At risk for bipolar disorder

Mesman, Eshter

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Bipolar offspring followed from adolescence into adulthood

Esther Mesman

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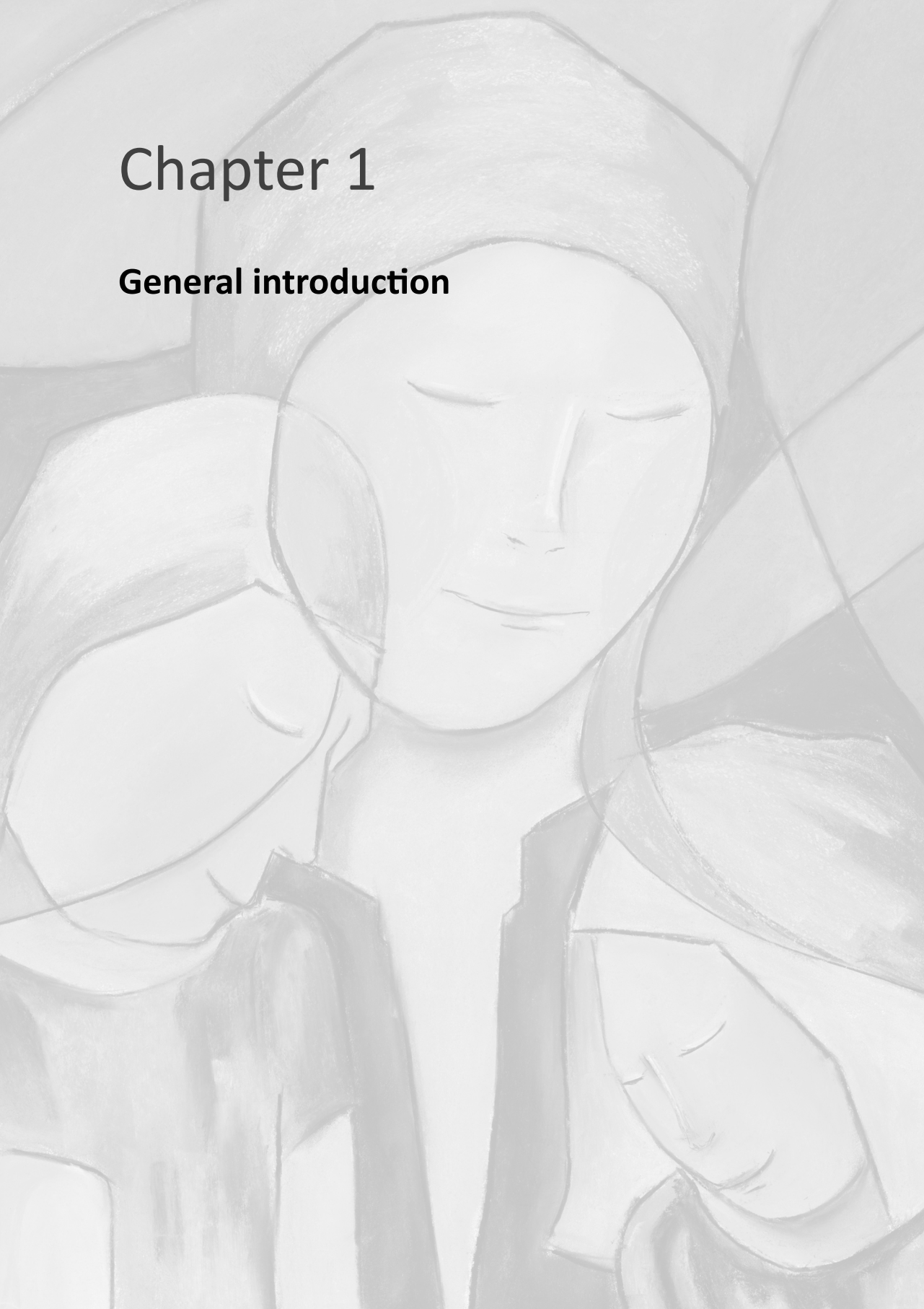

GENERAL INTRODUCTION

Bipolar disorder (BD), also known as manic-depressive illness, is characterized by episodes of depression and (hypo)mania in alternation with periods of euthymia. The illness can cause a significant mental health burden and psychosocial dysfunction (MacQueen, Young, & Joffe, 2001; Conus, Macneil, & McGorry, 2013; Institute for Health Metrics and Evaluation., 2013). Typically, BD debuts with a (mild) depressive episode, with the first (hypo)manic episode onset following years later (Duffy, Alda, Hajek, & Grof, 2009a; Mesman, Nolen, Reichart, Wals, & Hillegers, 2013). This typical early course hampers early recognition of BD and leads on average to a diagnostic delay of 10 years (Drancourt et al., 2013; Altamura et al., 2010; Suppes et al., 2001). As the majority of patients will have the onset of a first mood episode before the age of 25, there is a lost opportunity for adequate treatment in the essential years of psychosocial development. Therefore, improving recognition of the early trajectories and determination of possible risk mechanisms is necessary to diminish the delay of treatment and ideally to decrease the burden of disease (Berk et al., 2010; Dean, Gerner, & Gerner, 2004).

To date the pathogenesis of BD remains poorly understood. So far, the most robust predictor for BD is a positive family history for BD (Gottesman, Laursen, Bertelsen, & Mortensen, 2010; Craddock & Jones, 1999). Therefore, the study of children of patients with BD (bipolar offspring) provides an ideal opportunity to explore the familial transmission, the early course and determinants of BD. This thesis focuses on the development of bipolar offspring within a longitudinal design and present a series of studies of the Dutch Bipolar Offspring Study, a prospective study of bipolar offspring followed from adolescence into early adulthood.

In this chapter, we describe the diagnostic criteria of BD according to the DSM-IV (American Psychiatric Association., 1994), clinical characteristics and potential risk mechanisms in BD, followed by an overview of bipolar offspring studies and Dutch Bipolar Offspring Study. Subsequently, the study design and a summary of previous findings of the Dutch Bipolar Offspring Study are presented. Finally the specific chapters of this thesis are introduced.

BIPOLAR DISORDER

Diagnostic criteria

BD is characterized by episodes of depression, mania, hypