a lifetime unipolar disorder perceived their mothers as significantly less rejecting, less overprotecting, and more emotionally warm and their fathers as less emotionally warm and less overprotecting.

Table 3 shows the results of the regression analyses regarding the association, indicated by betas, between parent and offspring factors with perceived rejection, emotional warmth and overprotection by father and mother.

Table 3: Regression analyses of parental bipolar disorder (father or mother with bipolar disorder), child psychopathology, gender and interaction gender and parental disorder predicting sores on the EMBU (rejection, emotional warmth and overprotection)

Predictor variables	Dependent variables EMBU					
	Rejection by father	Rejection by mother	Emotional warmth of father	Emotional warmth of mother	Over-protection by father	Over-protection by mother
	β	β	β	β	β	β
Gender of parent with bipolar disorder	-0.25*	-0.27*	-0.13	0.04	-0.07	-0.26*
Gender of child	0.09	-0.11	-0.11	-0.15	-0.04	-0.13
Interaction gender bipolar parent and gender child	-0.08	0.34*	0.08	-0.11	0.15	0.28
Child psychopathology						
Bipolar disorder	0.30**	0.23*	-0.12	-0.06	0.01	0.06
Unipolar disorder	0.10	0.01	-0.24*	-0.11	-0.12	0.03
Other disorder	0.07	0.07	-0.19*	0.03	-0.05	0.07
Explained variance (%)	8.8	6.4	3.8	2.5	1.1	5.0

*P < 0.05; ** P < 0.01

Regarding the gender of the bipolar parent, offspring with a bipolar father perceived their fathers as more rejecting than offspring with a bipolar mother and offspring with a bipolar mother perceived their mothers as less rejecting and less overprotecting than offspring with a bipolar father.

Regarding their own lifetime psychopathology, offspring with a bipolar disorder perceived their fathers and their mothers as more rejecting than offspring without a disorder and offspring with a unipolar disorder and with another disorder perceived less emotional warmth by their fathers than offspring without a disorder.

Table 3 shows a significant interaction between gender of the bipolar parent and gender of the offspring. Sons of bipolar fathers and daughters of bipolar mothers perceived their mothers as more rejecting than daughters of bipolar fathers or sons of bipolar mothers.

Severity of bipolar disorder of the bipolar parent (number of hospitalizations, age at first episode) as well as psychiatric disorder of the non-bipolar parent did not predict the EMBU scores.

Discussion

Compared to young adults from the general population, offspring living in a family with a bipolar parent perceived their parents overall in a more positive way. More specifically, offspring of bipolar parents perceived their mothers as less rejecting, more emotionally warm and less overprotecting, and their fathers as less overprotecting, but also as less emotionally warm. Though significant, the differences in perceived parental rearing between bipolar offspring and young adults from the general population were small according to Cohen´s (Cohen, 1988) criteria for effect sizes.

The positive evaluation by bipolar offspring of their upbringing may be surprising and did not confirm findings as reported in the literature (Reinares & Vieta, 2004; Targum et al., 1981; Dore & Romans, 2001; Chakrabarti et al., 1992) that stress has great impact on bipolar disorder and on family functioning. However, within the offspring group perceived parental rejection depended on psychopathology in the offspring. Offspring with a bipolar disorder reported more rejection by their fathers and mothers compared to offspring with other diagnoses or without diagnosis and compared to individuals from the general population. Offspring without a disorder reported less

rejection than subjects from the general population. These findings are not in line with the study by Chang et al. (2001) who demonstrated that families in which one or both parents had bipolar disorder, reported more conflict, less organization, and less cohesion compared to controls, but also that these features of family interaction were not associated with the presence of psychopathology in the children. However, these results were based on the perception of the parents, and not on the perceptions of the children, of whom some of them were at that time to young to be able to report on family functioning (age 6-18 years).

Remarkably, offspring with a lifetime unipolar mood disorder reported less rejection and more emotional warmth from their mothers. In our offspring sample, 38 respondents had a lifetime unipolar mood disorder, but only 5 of them (13%) had a current unipolar mood disorder. This means that most respondents with a lifetime unipolar mood disorder did not meet diagnostic criteria for a mood disorder when they were interviewed. A possible explanation for this finding is that in recovered depressed patients, when defense mechanisms are restored (mainly denial and repression), there is a tendency to idealize rather than to blame their parents (Arieti & Bemporad, 1978; Wolfenstein, 1955; Miller, 1981).

Another possible factor influencing the child's perception of rejection by the parent is the gender of parent and child. In families where the father has a bipolar disorder, sons feel the most rejected by their mothers and daughters experience the least rejection by their fathers. In most other studies on perceived parental rearing using the EMBU there are significant gender differences in relation to rejection, with boys experiencing greater rejection than girls. However, in those studies, boys especially experience rejection from their fathers (Markus et al., 2003). In our study, the high perceived rejection of son's by their nonbipolar mothers may be explained by the similarity of the son and the bipolar father as perceived by the mother. The high perceived rejection of daughters by their bipolar mothers seems in line with the expectations.

In contrast to our expectations, severity of illness of the bipolar parent, as expressed by the number and severity of episodes, and the age of onset of the first episode did not have an effect on the perception of parental rearing practices by the offspring. Thus, we could not support the suggestions by Reinares et al. (1) that (especially manic) episodes are the most exasperating for the family functioning. Also unexpectedly, the presence of a psychiatric disorder in the non-bipolar parent did not have an influence on perceived parental rearing. This does not support the findings by Merikangas et al. (1983) who found that affectively ill patients who were married to

persons who are also psychiatrically ill have a significantly poorer global outcome than those married to persons without mental illness.

According to Dore and Romans (2001) 62% of the partners of patients with a bipolar disorder felt that they would probably not have entered into the relationship if they had had more knowledge about the illness and its effects. And in a study by Kessler et al. (1998) persons with a bipolar disorder had a 3.2 times higher chance to divorce. Strikingly, in our sample, 77% of the parents with a bipolar disorder (mean age 45 years) was married, and 5 years later 64% was still married to the same person. In the year 2000, 34% of the general population in the Netherlands was divorced after a marriage of 12.9 years, with a mean age of 41.9 years for men, and 39.0 years for women (Netherlands Central Bureau of Statistics, 2003). This means that there are no large differences in divorce rates in our sample compared to the general population in the Netherlands. A possible explanation for this finding is that more than half of the families in our sample were members of the 'Dutch Patient Association for Bipolar Patients and their Relatives'. Possibly our sample is to some extent overrepresented by motivated parents with stable relationships, living in well organized families. There are however more studies on bipolar patients with positive evaluation of marriages. In a study by Frank et al. (1981) on aspects of marital adjustment in a clinical sample of bipolar patients and controls, the non-patient couples rated their marriages as only slightly more satisfying as did the bipolar patient-well spouse couples. An explanation by the authors for this finding is that all patients in their study were in remission. This was also the case when we recruited the parents for our study. However, in the 5 years of follow-up, several of the parents suffered episodes, while one of the fathers committed suicide.

A strong point of our study is the sample size, as far as we know, there are no larger studies among bipolar offspring. Although it has to be noted that even this sample size limits the power to detect even strong effects. A limitation is that our sample is a selected sample of motivated parents (see before). It may be possible that patients recruited via a patients association are the relatively good functioning patients as compared to those of the outpatient clinics. With regards to social functioning and severity of the psychopathology of the bipolar parents, however, parents recruited via the outpatient clinics did not show significant differences in number of hospitalizations ($t = .52$; $df = 127$; $p = .60$), age at onset first episode ($t = 60$; $df = 124$; $p = .54$), number of manic episodes ($t = 1.41$; $df = 126$; $p = .16$), SES ($t = .14$; $df = 127$; $p = .88$) and divorce rate; ($\chi^2 = .08$; $df = 1$; $p = .78$) compared to parents recruited via a patients

association. In addition, we are not aware of differences in severity between bipolar patients under treatment in outpatient clinics in the Netherlands compared to these patients in other countries.

Conclusions

Adolescents and young adults growing up in a family with a bipolar parent perceive the quality of their upbringing in general as more positive compared to subjects in the general population. The most salient finding in the present study was that the psychiatric disorder of the offspring had more impact on the perceived rearing practices of the parents than the bipolar disorder of the parents. Higher perceived rejection was associated with the presence of psychopathology in the offspring.
Although it is generally acknowledged that psychosocial variables play an important role in the course of bipolar disorder, the results of this study suggest that substantial difficulties in upbringing may not be present. Therefore, special treatment programs employing family therapy on an a priori indication in families with a bipolar parent may not be indicated, at least not in families who are aware of their illness (such as members of a patient organization). However general psycho-education, evaluation of family relations and rearing practices, and assistance with concrete and specific problems concerning living with a bipolar parent, may be beneficial. In addition, we support a suggestion of Lachenmeyer (2000) who states that family narratives in which parents and offspring provide accounts of the experiences of growing up and living in families with a bipolar patient can be an antidote against the silence, guilt and responsibility among relatives of individuals with bipolar disorder. Such narratives may be a useful adjunct in self-help groups of patient associations and in psycho-education groups.

Chapter 8

General discussion and conclusions

General discussion and conclusions

Recapitulation of research questions

The main aims of this thesis were to determine early symptoms and prospective course of symptoms among offspring of bipolar parents, to evaluate a diagnostic instrument for the prediction of bipolar disorder and to determine the consequences on social functioning and family of being a child of bipolar parents.

More specifically the main questions of this thesis were:

1. What is the prevalence and incidence of psychopathology, especially mood disorders among the offspring of bipolar parents? (chapter 2)
2. What is the course of affective symptomatology and what are determinants for the age of onset of mood disorders, including bipolar disorder in bipolar offspring? (chapter 3)
3. Is it possible to use the General Behavior Inventory (GBI), an instrument to identify bipolar and unipolar mood disorders across the full spectrum of severity, in a population of adolescent offspring of parents with a bipolar disorder? (chapter 4)
4. Is it possible to use the GBI as a predictor of bipolar disorder in a population of adolescent offspring of parents with a bipolar disorder? (chapter 5)
5. How is the social functioning of the bipolar offspring? (chapter 6)
6. What is the experience of parental rearing in the bipolar offspring? (chapter 7)

The study was started in 1997 by determining the prevalence of psychopathology among children of bipolar parents in the Netherlands, because the reported prevalences in other studies varied greatly, and the prevalence in the Netherlands might be different from the prevalence in other countries. At the second measurement in 1999 and the third measurement in 2004 we determined the prevalences again and also the incidence of psychopathology in this cohort. Next we investigated the development of psychopathology and the prospective course of psychopathology as well as social functioning and family functioning in bipolar offspring with a focus on the clinical characteristics that differentiate bipolar offspring with and without psychopathology. We also investigated the validity of the General Behavior Inventory (GBI, Depue, 1983) as

an instrument for the early detection of bipolar disorder in a high risk sample of bipolar offspring.

This study was inspired by the question of parents with a bipolar disorder, who asked if it is possible to detect bipolar disorder in an early stage of the illness to prevent or at least ameliorate the severity of the illness in their offspring.

Prevalence and incidence of psychopathology

To give a comprehensive overview of the lifetime DSM-IV diagnoses across the three measurements, the 129 subjects who participated in all three measurements were classified into four groups according to their primary DSM-IV lifetime diagnoses: bipolar disorder, unipolar mood disorder, other non-mood disorder and no disorder. In this classification comorbid diagnoses were not taken into account (figure 1).

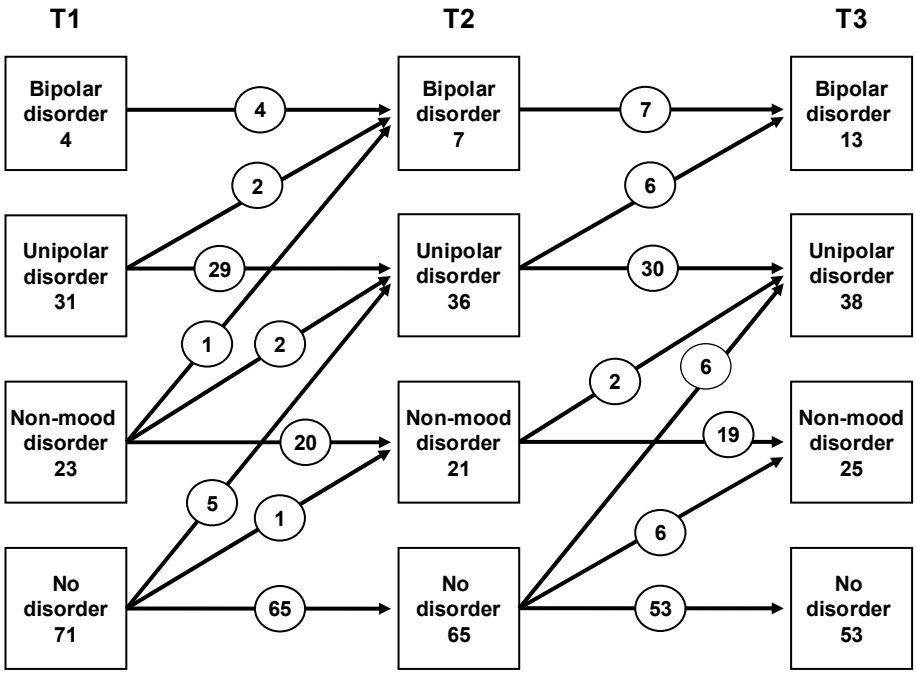

Figure 1: Lifetime DSM-IV diagnoses at the first (T1), second (T2) and third measurement (T3). The "non-mood disorder" category consists of ADHD, behavioral disorders, anxiety disorders, substance use disorders, enuresis, encopresis, pervasive developmental disorder, tic and eating disorders.

Across the three measurements there was a gradual increase of psychopathology in the bipolar offspring. Of course we expected to find an increase in lifetime DSM-IV diagnoses, but this increase concerned especially lifetime DSM-IV mood disorders. The lifetime prevalence of mood diagnoses increased from 27% at the first measurement via 33% at the second measurement to 40% at the third measurement, and of bipolar disorders from 3% via 5% to 10%, respectively. Of the offspring with a lifetime DSM-IV diagnosis, 67% had a mood disorder at the third measurement.

The lifetime prevalence of 40% mood disorders at the third measurement, although high when compared to the general population (19 % in the Dutch NEMESIS study in the age range of 18-64 years; Bijl et al., 1998), is in the middle range (9%-61%) of the prevalence of mood disorders in comparable high risk studies with offspring in the adolescent and young adult age range (see chapter 1, table 1, page 6). The lifetime prevalence of 10 % bipolar disorders in our study is still moderate compared to other studies among bipolar offspring in the older adolescent/young adult age range. These studies show a range of 3-35% of lifetime bipolar disorders in bipolar offspring. In terms of age distribution our study population is best compared with the Canadian study of Duffy et al. (1998). They included 36 bipolar offspring subjects aged 10-25 years and found in 53% any lifetime psychiatric diagnosis and in 14 % a lifetime bipolar disorder.

Of the offspring who developed a bipolar disorder, all but one started with a unipolar mood disorder (chapter 5). Although it is generally well recognized that in the majority of bipolar patients the illness starts with one or more depressions (Goodwin et al., 1990), our findings suggest that this is probably the case in almost all patients. A possible explanation for the higher number of debuts with depression in our study is the difference between prospective and retrospective data. When the illness starts with a full blown mania or severe major depression, such episodes are easily acknowledged, also retrospectively, as the debut of the illness. However, minor/mild depressions and hypomanic episodes are often not recognized retrospectively, especially when they are overshadowed by subsequent more severe episodes. In our study because of its repeated assessments, probably most (if not all) mild mood disorders were detected.

Comorbid diagnosis

In conformity with most other high risk studies of bipolar offspring, the comorbidity in our offspring sample was high. At the third measurement the offspring with a bipolar disorder themselves (mean age 21 years, range 16-26 years) had in 46% a comorbid lifetime anxiety disorder, in 15% a comorbid lifetime attention deficit hyperactivity

disorder (ADHD) and to our surprise, only in 7% a comorbid lifetime substance use disorder (table 1).

Table 1: Comorbid diagnoses at third measurement

	Anxiety disorder	ADHD	Substance use disorder
Total offspring group	21%	5%	16%
Offspring with:			
Bipolar disorder	46%	15%	7%
Unipolar mood disorder	29%	3%	21%

In the Epidemiological Catchment Area study (ECA, Regier et al., 1990) the comorbidity of bipolar disorder and substance use disorder was 61%. Substance use under the age of 25 years is difficult to interpret. More than one third in that age group fulfils the criteria for a substance use disorder (especially alcohol abuse) and this percentage drops to 5 to 10% when they grow older (Bijl e.a., 1997; Van den Brink, 1999). The low percentage of substance use disorder in the offspring with a bipolar disorder themselves may be a chance finding, but it is also possible that in adolescent and early young adult years, children of bipolar parents are aware of the risks of substance abuse, possibly through their parent's experiences with substance abuse. A different explanation could be that substance abuse in our sample is relatively low, because of sample selection. It is possible that parents and their offspring with already developed substance use disorders (and other disorders) did not want to participate in this study or were the first to drop out from this prospective study of over 5 years.

A point of consideration is how to evaluate the reported differences in prevalence of ADHD in the bipolar offspring studies (table 2). From 1989 till now, there has been a trend to probe for externalizing problems, especially ADHD, in bipolar offspring. ADHD was reported in bipolar offspring for the first time in 1983 (Decina et al., 1983), but neglected as a relevant disorder until after 1988.

Table 2: High risk studies after 1988

Author (year)	n	Age range	Bipolar disorder %	ADHD %	Any disorder %
Grigoroiu-Serbanescu et al. (1989)	72	10-17	1	21	61
Hammen et al. (1990)	18	8-16	0	6	72
Carlson et al. (1993)	128	At school age	5	30	??
Duffy et al. (1998)	36	10-25	14	3	53
Chang et al. (2000)	60	6-18	13	27	52
This study (at third measurement)	129	16-26	10	5	59

ADHD= attention deficit hyperactivity disorder

The bipolar offspring studies conducted after 1989 in the United States (Grigoroiu-Serbanescu et al., 1989; Carlson et al., 1993; Chang et al., 2000) reported high prevalences of lifetime ADHD (up to 30%). However, in our offspring study and in the Canadian offspring study by Duffy et al. (1998) the lifetime prevalences of ADHD were 5% and 3%, respectively. One explanation might be that in the Canadian study and in our study school-age children were not included, possibly accounting for less reporting of past ADHD symptoms.

Another possible explanation are the differences in accessibility to mental health care. Canada and the Netherlands have, in contrast to the United States, universal health insurance coverage. One consequence of this health system organization is that in the US, only about one-third of serious cases receive treatment, and in the Netherlands and Canada 54-66% (Bijl et al., 2003). In the US, people who cannot pay for mental health care may be more inclined to participate in a study when they can receive free care, while in Canada and in the Netherlands really problematic offspring with psychiatric problems (ADHD, conduct disorder etc.) were already under medical care and not presented to and included in our study. Therefore, it is possible that the American samples were overrepresented with patients who were more impaired.

Age at onset of mood disorders of offspring

In our study, the offspring (aged between 16-25 years) as assessed at the third measurement developed a bipolar disorder at a mean age of 18 years, with a first DSM-IV mood episode at a mean age of 13.1 years (chapter 3 and table 3).

Table 3: Age at onset of mood disorders (assessed at third measurement)

	n	Mean	Range	SD
Age first mood episode in offspring with bipolar disorder	13	13.1	8.6-21.7	3.8
Age first (hypo)manic episode in offspring with bipolar disorder	13	18.2	13.9-24.6	2.8
Age first mood episode in offspring with unipolar disorder	38	15.6	6.8-23.7	4.1

In our high risk sample, only 4 subjects with a bipolar disorder (30%) had their first mood episode before the age of 12 and none had their first manic episode before the age of 12 (mean age 18 years, range 14-25 years). Thus, our study suggests that most patients with bipolar disorder have their first manic episode in adolescence or young adulthood and not during childhood. Moreover, while the mean age of our sample at the third measurement was 21 years, it is to be expected that more offspring will develop a bipolar disorder, resulting in the further increase of the mean age at onset of bipolar disorder. This is in contrast with findings in the US, where many patients with a bipolar disorder have their first manic episode before puberty. Mean age at onset of bipolar disorder in a comparable US high risk study (Chang et al., 2000), was 10.9 years (SD = 3.2). Another recent study, using adult criteria for diagnosing bipolar disorder, that also reported a high percentage of patients with an early onset of bipolar disorder is the study by STEP-BD (Perlis et al., 2004). In that sample of 983 bipolar patients, 27.7% reported an onset of bipolar disorder before the age of 13 years and 37.6% between the ages of 13 and 18 years. However, an important limitation of this study is its retrospective approach. Errors in recall, as well as other potential confounders, such as "effort after meaning", might distort the determining of age at onset.

One explanation for this difference in age at onset of bipolar disorder between our study and the US studies could be a diagnostic artefact. For diagnosing bipolar disorder

in prepubertal children, US child psychiatrists use the broad phenotype of bipolar disorder (Kowatch et al., 2005). However, there are also other possible explanations. In pre-pubertal children early manifestations of bipolar disorder can be either full depressive episodes and subsyndromal states or periods with hyperactivity leading to a diagnosis of ADHD (Faedda et al., 1995; chapter1). In these children there may be an indication for treatment: of either depression with antidepressants or ADHD with stimulants. However, these treatments also could bear the risk of a switch into (hypo)mania. Among adults it is well documented that antidepressants can trigger a manic episode in patients with unipolar or bipolar depression (Altshuler et al., 1995). Depression in children is often the first episode of bipolar disorder. When treated with antidepressants these children have possibly a strongly increased risk to switch into a manic episode (Biederman et al., 1999; Kowatch et al., 2005). Geller et al. (2001) did a prospective study among 72 prepubertal children with a depression. She treated all of them with nortriptyline. As young adults, up to 33% of these children with a prepubertal depression had developed a bipolar disorder. A study among children and adolescents with bipolar disorder showed that those who received prior antidepressants or stimulants had an earlier diagnosis (10.7 $\pm$ 3.1 years) than those who were never exposed to these medications (12.7 $\pm$ 4.3 years) (El-Mallakh et el., 2001).

With regard to stimulants, it has also been suggested that these drugs can cause mania (Vitiello, 2001). Two reports indicate that they indeed can lead to a switch. In a study into the treatment of 42 children and adolescents with a manic episode, 30 (71%) of the children had co-morbid ADHD (Kowatch et al., 2000). How many of these children had been treated with stimulants was not reported, but the demographic data of this study show a mean age of onset of ADHD of 5.5 ($\pm$ 2.7) years, a mean age of start with stimulants of 6.9 ($\pm$2.8) years, and a mean age of onset of bipolar (hypomanic or manic) symptoms of 7.1 ($\pm$ 3.4) years. In another study of 34 adolescents hospitalized with mania, subjects with a history of stimulant exposure had an earlier age of onset of BD than without prior stimulants, 10.7 ($\pm$ 3.9) versus 13.9 ($\pm$ 3.9) years, respectively (DelBello et al., 2001).

So, there are arguments that support the notion that antidepressants and possibly also stimulants may trigger a (hypo)manic episode in a subgroup of children. But can this explain the possible earlier onset of bipolar disorder in the US compared to the Netherlands? Therefore, it is important to take into account two other differences between both countries: the treatment rates with antidepressants and with stimulants. Compared to the Netherlands, the prescription of antidepressants and stimulants to

children is much higher in the US. A recent study in Dutch pharmacies revealed that between 1995-1999 per year 0.44% of children aged 0-19 years did receive at least one prescription with an antidepressant and that the use of stimulants in this period had increased from 0.15 to 0.74% (Schirm et al., 2001). In the US in 1995 2,8% of the 5-18 years old used stimulants (Safer et al., 1996), while the estimated prescription of antidepressants is about half, i.e. 1-1.5% (Jensen et al., 1999). Based on these figures, we assume that in the US compared to the Netherlands relatively more children diagnosed with a depression or ADHD are treated with either antidepressants or stimulants, resulting in relative more switches into hypo(mania). Probably, part of these children has their depression or ADHD as a prodromal phase of bipolar disorder and especially these children may be at risk for a switch. Thus, may be in children genetically predetermined to develop bipolar disorder, the use of antidepressants and/or stimulants may advance the onset of bipolar disorder even before puberty.

Obviously, this is only a hypothesis for which there is so far only circumstantial evidence (Reichart & Nolen, 2004). A different explanation for the early switching in the studies by El-Mallakh et al. (2001), DelBello et al. (2001) and Kowatch et al. (2000) could be selection. Maybe the children with stimulant medications were the most problematic children, with the most severe early forms of bipolar disorder and for that reason showed an early switch. Severity of bipolar disorder is associated with an early onset of bipolar disorder (Tohen et al., 2000). Clearly, further research is needed. For instance a prospective comparison study between children with a positive family history of bipolar disorder and treated with stimulants versus children with a positive family history of bipolar disorder without stimulant treatment. However, until proven wrong: physicians should be careful when prescribing antidepressants or stimulants to children with ADHD or a depression when there is a family history of bipolar disorder. There is no evidence for bipolar switching in the total group of children with ADHD using stimulants (Craddock & Geller, 2003) and stimulants are the agents of choice for the treatment of ADHD (Connor et al., 2002).

Age at onset of mood symptomatology

Although changes in lifetime prevalence across time can give us information on the incidence of disorders, this kind of diagnostic information does not tell us about changes

in symptomatology occurring below the diagnostic threshold. From a developmental perspective it is important to obtain a picture of changes in symptomatology across time and across the whole range of symptom severity, including changes that occur at a diagnostic subthreshold level. We therefore determined the developmental course of self-reported mood symptoms scored on continuous scales in this sample of bipolar offspring (chapter 3). Thanks to recent advances in statistical techniques we were able to analyze longitudinal data to address questions about change over time. In the general population five different developmental trajectories of affective problems were found (Bongers et al., submitted) and for each subject in the bipolar offspring sample, the posterior probability of group membership for each of the developmental trajectories that were determined for the general population was estimated. More subjects in the bipolar offspring sample were assigned to the two trajectories reflecting a more problematic developmental course than subjects from the general population, indicating that this is really a high risk group. The two trajectories representing the most problematic development in affective problems differed in age at onset of affective problems and in their course over time, with an early onset trajectory showing increasingly high levels of affective problems and an adolescence onset trajectory with an increase in affective problems until the age of 20-21 years and a gradual decrease up to age 26.

The major finding in this study was that bipolar offspring are indeed at risk for the development of affective problems. This is in contrast with the findings at the first and second measurements based on cross-sectional information, in which we did not find such increased levels of affective problems. In addition, our study showed that bipolar offspring with increasing levels of affective problems have a significantly higher chance to develop bipolar disorder.

Factors associated with age at onset

Early age at onset could simply indicate greater overall severity, or it could predispose the patient to other features of illness course that contribute to poor outcome. For example, it has been associated with increased risk for suicide attempt (Bellivier et al., 2001 and Tsai et al., 1999), poorer lithium response (Schurhoff et al., 2000), more psychotic features (Bellivier et al., 2001; McGlashan 1988 and Schurhoff et al., 2000), more mixed episodes (Schurhoff et al., 2000), greater rates of neuropsychological dysfunction (Taylor and Abrams 1981), and greater comorbidity with panic disorder (Schurhoff et al., 2000) or drug or alcohol abuse (Bashir et al., 1987). If the factors

associated with early onset that contribute to poorer outcome could be identified, they might suggest more specific approaches to early intervention to limit the morbidity of early-onset bipolar disorder.

In our study we tested differences between early onset (i.e. before 12 years) and adolescence onset of affective problems trajectories for the following variables: number of severe life events before the age of 12 years, family loading for bipolar disorder and unipolar disorder, birth weight in offspring, and age of onset of first manic episode and severity of bipolar disorder in bipolar parents. Early onset of illness has been suggested as a marker of greater genetic loading in bipolar disorder (Bellivier et al., 1998; McMahon et al., 1994; Pauls et al., 1992; Somanath et al., 2002; Strober et al., 1988 and Taylor and Abrams 1981), perhaps indicative of a unique mode of inheritance (Grigoroiu-Serbanescu et al., 2001). We did not find a significantly higher familial loading for bipolar disorder in the subjects in the early onset trajectory of affective problems, indicating that we could not confirm these suggestions. A possible explanation could be, as in the study by Wals et al. (2004) on this cohort, that every participating adolescent in our sample had a bipolar parent, resulting in a ceiling effect; the variance of familial loading of bipolar disorder ranged from individuals with high familial loading to individuals with extremely high familial loading. Familial loading with unipolar disorder was also not significantly different between the two trajectories, as well as birth weight and number of severe life events before the age of 12 years. A problem with these comparisons was the statistical power. Existing literature and previous studies in this cohort (Wals et al., 2004; Hillegers et al., 2004) indicate that familial loading with bipolar disorder, birth weight and the occurrence of life events are important determinants for the development of bipolar disorder.

Regarding the determination of predictors of the age at onset of bipolar disorder, longer follow-up of our cohort is needed in order to assemble a larger number of offspring with a bipolar disorder. We did find however, a significant difference for the age at onset of bipolar disorder when looking at the offspring and the parents. Offspring in the early onset trajectory of affective problems and with a bipolar disorder at an early age, have parents with an early onset bipolar disorder (mean age of 25 years). A very important issue still remains to be explored: when parents have an early onset of bipolar disorder, are their offspring (as a group) also at risk for an early development? To answer this question, again, a longer follow-up of this sample is needed.

Early prediction of bipolar and unipolar mood disorder

We tested the usefulness of the General Behavior Inventory (GBI) as an instrument to predict the development of bipolar disorder in our sample of offspring of parents with bipolar disorder over a follow up period of five years (chapter 5). In adult and adolescent populations the GBI has demonstrated to be a valid self-report measure for mood disorders (Depue et al., 1988; Findling et al., 2002) and a valid instrument to discriminate between mood disorders and behavioral disorders (Danielson et al., 2003).

Unlike the other studies, we found that especially the Depression scale and not the Hypomanic/Biphasic scale of the GBI discriminated well between the development of bipolar disorder versus unipolar disorder, non-mood disorder or no disorder across the 5-year follow-up interval. For the offspring with a unipolar mood disorder at T1 the Depression scale discriminated well between those who switched to bipolar disorders versus those who remained unipolar across the 5-year follow-up interval. The score on the Depression scale at T1 for offspring with a unipolar disorder who later developed a bipolar disorder was significantly higher than for offspring who persistently showed a unipolar mood disorder across the five year interval. A higher score on the Depression scale predicted the development of a new bipolar disorder. Our findings indicate that in the offspring of parents with bipolar disorder prior to the development of any mood disorder a higher number of depressive symptoms but not of (hypo)manic symptoms predict the eventual bipolar disorder. And, when the disorder has started with a depression, a higher level of depressive symptoms predicts the switch to bipolar disorder.

According to Depue et al. (1981) it is to be expected that on the GBI, the hypomanic/biphasic symptoms and not the depressive symptoms discriminate between bipolar versus unipolar disorders. Bipolar disorder starts, however, in more than 80% of the cases with a unipolar mood disorder (Werry, 1991) which was also found in our study (Hillegers et al., in press). High scores on the Depression scale in the early phase of bipolar disorder are in conformity with this course. Therefore, taking the developmental pathway of bipolar disorder into account, high scores on the Depression scale are to be expected prior to onset of the illness. The distribution of the offspring sample over the developmental trajectories of affective problems (chapter 3) is in conformity with this suggestion. More than 75% of the offspring who developed a bipolar disorder followed trajectories with increasing or chronically high level of affective

problems, indicating the presence of affective problems before the onset of the bipolar disorder. This finding also shows that the clinical-diagnostic (DSM-IV) approach and the empirical-quantitative (GBI) approach generate supplementary information. For example, at the first measurement, 31 adolescent offspring had a unipolar mood disorder according to the DSM-IV. With the supplementary information on the GBI it was possible to discriminate between those subjects who switched to bipolar disorder across the five year interval versus those who did not.

In conclusion, the present findings demonstrate that the GBI may be used for early detection of bipolar disorders in adolescent offspring of parents with a bipolar disorder.

Consequences of being a child of a bipolar parent

We expected that growing up in a family with a bipolar parent would have great impact on the social functioning of bipolar offspring. And, if their social functioning during childhood or adolescence is impaired, this may have negative effects on their adult functioning over and above the effects of a possible development of bipolar disorder itself.

We compared the social functioning of offspring of bipolar parents with that of individuals in the general population divided into two age groups: 11 to 18 years and 18 to 26 years (chapter 6). Comparisons revealed different results for these two age groups. For 11- to 18-year-olds, mothers scored their offspring on total social functioning in the same range as mothers in the general population. Adolescent offspring scored themselves even as more favourably functioning on the Activities scales than adolescents from the general population. In contrast, in the age group of 18 to 26 years, offspring with bipolar disorder or unipolar disorder had significantly lower scores on the Mean Adaptive Functioning Scale than young adults from the general population. Offspring without disorder had similar levels of social functioning as young adults from the general population.

In conclusion, the most salient finding in our study concerning the social functioning of the bipolar offspring was that the overall level of social functioning of bipolar offspring under the age of 18 years did not differ from that of adolescents from the general population. In contrast, after the age of 18 years subjects with bipolar disorder or another mood disorder had impaired social functioning, especially in the domain of family functioning.

To further explore family functioning we also determined how the offspring perceived their upbringing (chapter 7). Compared to young adults from the general population, offspring living in a family with a bipolar parent perceived their parents overall in a more positive way. More specifically, offspring of bipolar parents perceived their mothers as less rejecting, more emotionally warm and less overprotecting, and their fathers as less overprotecting, but also as less emotionally warm. Though significant, the differences in perceived parental rearing between bipolar offspring and young adults from the general population were small according to Cohen´s (1988) criteria for effect sizes. The positive evaluation by bipolar offspring of their upbringing may be surprising and did not confirm findings as reported in the literature that a person with bipolar disorder has a (negative) effect on family functioning. However, as was the finding for differences in social functioning in the bipolar offspring, within the offspring group, perceived parental rejection depended on psychopathology in the offspring. Offspring with a bipolar disorder reported more rejection by their fathers and mothers compared to offspring with other disorders or without a disorder and compared to individuals from the general population. Offspring without a disorder reported less rejection than subjects from the general population. In contrast to our expectations, severity of illness of the bipolar parent, as expressed by the number and severity of episodes, and the age at onset of the first episode did not have an effect on the perception of parental rearing practices by the offspring.

Thus, in summary, adolescents and young adults growing up in a family with a bipolar parent do not show impaired social functioning and perceive the quality of their upbringing in general as more positive compared to subjects in the general population when they do not have a psychiatric disorder themselves. However, psychiatric disorder in the offspring, and not the severity of the bipolar disorder of the parents, was associated with poorer social functioning and with the perceived rearing practices of the parents.

It is generally acknowledged that psychosocial variables play an important role in the course of bipolar disorder. In studies among adults, reported psychosocial variables concern decline in job status, decline in income and problems in relationships with spouses (Coryell et al., 1993; Calabrese et al., 2003). The results of our study suggest that substantial difficulties in social functioning of the bipolar offspring and in upbringing may not be present in the bipolar offspring until the development of a psychiatric disorder. A point of consideration, however, is that the offspring sample is in the age range between 16 and 26 years. In line with that age, half of the offspring sample is still

living at home, does not have a job and is not married yet. Therefore, it is to be expected that when they grow older, they will be at risk for more substantial changes in their psychosocial functioning. Maybe, timely psychoeducation could diminish these consequences. However, research to confirm these "hopeful thoughts" is very difficult to execute.

Bipolar offspring and divorce

In a study by Kessler et al. (1998) persons with a bipolar disorder had a 3.2 times higher chance to divorce. Strikingly, in our sample, 77% of the parents with a bipolar disorder (mean age 45 years) was married, and 5 years later 64% was still married to the same person. In the year 2000, 34% of the general population in the Netherlands was divorced after a marriage of 12.9 years, with a mean age of 41.9 years for men, and 39.0 years for women (CBS, 2000). This means that there are no large differences in divorce rates in our sample compared to the general population in the Netherlands. There are, however, differences within the offspring group with respect to the divorce rate of the parents and the diagnoses of the offspring.

Table 4: Divorce rate of parents and DSM-IV lifetime diagnoses of offspring at T3

	Total	Divorced	Not divorced	Father died
Bipolar disorder	13	7 (54%)	6 (46%)	
Unipolar disorder	38	16 (42%)	22 (58%)	
Other disorder	25	9 (36%)	14 (64%)	2
No disorder	53	8 (15%)	44 (85%)	1

Pearson Chi-Square 19.46; df:9; p=.022

In our sample we see a significant association between divorce rate of the parents and disorders in the offspring. Offspring with a bipolar disorder have parents with a divorce rate of 54% and offspring with no disorder have parents with a divorce rate of 15% (chi square 8.67, p=.003). In a two-year prospective follow-up of children with a prepubertal and early adolescent bipolar disorder, living with an intact biological family significantly predicted rate of recovery. (Geller et al., 2002). Until now we have few data on the course of the illness of the offspring and on their treatment history. An interesting

question would be, whether the instability in the family of origin (for example divorce of parents) moderates the course of the illness of the offspring.

However, the association between divorce and psychopathology has recently received much attention. Lyons et al. (2004) found that identical twins were more likely to follow the same patterns of divorce than non-identical twins, suggesting that whether or not marriages last, may be under genetic influence. In addition, this genetic influence appears to be related to other factors with a genetic component such as drug abuse, depression and alcoholism. May be, the genetic vulnerabilities for divorce and for bipolar disorder are also shared.

Strengths and limitations of the study

Our study has several (methodological) strengths:

1. A major strength of the present study above other bipolar offspring studies is the relatively large sample of bipolar offspring. As shown in chapter 1, our sample is the largest sample of bipolar offspring studied up until now.
2. The examination of longitudinal data in this population provides unique information in a population at risk. Because we had data on three measurements, we could determine the developmental course of for instance self-reported mood symptoms scored on continuous scales in this sample of bipolar offspring. Recent advances in statistical techniques have improved the ability to analyze longitudinal data to address questions about change over time.
3. Thanks to the prospective design of our study it was possible to determine the onset and course of affective problems as well as the age at onset of the first DSM-IV mood episode in the offspring sample with more precision than in previous retrospective studies.
4. The follow-up completion rate is very high; at the second measurement after 14 months 132 of the 140 offspring (94%) participated again, and five years after the first measurement 129 (92%) still participated.
5. Our study is the first study in the field that assesses the impact of social functioning and family functioning from the perspective of the offspring themselves.

6. Our study used different assessment procedures (questionnaires and interviews) and three sources of information (offspring and parents in chapter 2-7 and offspring, parents and teachers in chapter 2 and 6) in order to determine the level and type of psychopathology and social functioning in adolescent children of bipolar parents.

Our study also has a number of limitations:

1. The most important limitation of our study is the lack of normative data for psychiatric interviews under the age of 18 years. This makes interpretation of the prevalence findings difficult. Whereas normative data on the CBCL, YABCL, YSR, YASR and TRF were available, this was not the case for lifetime DSM-IV diagnoses based on the K-SADS interviews. For the DSM-IV lifetime diagnoses based on the SCID-I normative data from the Nemesis study were available, but not for the same age group. For our research on the various determinants of psychopathology among children of bipolar parents a comparison sample was less an issue, since within the sample we compared subgroups of offspring, for example offspring with mood disorders versus offspring without any diagnosis.
2. Another limitation, shared with most other studies of psychopathology in offspring of bipolar parents, is the lack of information on the representativeness of the sample (see recruitment, chapter 1, figure 1). More than two-third (73%) of the families was recruited via a patient association (the Dutch Association for Manic-Depressives and Relatives, VMDB). It may be possible that patients recruited via a patient association are the relatively good functioning patients as compared to those of the outpatient clinics. With regards to social functioning and severity of the psychopathology of the bipolar parents, however, parents recruited via the outpatient clinics did not show significant differences in number of hospitalizations, age at onset first episode, number of manic episodes, social economic status and divorce rate, compared to parents recruited via a patients association. And, we are not aware of differences in severity between bipolar patients under treatment in outpatient clinics in the Netherlands compared to these patients in other countries.
3. A limitation of our study is the relative short follow-up interval of 5 years. Consequently, the number of bipolar disorder onsets during this period was relatively small (9 new cases), resulting in limited statistical power to demonstrate significant associations, especially interactions. A longer interval

with more disorder onsets would have increased the statistical power of the study. Another consequence of the relative short follow-up is the uncertainty about the diagnoses of unipolar depressive disorder in this study, since it is clear that the group of recurrent depressives includes hidden bipolar subjects whose depression may develop into hypomania or mania at any time. One factor in this is the long time elapsing between the onset of depression and a diagnosis of bipolar disorder. This period was more than 7.5 years in a retrospective study of Ghaemi et al. (1999), 8 years in a national survey of the NDMDA (1993) in the United States and 5 years in our own prospective study (Hillegers et al., in press). It is to be expected that a substantial percentage of the 38 offspring with a lifetime unipolar mood disorder at the third measurement will develop a bipolar disorder in the upcoming years. This will change our predictions concerning the risk factors for the development of a bipolar disorder.

4. As a consequence of the broad age range in our cohort, we have used different instruments that assessed partly different domains of social functioning for different ages. The use of different instruments may have contributed to differences in results for the two age groups that we found.

Implications of our study for further research

In our study evidence was found that over a period of five years the offspring of bipolar parents run a high risk of developing mood disorders and especially bipolar disorder. Our study population of bipolar offspring is still relatively young; they were aged between 16 and 26 years at the third measurement. This means that it is to be expected that still a substantial percentage of the offspring will develop a mood disorder, including switches from unipolar mood disorder to bipolar disorder in the upcoming years. The future changes in psychopathology may change our predictions concerning the risk factors and protective factors for the development of a bipolar disorder. Therefore, a longer follow-up of this cohort is needed in order to determine which of the present findings will hold. A longer interval with more bipolar disorder onsets (up till now 9 new cases with bipolar disorder) will also increase the statistical power of the study.

In our study we used a limited age range for inclusion. We only included offspring in the age range of 12-21 years, in order to capture a group shortly before and during the emergence of the possible first episodes. This choice, among other reasons, was made in order to limit the needed follow-up time. A consequence of this choice could have been a further selection, as offspring with already developed psychopathology before the age of 12 years (such as depression or ADHD) may not have been included in our sample. To avoid this (possible) selection bias, future studies should include also younger children. An additional reason to include younger children is, of course, the opportunity to determine early symptoms and life events prospectively.

In our study we did find that the severity of the psychopathology of the bipolar parent, as determined at the first measurement, seems to have no influence on the way the offspring perceived their upbringing. Data on changes in the psychopathology of the parents, as well as in their social functioning, was not assessed during the follow-up of this study. To determine the mutual influence of psychopathology and social functioning of parents and offspring, not only data on the development of psychopathology and social functioning of the offspring is needed, but also of the parents.

Data on psychopathology and social functioning of parents and offspring, however, is not enough to answer the question to what extend psychopathology in offspring is due to specific factors related to having parents with a bipolar disorder. Future studies should compare children of parents with bipolar disorder not only with children from normal parents, but also, like in the study by Hammen et al. (1990), with children of parents with other psychiatric disorders and with parents with chronic medical illnesses.

Implications of our study for clinical practice

In our study bipolar offspring with affective problems starting before the age of 12 years showed a chronic course of these problems across adolescence and into young adulthood. Moreover, offspring with increasing levels of affective problems in childhood or adolescence run a substantial risk of developing a bipolar disorder themselves. Therefore, this subgroup with an early start and chronic course of affective problems as well as the subgroup with increasing affective problems in adolescence should receive special attention in order to detect bipolar disorder as soon as possible. By intervening

before the onset of full-blown bipolar disorder, the disorder may be prevented or at least ameliorated in its severity, preventing poor social and vocational functioning.

Our finding of a debut of bipolar disorder with a depression indicates that bipolar offspring with a depression can be regarded at risk for developing bipolar disorder. Therefore, clinicians should follow bipolar offspring with a depression closely. Furthermore, although our study did not address treatment in general and the issue of antidepressant-induced switch to bipolar disorder in particular, literature and clinical experience suggest that clinicians should be cautious to use antidepressants as monotherapy in bipolar offspring with a depression.

In our study, we found that bipolar offspring still without a disorder but with high scores on the Depression scale of the GBI had an increased probability of a later mood disorder and especially a later bipolar disorder. In order to detect bipolar disorder as soon as possible, we therefore suggest using the GBI in clinical practice to monitor children of parents with a bipolar disorder for the development of mood symptoms.

From the present study's findings we concluded that in general, our offspring group with a high risk for developing bipolar disorder did not show impaired psychosocial functioning. Only those subjects who had a lifetime DSM-IV disorder at the third measurement showed increased levels of impairment, especially with regard to family functioning. Thus, our results support the idea that psychosocial functioning of bipolar (and also unipolar) patients prior to illness onset is largely unimpaired and that impairment is associated with the development of the disorder. It is therefore that clinicians should extend their interventions beyond mere treatment of mood symptoms. They should also pay attention to restoring or improving social functioning, e.g. via rehabilitative interventions. A salient finding in the study was that substantial difficulties in upbringing in families with bipolar parents may not be present. Therefore, special treatment programs employing family therapy on an a priori indication in families with a bipolar parent may not be indicated, at least not in families who are aware of their illness (such as members of a patient organization). However general psycho-education, evaluation of family relations and rearing practices, and assistance with concrete and specific problems concerning living with a bipolar parent, may be beneficial.

Final conclusion

The studies described in this thesis concerned the first, second (after 14 months) and third measurement (after 5 years) of the KBO (Children of Bipolar Parents) project. Evidence was found that over a period of 5 years the offspring of bipolar parents run a high risk of developing mood disorders and especially bipolar disorder. Onset and course of self-reported affective problems were predictive for the development of mood disorders. Early detection of bipolar disorder was possible with the General Behavior Inventory. Psychosocial functioning of bipolar offspring prior to their illness onset is largely unimpaired and impairment seems to be the result of mood disorders in the offspring rather than in their parents.

Considering these findings, it is important to closely monitor children of bipolar parents on the development of bipolar disorder, especially when they have affective problems or depressions. In addition, treatment is considered indicated when they have developed a first depression of manic episode, and may already be considered when there are affective problems.

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Summary

Bipolar disorder (manic depressive illness) "runs in families", indicating that it is partly genetically determined. Consequently, patients with bipolar disorder are often concerned that also their children might develop the illness. This study was inspired by the question of parents with a bipolar disorder, who asked whether it would be possible to detect bipolar disorder in an early stage of the illness in the hope that it would be possible to prevent the further development of the illness or at least to ameliorate its severity in their offspring.

Bipolar disorder is a mood disorder in which episodes of depression and episodes of (hypo) mania with elevated mood, irritability or both occur in any order over a lifetime. Episodes of mania and depression can vary from a few weeks to several months and are usually severe enough to affect daily functioning at home or at work. It is a lifelong condition for which no curative treatment is available. However, adequate treatment reduces the number and severity of episodes and thereby reduces the level of handicap in the majority of patients.

In most patients bipolar disorder starts after puberty, and in half of the patients before 25 years. However, it is often formally diagnosed by a clinician many years after the illness has started. Consequently, adequate treatments are postponed or inadequate treatments are given. Therefore, one would like to know how to detect people at risk to develop bipolar disorder: what are the early signs (prodromal features) of the illness? How does the illness develop from these early signs to the full disorder? What are the risk factors? What are the protective factors?

To find answers to these and other questions we started in 1997 a study among 140 children at that time aged between 12-20 years, of 86 parents with a bipolar disorder: the KBO ("Kinderen van Bipolaire Ouders", Dutch for "Children of Bipolar Parents") study. We assessed all these children as well as their parents three times: at baseline, after one year (second measurement) and after five years (third measurement).

The focus of this thesis is on the functioning and development of children of bipolar parents for two main reasons. First, children of bipolar parents are at genetic risk for developing psychopathology, including bipolar disorder themselves (Alda, 1997; Gershon et al., 1987; McGuffin & Katz, 1989). Second, children of bipolar parents are subject to environmental stressors partially associated with parental psychopathology

and its consequences. These multiple risks may contribute to multiple types of psychopathology that, in addition, are subject to developmental changes over time. For example, it is possible that the first signs of bipolar disorder are non-specific problems, such as anxiety problems, later followed by the development of a depression that subsequently evolves into a bipolar disorder with also manic episodes. In addition, little is known about the functioning of children of bipolar parents.

In the various studies of this thesis we addressed the following research questions:

1. What is the prevalence and incidence of psychopathology, especially mood disorders among the offspring of bipolar parents? (chapter 2)
2. What is the course of affective symptomatology and what are determinants for the age of onset of bipolar disorder in the bipolar offspring? (chapter 3)
3. Is it possible to use the General Behavior Inventory (GBI), an instrument to identify bipolar and unipolar mood disorders across the full spectrum of severity, in a population of adolescent offspring of parents with a bipolar disorder? (chapter 4)
4. Is it possible to use of the GBI as a predictor of bipolar disorder in a population of adolescent offspring of parents with a bipolar disorder? (chapter 5)
5. How is the social functioning of the bipolar offspring? (chapter 6)
6. What is the experience of parental rearing of the bipolar offspring? (chapter 7)

Psychopathology as defined by DSM-IV was assessed at all three assessment points. The results obtained at the second measurement are described in chapter 2. The results obtained at the third measurement (Hillegers et al., in press) are discussed in chapter 8. Across the three measurements there was a gradual increase of psychopathology, which concerned especially lifetime DSM-IV mood disorders. The lifetime prevalence of mood diagnoses increased from 27% at the first measurement via 33% at the second measurement to 40% at the third measurement, and of bipolar disorders from 3% via 5% to 10%, respectively. Of the offspring with a lifetime DSM-IV diagnosis, 67% had a mood disorder at the third measurement.

In conformity with most other high risk studies of bipolar offspring, the comorbidity in our offspring sample was high. At the third measurement the offspring with a bipolar disorder themselves (mean age 21 years, range 16-26 years) had in 46% a comorbid lifetime anxiety disorder, in 15% a comorbid lifetime attention deficit hyperactivity disorder (ADHD) and to our surprise, only in 7% a comorbid lifetime substance use disorder.

The bipolar offspring studies conducted after 1989 in the United States (Grigoroiu-Serbanescu et al., 1989; Carlson et al., 1993; Chang et al., 2000) reported high percentages of lifetime ADHD (up to 30%). However, in our offspring study and in the Canadian offspring study by Duffy et al. (1998) the overall percentage of lifetime ADHD was 5% and 3% respectively. One explanation might be that in the Canadian study and in our study school-age children were not included, possibly accounting for less reporting of past ADHD symptoms.

In our study, the offspring (aged between 16-25 years) as assessed at the third measurement with a bipolar disorder (n=13) had developed their first (hypo)manic episode at a mean age of 18 years (range 14-25 years), with a first DSM-IV mood episode at a mean age of 13.1 years (chapter 3). Only 4 subjects with a bipolar disorder (31%) had their first depressive episode before the age of 12 and none had their first (hypo)manic episode before the age of 12. This suggests that most patients with bipolar disorder have their first manic episode in adolescence or young adulthood and not during childhood. Moreover, while the mean age of our sample at the third measurement was 21 years, it is to be expected that more offspring will develop a bipolar disorder, resulting in the further increase of the mean age at onset of bipolar disorder in this group.

Although changes in lifetime prevalence of DSM-IV diagnoses across time can give us information on the incidence of disorders, this kind of diagnostic information does not tell us about changes in symptomatology occurring below the diagnostic threshold. From a developmental perspective it is important to obtain a picture of changes in symptomatology across time and across the whole range of symptom severity, including changes that occur at a diagnostic subthreshold level. We therefore determined the developmental course of self-reported mood symptoms scored on continuous scales in this sample of bipolar offspring (chapter 3).

The major finding in this study was that bipolar offspring are indeed at risk for the development of affective problems. More subjects in the bipolar offspring sample were assigned to trajectories with increasing or chronically high level of affective problems reflecting a more problematic developmental course than subjects from the general population. This finding shows that the clinical-diagnostic (DSM-IV) approach and dimensional approach generate supplementary information. In addition, we found that the subjects in these problematic trajectories have a significantly higher chance to develop bipolar disorder. We also detected an early onset (i.e. with a start before 12

years) trajectory showing increasingly high levels of affective problems and an adolescence onset trajectory with an increase in affective problems until the age of 20-21 years and a gradual decrease up to age 26. Early age at onset could simply indicate greater overall severity, or it could predispose the patient to other features of illness course that contribute to poor outcome.

In our study we tested differences between the subgroups with an early onset versus with an adolescence onset of affective problems. Familial loading with bipolar disorder or unipolar disorder, birth weight and number of severe life events before the age of 12 years were not significantly different between the two trajectories. However, we did find a significant difference for the age at onset of bipolar disorder when looking at the offspring and their parents. The offspring with an early onset of affective problems and with a bipolar disorder at an early age, have parents with an early onset bipolar disorder (mean age of 25 years). This suggest that children of parents with an early onset of bipolar disorder (as a group), are also at risk for an early development of a mood disorder. If this is indeed the case, cannot be answered so far: therefore a longer follow-up of this cohort is needed, with probably more subjects who will develop a bipolar or other mood disorder or affective problems.

A problem with the above comparisons was the low statistical power. Existing literature and previous studies in this cohort (Wals et al., 2004; Hillegers et al., 2004) indicate that familial loading with bipolar disorder, low birth weight and the occurrence of life events are determinants for the development of bipolar disorder. That we were not able to differentiate between children with an early age of onset (before 12 years) versus an adolescence onset may be due to low statistical power in this study, i.e. the small number of subjects in both trajectories.

One of the instruments for the assessment and possible early detection of bipolar disorder is the General Behavior Inventory (GBI). The GBI is a self-report that was designed to quantify affective problems in adults. The instrument consists of two scales, designated as depression and biphasic/hypomania that were constructed on an a priori, clinical basis.

First, we tested the usefulness of the GBI in the evaluation of adolescent mood disorders (chapter 4). Principal component analyses resulted in the same two-factor solution as reported for adults. The Depression scale of the GBI discriminated between adolescents with a DSM-IV mood disorder, a non-mood disorder and no disorder on Axis I. Significant correlations between GBI scales and the corresponding Internalizing and

Externalizing scales of the Youth Self report (YSR) showed convergent validity. Therefore, we concluded that the GBI can be used in the adolescent age range as a self-report to discriminate mood disorders from non-mood disorders or no disorders.

We also tested the usefulness of the GBI as an instrument to predict the development of bipolar disorder in our bipolar offspring group over a follow up period of five years (chapter 5). A higher score on the Depression scale at the first measurement predicted the development of a new bipolar disorder during the five years between the first and third measurement. Our findings indicate that in the bipolar offspring prior to the development of any mood disorder, a higher number of depressive symptoms but not yet of (hypo)manic symptoms at the first measurement predict the eventual bipolar disorder. And, when the disorder has started with a depression, a higher level of depressive symptoms predicts the switch to bipolar disorder. This is in conformity with the finding in our subjects with bipolar disorder at the third measurement (n=13) that in 12 of them (92%) the illness had started with a (up till then unipolar) depressive mood disorder. Therefore, taking the developmental pathway of bipolar disorder into account, high scores on the Depression scale are to be expected prior to onset of the illness.

We expected that growing up in a family with a bipolar parent would have great impact on the social functioning of the offspring. And, if their social functioning during childhood or adolescence is impaired, this may have negative effects on their adult functioning over and above the effects of a possible development of an own bipolar disorder. To test these hypotheses we assessed social functioning of the bipolar offspring at the three measurements (chapter 6). To explore family functioning we also determined how the offspring perceived their upbringing (chapter 7).

The most salient finding was that the overall level of social functioning of bipolar offspring under the age of 18 years did not differ from that of adolescents from the general population. In contrast, after the age of 18 years subjects with bipolar disorder or another mood disorder had impaired social functioning, especially in the domain of family functioning.

Compared to young adults from the general population, offspring living in a family with a bipolar parent perceived their parents overall in a more positive way. Psychiatric disorder in the offspring, and not the severity of the bipolar disorder of the parents, was associated with poorer social functioning and with the perceived rearing practices of the parents.

It is generally acknowledged that psychosocial variables play an important role in the course of bipolar disorder. In studies among adults, reported psychosocial variables concern decline in job status, decline in income and problems in relationships with spouses (Coryell et al., 1993; Calabrese et al., 2003). The results of our study suggest that substantial difficulties in social functioning of the bipolar offspring and in upbringing may not be present in the bipolar offspring until the development of a psychiatric disorder.

The studies described in this thesis concerned the first, second (after 14 months) and third measurement (after 5 years) of the KBO (Children of Bipolar Parents) project.

Evidence was found that over a period of 5 years the offspring of bipolar parents run a high risk of developing mood disorders and especially bipolar disorder. Onset and course of self-reported affective problems as well as depressions were predictive for the development of bipolar disorders. Early detection of bipolar disorder was possible with the General Behavior Inventory. Psychosocial functioning of bipolar offspring prior to their illness onset is largely unimpaired and impairment seems to be the result of mood disorders in the offspring rather than in their parents.

Considering these findings, it is important to closely monitor children of bipolar parents on the development of bipolar disorder, especially when they have affective problems or depressions. In addition, treatment is considered indicated when they have developed a first depression or manic episode, and may already be considered when there are milder affective problems.

Finally, longer-term follow-up of this cohort is needed in order to determine which of the present findings will hold.

Samenvatting

Als iemand een bipolaire (manisch-depressieve) stoornis heeft, hebben ook zijn/haar familieleden een verhoogde kans op deze stoornis. Dit betekent dat de bipolaire stoornis voor een deel genetisch bepaald is. Aan de wieg van dit onderzoek staat de vraag van ouders met een bipolaire stoornis: Is het mogelijk de bipolaire stoornis in een vroeg stadium te onderkennen, zodat bij hun kinderen deze stoornis voorkomen kan worden of ten minste het beloop zodanig beïnvloed kan worden dat ernstige gevolgen voorkomen kunnen worden?

De bipolaire stoornis is een stemmingsstoornis die wordt gekenmerkt door het optreden van perioden met een verhoogde stemming en overactiviteit (de lichte hypomanische episoden of de meer ernstige manische episoden) afgewisseld met perioden met een verlaagde stemming en verminderde activiteit (meer of minder ernstige depressieve episoden). Soms lopen manische en depressieve verschijnselen door elkaar heen (gemengde episode). De stemmingsepisoden kunnen enkele weken tot vele maanden duren en worden veelal afgewisseld met kortere of langere perioden waarin de betrokkene min of meer normaal functioneert. De episoden zelf zijn vaak zo ernstig dat dit gevolgen heeft voor het dagelijks functioneren thuis en op het werk.

De bipolaire stoornis komt voor bij zo'n 2% van de algemene bevolking en begint meestal tussen het 15^{e} en 25^{e} levensjaar. Over de oorzaak is nog weinig bekend. Wel is duidelijk dat het gaat om een samenspel van genetische kwetsbaarheid, factoren in de ontwikkeling van het individu en psychosociale factoren die een episode kunnen uitlokken. Bij de behandeling is medicatie naast psycho-educatie essentieel. De bipolaire stoornis is overigens niet in alle gevallen te behandelen; een deel van de patiënten reageert slechts gedeeltelijk of zelfs helemaal niet. Een adequate behandeling vermindert bij het merendeel van de patiënten echter veelal wel het aantal en de duur van de episoden, met als gevolg dat hun functioneren verbetert.

Een groot probleem is dat de diagnose bipolaire stoornis vaak 5 tot 10 jaar na het ontstaan van de eerste stemmingsepisode wordt gesteld, met als gevolg dat de adequate behandeling wordt uitgesteld of dat er inadequaat wordt behandeld. Het is dan ook van groot belang om mensen die een hoog risico lopen om een bipolaire stoornis te ontwikkelen zo snel mogelijk op te sporen. Vragen die hier hierbij spelen zijn: Wat zijn vroege symptomen (ofwel prodromale verschijnselen) van de stoornis? Op welke wijze

ontwikkelen die vroege symptomen zich tot een bipolaire stoornis? Wat zijn beschermende factoren en wat zijn risicofactoren?

Om antwoord te vinden op deze en andere vragen zijn we in 1997 begonnen met een studie onder 140 kinderen, op dat moment in de leeftijd van 12 tot 20 jaar, van 86 ouders met een bipolaire stoornis: het KBO (Kinderen van Bipolaire Ouders) project. We hebben deze kinderen en hun ouders op drie tijdstippen uitgebreid geïnterviewd, vragenlijsten bij hen afgenomen en bloedwaardes bepaald: bij de start in 1997, na één jaar (tweede meting) en na vijf jaar (derde meting).

Het thema van dit proefschrift is het functioneren en de ontwikkeling van kinderen van ouders met een bipolaire stoornis en het beloop van eventuele psychopathologie bij deze kinderen. Dit heeft twee redenen. Ten eerste hebben deze kinderen een genetisch risico op het ontwikkelen van psychopathologie, inclusief de bipolaire stoornis (Alda, 1997; Gershon e.a., 1987; McGuffin & Katz, 1989). Ten tweede zijn deze kinderen onderhevig aan allerlei omgevingsinvloeden die voor een deel samenhangen met de bipolaire stoornis van hun ouders en de gevolgen die deze stoornis heeft voor de ouder en dus ook het gezin. Dit genetische risico én het risico van het opgroeien in een gezin met een ouder met een bipolaire stoornis kunnen bijdragen aan het ontwikkelen van verschillende vormen van psychopathologie, wat ook door de tijd heen weer kan veranderen. Het is bijvoorbeeld mogelijk dat de eerste verschijnselen van een bipolaire stoornis aspecifieke problemen zijn, bijvoorbeeld motorisch onrust en impulsiviteit of juist angstsymptomen, en dat deze later gevolgd worden door depressieve symptomen, vervolgens een depressieve stoornis en uiteindelijk, na een manische episode, een bipolaire stoornis.

In de verschillende hoofdstukken van dit proefschrift worden de volgende onderzoeksvragen behandeld:

1. Wat is de prevalentie (het vóórkomen) en de incidentie (het aantal nieuwe gevallen) van psychopathologie, en in het bijzonder stemmingsstoornissen, bij kinderen van ouders met een bipolaire stoornis? (hoofdstuk 2)
2. Wat is het beloop van stemmingssymptomen en welke factoren bepalen op welke leeftijd stemmingssymptomen en uiteindelijk de bipolaire stoornis ontstaat? (hoofdstuk 3)
3. Is het mogelijk de General Behavior Inventory (GBI), een zelf-invul-vragenlijst voor het vaststellen van bipolaire en de unipolaire stemmingsstoornissen bij

volwassenen, te gebruiken in een populatie van 12 tot 18 jarige kinderen van ouders met een bipolaire stoornis? (hoofdstuk 4)

4. Is het mogelijk de GBI te gebruiken als een voorspeller van de bipolaire stoornis in een groep kinderen (12 tot 21 jaar) van ouders met een bipolaire stoornis? (hoofdstuk 5)
5. Hoe is het sociale functioneren van kinderen van ouders met een bipolaire stoornis? (hoofdstuk 6)
6. Hoe ervaren kinderen van ouders met een bipolaire stoornis hun opvoeding? (hoofdstuk 7)

Psychopathologie zoals gedefinieerd door de DSM-IV (de Diagnostic and Statistical Manual of Mental Disorders, IVth Edition, het classificatiesysteem van de American Psychiatric Association dat ook in Nederland algemeen gebruikt wordt) werd bepaald op alle drie meetmomenten. De resultaten van de tweede meting worden beschreven in hoofdstuk 2. De resultaten die bij de derde meeting zijn verkregen (Hillegers et al., in druk) worden besproken in hoofdstuk 8.

Gedurende de drie meetmomenten was er een geleidelijke toename van psychopathologie, welke vooral bestond uit een toename van stemmingsstoornissen. En dit betrof dan vooral de lifetime (ooit in het leven) stemmingsstoornissen en niet de huidige (op het moment van interview) stemmingsstoornissen. Het percentage kinderen met een lifetime stemmingsstoornis nam toe van 27% bij de eerste meting, via 33% bij de tweede meting, naar 40% bij de derde meting. De bipolaire stoornis nam toe van 3% bij de eerste meting via 50% bij de tweede meting naar 10% bij de derde meting. Van de kinderen die ooit een psychiatrische stoornis hadden gehad, betrof dat in 67% een stemmingsstoornis.

In overeenstemming met de meeste andere zogenaamde “high risk studies” bij kinderen van ouders met een bipolaire stoornis was de comorbiditeit (het gelijktijdig voorkomen van meerdere psychiatrische stoornissen) in onze groep hoog. Bij de derde meting hadden de kinderen die zelf een bipolaire stoornis hadden ontwikkeld in 46% ook een (lifetime) angststoornis, in 15% (lifetime) aandachtstekortstoornis met hyperactiviteit (ADHD) en tot onze verrassing slechts in 7% (lifetime) een stoornis in het gebruik van middelen (alcohol of drugs).

De onderzoeken bij kinderen van ouders met een bipolaire stoornis die na 1989 in de Verenigde Staten zijn verricht (Grigoroiu-Serbanescu e.a., 1989; Carlson e.a., 1993; Chang e.a., 2000) vermelden hoge percentages ADHD (tot 30%). In onze studie en ook

in de Canadese studie van Duffy e.a. (1998) bedroeg het percentage kinderen met ADHD echter 5%, respectievelijk 3%. Een verklaring hiervoor zou kunnen zijn dat in deze twee studies geen kinderen jonger dan 10 jaar zijn ingesloten. Het is daardoor mogelijke dat ADHD symptomen die in het verleden aanwezig zijn geweest, niet gerapporteerd werden.

De leeftijd waarop de 13 kinderen met een bipolaire stoornis tot aan de derde meting (leeftijd tussen de 16 en 26 jaar) hun eerste (hypo)manische episode hadden gekregen, was gemiddeld 18 jaar (spreiding tussen 14 en 25 jaar). Daarbij kreeg deze groep hun eerste (veelal depressieve) stemmingsepisode op een gemiddelde leeftijd van 13.1 jaar (hoofdstuk 3). Slechts vier van de kinderen met een bipolaire stoornis (31%) kregen een eerste depressieve episode voor de leeftijd van 12 jaar en geen van de kinderen kreeg een eerste (hypo)manische episode voor de leeftijd van 12 jaar. Deze bevinding suggereert dat de meeste patiënten met een bipolaire stoornis hun eerste manische episode tijdens de adolescentie of jongvolwassenheid krijgen en niet gedurende de kindertijd. Overigens was de gemiddelde leeftijd van onze groep bij de derde meting 21 jaar. Het is daarom te verwachten dat nog een aantal van hen alsnog een bipolaire stoornis zal ontwikkelen, wat dan zal resulteren in een verdere stijging van de gemiddelde leeftijd waarop de bipolaire stoornis ontstaat in deze groep.

Veranderingen in de prevalentie van psychiatrische diagnoses over een tijdsperiode kan ons informatie verschaffen over het aantal psychiatrisch diagnoses en het ontstaan van nieuwe psychiatrische diagnoses, maar het verschaft ons geen informatie over veranderingen in symptomatologie op een zogenaamd subklinisch niveau (het niveau waarbij net niet voldaan wordt aan de criteria van de stoornis). Vanuit een ontwikkelingsperspectief is het echter belangrijk om een beeld te krijgen van veranderingen in symptomatologie zowel over de tijd als in de mate van ernst, inclusief de veranderingen die zich afspelen op een subklinisch niveau. We hebben daarvoor in een analyse gebruik gemaakt van vijf verschillende “groeitrajecten” van stemmingssymptomen zoals deze door adolescenten uit de algemene bevolking zelf zijn gescoord op continue meetschalen (Bongers e.a.). Vervolgens hebben we gekeken welk percentage van de kinderen van ouders met een bipolaire stoornis die groeitrajecten volgde met de meer ernstige stemmingssymptomen (hoofdstuk 3).

De belangrijkste bevinding in dit hoofdstuk was, dat kinderen van ouders met een bipolaire stoornis inderdaad een risico lopen op het ontwikkelen van stemmingssymptomen. Meer kinderen van ouders met een bipolaire stoornis volgden de

groeitrajecten met een stijgend of chronisch hoog niveau van stemmingsproblemen dan kinderen uit de algemene bevolking. Deze bevinding laat zien dat de klinisch-diagnostische (DSM-IV) benadering en de dimensionele benadering elkaar aanvullende informatie genereren. De kinderen van ouders met een bipolaire stoornis die een meer problematisch groeitraject volgden, hadden ook een significant hogere kans om een bipolaire stoornis te ontwikkelen. Binnen de vijf verschillende groeitrajecten vonden we één traject met een vroeg begin (voor het 12e jaar) van de stemmingsproblemen om daarna hoog te blijven, en één groeitraject dat begint na het 12e jaar waarbij de stemmingsproblemen blijven toenemen tot het 21e jaar om daarna weer af te nemen. Een vroeg begin van stemmingsproblemen kan duiden op ernstige problematiek, maar het kan patiënten ook predisponeren voor andere kenmerken van de stoornis en zo ook tot een slechtere uitkomst/

In dit onderzoek hebben we nagegaan of de groep met stemmingsproblemen voor het 12e jaar en de groep waarbij de stemmingsproblemen in de adolescentie begonnen van elkaar verschilden. Familiale belasting met unipolaire en met bipolaire stoornissen, geboortegewicht en aantal ernstige levensgebeurtenissen voor het 12e jaar verschilden niet significant tussen beide groepen. Wel vonden we een significant verschil voor de leeftijd waarop de bipolaire stoornis ontstond. De kinderen met stemmingsproblemen voor het 12e jaar die zelf inmiddels al een bipolaire stoornis hadden ontwikkeld, bleken ouders te hebben die ook op jonge leeftijd hun bipolaire stoornis hadden ontwikkeld (voor het 25e jaar). Dit zou er op kunnen duiden dat kinderen van ouders die zelf op jonge leeftijd een bipolaire stoornis hebben ontwikkeld, zelf ook het risico lopen om op jonge leeftijd een stemmingsstoornis te ontwikkelen. Of dit werkelijk zo is weten we (nog) niet. Om deze vraag te kunnen beantwoorden is een langere follow-up van dit cohort nodig, waarin waarschijnlijk meer kinderen een bipolaire stoornis of een andere stemmingsstoornis zullen ontwikkelen.

Een probleem met bovenbeschreven vergelijkingen tussen de twee groepen was de geringe statistische power. Bestaande literatuur en eerdere onderzoeken in dit cohort (Wals e.a., 2004; Hillegers e.a., 2004) hebben aangetoond dat familiale belasting met de bipolaire stoornis, laag geboortegewicht en het optreden van ernstige levensgebeurtenissen determinanten zijn voor de ontwikkeling van de bipolaire stoornis. Dat we niet in staat waren te differentiëren tussen de groep met stemmingsproblemen voor het 12e jaar en de groep met stemmingsproblemen ontstaan in de adolescentie wordt waarschijnlijk veroorzaakt door het relatief kleine aantal kinderen in de beide groeitrajecten.

Een van de instrumenten voor de vaststelling en mogelijk ook de vroege detectie van de bipolaire stoornis is de General Behavior Inventory (GBI). De GBI is een zelfinvulvragenlijst die is ontworpen om stemmingsproblemen bij volwassenen te kwantificeren. Het instrument bestaat uit twee schalen, aangeduid als de Depressie schaal en de Bifasische/Hypomanie schaal, die samengesteld zijn op een a priori, klinische basis.

Eerst hebben we de bruikbaarheid van de GBI onderzocht bij de evaluatie van stemmingsstoornissen tijdens de adolescentie (hoofdstuk 4). Principale componenten-analyse resulteerde in dezelfde twee factoren (schalen) als bij volwassenen is gevonden. De Depressie schaal van de GBI discrimineerde tussen adolescenten met een DSM-IV stemmingsstoornis, een andere DSM-IV stoornis of geen stoornis. Significante correlaties tussen de GBI schalen en de corresponderende Internaliserende en Externaliserende schalen van de Youth Self Report (YSR) liet de convergente validiteit van de GBI zien in deze leeftijdsgroep. Op basis van deze bevindingen hebben we geconcludeerd dat de GBI ook in de leeftijd van 12 tot 18 jaar gebruikt kan worden als een zelfinvulvragenlijst om stemmingsstoornissen te onderscheiden van andere stoornissen of geen stoornissen.

We hebben ook de bruikbaarheid van de GBI onderzocht als een instrument om in onze groep van kinderen met een ouder met een bipolaire stoornis de ontwikkeling van de bipolaire stoornis te voorspellen over een periode van vijf jaar (hoofdstuk 5).

Een hoge score op de Depressie schaal tijdens de eerste meting voorspelde de ontwikkeling van een bipolaire stoornis gedurende de vijf jaar tussen de eerste en de derde meting. Onze bevindingen geven aan dat bij deze groep, in de periode vóór het ontstaan van de bipolaire stoornis, een hoger niveau van depressieve symptomen en (nog) niet het niveau van manische symptomen het ontstaan van de bipolaire stoornis voorspelt. En wanneer de stoornis is begonnen met een depressie, voorspelt een hoger niveau van depressieve symptomen de switch naar een bipolaire stoornis. Dit is in overeenstemming met onze bevindingen bij de derde meting dat bij 12 van de 13 kinderen (92%) de bipolaire stoornis is begonnen met één of meer depressieve episoden voorafgaand aan de eerste (hypo)manische episode.

We hadden verwacht dat het opgroeien in een gezin met een ouder met een bipolaire stoornis grote gevolgen zou hebben voor het sociale functioneren van de kinderen. En,

indien het sociale functioneren tijdens de kindertijd of adolescentie minder goed zou zijn, dat dit negatieve gevolgen zou hebben voor het functioneren in de vroege volwassenheid, nog afgezien van de gevolgen van een mogelijke ontwikkeling van een eigen bipolaire stoornis. Om deze hypothese te onderzoeken hebben we het sociale functioneren van de kinderen van ouders met een bipolaire stoornis in kaart gebracht tijdens de drie metingen (hoofdstuk 6). En om het functioneren van het gezin te onderzoeken hebben we de oordelen van de kinderen over hun opvoeding in kaart gebracht (hoofdstuk 7).

De meest opvallende bevinding is dat het gemiddelde niveau van sociaal functioneren van de kinderen in onze groep onder de leeftijd van 18 jaar niet verschilde van dat van adolescenten uit de algemene bevolking. In de leeftijdsgroep van boven de 18 jaar hadden de degenen met een bipolaire of unipolaire stemmingsstoornis uit onze groep echter wel problemen met sociaal functioneren en in het bijzonder op het gebied van het gezinsfunctioneren.

Vergeleken met jong volwassenen uit de algemene bevolking, beoordelen kinderen die opgegroeid zijn in een gezin met een ouder met een bipolaire stoornis, hun ouders globaal meer positief. Een psychiatrische stoornis bij de kinderen, en wederom niet de ernst van de bipolaire stoornis van de ouder, was geassocieerd met slechter sociaal functioneren van de kinderen en met een meer negatieve beoordeling door de kinderen van de opvoeding door de ouders.

Het is algemeen erkend dat de bipolaire stoornis gepaard gaat met psychosociale gevolgen een. In onderzoeken onder volwassenen worden genoemd daling in status op het werk, daling in inkomen en problemen in relaties met echtgenoten en kinderen (Coryell e.a., 1993; Calabrese e.a., 2003). De resultaten van ons onderzoek laten zien dat uitgebreide problemen in de opvoeding en in sociaal functioneren bij kinderen van ouders met een bipolaire stoornis niet aanwezig zijn zolang deze kinderen niet zelf een psychiatrische stoornis hebben ontwikkeld.

De in dit proefschrift beschreven onderzoeken betreffen de eerste, de tweede (na 14 maanden) en de derde meting (na vijf jaar) van het KBO (Kinderen van Bipolaire Ouders) project. We hebben gevonden dat deze kinderen over een periode van vijf jaar een hoog risico lopen op het ontwikkelen van een stemmingsstoornis en in het bijzonder een bipolaire stoornis. Het ontstaan en het verdere beloop van zelfgerapporteerde stemmingsproblemen en van depressieve episoden bleek voorspellend voor de ontwikkeling van een bipolaire stoornis. Vroege herkenning van de bipolaire stoornis

bleek mogelijk met de General Behavior Inventory. Het psychosociale functioneren van kinderen van ouders met een bipolaire stoornis bleek, zolang ze zelf niet een stoornis hebben ontwikkeld, ongestoord en achteruitgang in het sociale functioneren bleek veeleer het gevolg van stemmingsstoornissen bij de kinderen dan bij bij de ouders.

Gezien deze bevindingen is het van het groot belang kinderen van ouders met een bipolaire stoornis intensief te vervolgen, zeker wanneer deze stemmingsproblemen of een depressie hebben ontwikkeld. Zodra ze een eerste depressie of manische episode hebben ontwikkeld is behandeling geïndiceerd en het zou overwogen kunnen worden wanneer er lichtere stemmingsproblemen zijn.

Ten slotte, een langere follow-up van het KBO-cohort is noodzakelijk om na te kunnen gaan welke van de huidige bevindingen “hard” zullen blijken.

Dankwoord

Velen hebben aan dit onderzoek meegewerkt. Graag wil ik al die mensen bedanken.

Allereerst de ouders en hun kinderen die iedere meting weer hun medewerking hebben verleend en hun verhaal hebben verteld. Ik dank jullie voor het enthousiasme en de belangstelling voor de resultaten van dit onderzoek.

Op de tussentijdse informatiebijeenkomsten lieten jullie duidelijk merken een bijdrage te willen leveren aan het verbeteren van de kennis over risicofactoren en beschermende factoren voor de bipolaire stoornis. Ik was onder de indruk van de vitale manier waarop jullie de toch soms ook confronterende verhalen konden incasseren. Ik hoop dat er ooit ook nog een antwoord komt op de vraag hoe bij kinderen met de aanleg tot een bipolaire stoornis het ontstaan ervan kan worden voorkomen.

Frank Verhulst, mijn promotor, jij durfde het met mij aan. Beste Frank, bedankt voor de vele inspirerend gesprekken, de marsen en de aardbeiensoep. De echte nieuwe ideeën en andere invalshoeken kwamen van jou, maar ik ben je zeer dankbaar dat je de vaardigheid bezit de ander het idee te geven aan deze ideeën te hebben bijgedragen. Ik ben je ook zeer erkentelijk dat je mij de ervaring hebt kunnen geven, dat onderzoek steeds leuker gaat worden als je je er echt in gaat verdiepen.

Ik denk met plezier terug aan je verbazing toen dit proefschrift toch werkelijk naar een afronding toe ging. Voor al je vele werk en je vriendschap onmetelijk veel dank.

Hans Ormel, mijn tweede promotor. Beste Hans, veel dank voor je snelle reacties op mijn aanzetten tot artikelen. Jij was altijd de eerste die reageerde en altijd met een iets andere, licht ontregelende draai aan de discussie.

Ik ben blij dat ik in ieder geval één maal, in het zicht van een aantal reeën, aangetoond heb tenminste harder te kunnen lopen dan jij.

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Beste Marjolein, al weer 6 maanden een echte doctor, met jou heb ik ook jaren samengewerkt in Rotterdam in de "gewone" patiëntenzorg. Bedankt voor de gezellige even-geen-proefschrift-etentjes en je gedegen kennis van de neuropsychologie waarmee ik nu in Groningen een beetje pronk.

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Het Bipolair Netwerk van Altrecht, nu onder leiding van Paula Rinkema en Ralph Kupka, daar werd het KBO-project georganiseerd.

Voor het rond maken van de derde meting dank ik verder (in alfabetische volgorde) Grard Akkerhuis, Dennis Beute, Frank ter Haar, Ellen de Jonge, Zahra Ochen, Monica Rosso, Jasper Toet, Marileen Verhoeven, Jeroen Visser en Maria van Weel.

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Door jou aan de hand genomen is statistiek zelfs leuk. Mali, de Galapagos eilanden en Verdi waren daarbij een luchtige afwisseling.

Ilja Bongers, toen jij van de grote baas mij een periode terzijde mocht staan met je statistische expertise, kwam bij mij voor het eerst de gedachte aan een promotiedatum op. Een zeer prettige gedachte.

Ilja, bedankt voor je onverwoestbare optimisme en je instelling dat we deze klus wel even zouden klaren.

Medewerkers van de adolescentenkliniek van het Erasmusmc-Sophia, de "ado´s". Jullie bewaakten mijn schrijfdagen beter dan ik zelf deed, al viel het ook wel eens tegen als alweer niemand mij nodig bleek te hebben op die dagen.

Marie-Louise Aendekerk, door jouw stabiele aanwezigheid en therapeutische talent bleef de adolescentenkliniek gevrijwaard van de meeste crises, een paradijs voor iemand die met een promotietraject bezig is.

Mariska Eekma, een secretaresse die niet alleen ongelooflijk accuraat is maar ook nog meedenkt, is goud waard. Bedankt dat ik ook na mijn vertrek nog bij je terecht kon.

Fop Verheij, hoofd patiëntenzorg van de kinder-en jeugdpsychiatrie van het Erasmus MC Sophia. Beste Fop, bedankt voor de soepele wijze waarop ik in een drukke patiëntenzorg baan "vrijgespeeld" kon worden om aan mijn proefschrift te werken.

Een goedgestructureerde, hiërarchisch georganiseerde afdeling is toch wel ideaal als zo'n klus geklaard moet worden.

Manuelle Flos en George Westermann, de integraal medisch unithoofden van de kinderkliniek, veel dank voor de loyale wijze waarop jullie mijn afwezigheid bij de "ado´s" hebben opgevangen.

Jammer dat ik deze gunst niet meer kan retourneren bij jullie promotietraject.

Inge Demmendaal, de "secretaresse van Fop", dank zij jou heb ik nu een respectabel vormgegeven literatuurlijst, en dat is meer dan velen van mij verwacht hadden.

Mijn nieuwe collega´s bij Accare. Iemand in het team krijgen, die bezig is met de laatste loodjes van haar proefschrift is niet alleen een aanwinst. Ik dank jullie voor het geduld en begrip, waarmee jullie deze periode verdragen hebben. Betere tijden breken aan.

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Lieve ouders, voor jullie had zo´n proefschrift niet gehoeven, ga toch eens een goed boek lezen hebben jullie vaak uitgestraald. Maar toch hebben jullie mij zo opgevoed dat ik een proefschrift ben gaan schrijven. Bedankt voor deze "drive".

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Ik hou van je, en als je je zo blijft gedragen, mag je in Groningen blijven.

Curriculum Vitae

Catrien Reichart werd geboren op 5 mei 1955 te Amsterdam. Nadat zij het HBS-B diploma had behaald studeerde zij gedurende 1 jaar scheikunde aan de Universiteit van Utrecht waar ze haar propedeuse behaalde. In 1973 startte ze aan dezelfde universiteit de studie geneeskunde en ze behaalde in 1980 haar artsexamen.

Na eerst 1 jaar werkzaam te zijn geweest als arts-assistent niet in opleiding in Psychiatrisch Ziekenhuis Brinkgreve (tegenwoordig Adhesie) te Deventer, begon ze in 1981 aan haar specialisatie tot psychiater: 3 jaar in psychiatrisch ziekenhuis Zon & Schild (tegenwoordig Symfora Groep) te Amersfoort (opleider: Dr. W. Hubert), 1 jaar op de afdeling neurologie van het Sint Franciscusziekenhuis te Roosendaal (opleider: Dr. A. Van Spreeken) en 1 jaar op Psychotherapeutisch Centrum de Viersprong te Halsteren (opleider: M. Bolten).

Na haar registratie als psychiater (1985) deed ze haar aantekeningsjaar kinder-en jeugdpsychiatrie in het AMC te Amsterdam (opleider: Dr. D. Cohen-Mathijssen). Aansluitend hieraan werd ze aangesteld als staflid op de afdeling Kinder- en Jeugd psychiatrie van het AMC Amsterdam: eerst 4 jaar op de kinderkliniek en daarna 6 jaar op de polikliniek en in het consultatieve team. In deze periode heeft zij de 3 jarige opleiding adolescentenpsychotherapie gevolgd (RINO Noord-Holland) en in 1998 werd ze supervisor kinder- en jeugdpsychotherapie.

In 1996 werd ze aangetrokken als staflid op de afdeling Kinder- en jeugdpsychiatrie van het Erasmus MC-Sophia te Rotterdam om een adolescentenkliniek op te zetten. Van 1997 tot 2005 was ze intergraal medisch unit hoofd van deze kliniek. Daarnaast werkte ze aan dit proefschrift.

Vanaf februari 2005 is zij werkzaam als kinder- en jeugdpsychiater bij UCKJP Accare te Groningen.

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Stellingen behorend bij dit proefschrift

1. Bij kinderen (gemiddeld 21 jaar) van ouders met een bipolaire stoornis (bipolaire ouders) is de lifetime prevalentie van stemmingsstoornissen, maar niet van andere psychiatrische stoornissen, in Nederland verhoogd in vergelijking met personen in dezelfde leeftijdsgroep uit de algemene bevolking.
   Dit proefschrift, hoofdstuk 2

2. Indien kinderen van bipolaire ouders affectieve problemen ontwikkelen voor de leeftijd van 12 jaar, hebben ze een verhoogde kans op het ontwikkelen van een stemmingsstoornis.
   Dit proefschrift, hoofdstuk 3

3. De General Behavior Inventory (GBI) kan in een groep van kinderen van bipolaire ouders gebruikt worden als een voorspeller voor het later ontwikkelen van een bipolaire stoornis.
   Dit proefschrift, hoofdstuk 5

4. Kinderen van bipolaire ouders functioneren, als zij zelf geen psychiatrische stoornis hebben, sociaal niet anders dan personen in dezelfde leeftijdsgroep uit de algemene bevolking.
   Dit proefschrift, hoofdstuk 6

5. Kinderen van bipolaire ouders beoordelen, als zij zelf geen psychiatrische stoornis hebben, hun opvoeding even positief als personen uit de algemene bevolking.
   Dit proefschrift, hoofdstuk 7

6. Wanneer kinderen van bipolaire ouders affectieve symptomen of een depressie ontwikkelen, dienen zijzelf, hun ouders en de behandelaars van hun bipolaire ouders alert te zijn op het ontstaan van een bipolaire stoornis.

7. Placebo-gecontroleerd onderzoek teneinde na te gaan of behandeling met een stemmingsstabilisator van kinderen van bipolaire ouders die affectieve symptomen of een depressie hebben ontwikkeld het ontstaan van een bipolaire stoornis kan voorkomen, is gewenst én ethisch verantwoord.

8. De in vergelijking met Europa hogere incidentie van de bipolaire stoornis bij kinderen onder de 12 jaar in de Verenigde Staten wordt waarschijnlijk (deels?) verklaard door het hogere gebruik in de VS van methylfenidaat en antidepressiva door kinderen in deze leeftijdsgroep.
   Reichart CG, Nolen WA. Earlier onset of bipolar disorder in children by antidepressants or stimulants? A hypothesis. J Affect Disord 2004;78:81-84

9. Een clinicus die onderzoek doet loopt het risico vooral op zoek te gaan naar "gunstige" data voor zijn/haar patiënten en "ongunstige" data niet te willen onderkennen.

10. Onderzoek doen levert een clinicus meer "diepgang" op, maar ook het risico van verlies van "breedte".

11. De hoge prevalentie van angststoornissen op de polikliniek kinder- en jeugdpsychiatrie van het Erasmus MC Rotterdam en van pervasieve ontwikkelingstoornissen op de polikliniek van Accare zou verklaard kunnen worden door selectiebias, maar wellicht ook door beoordelingsbias.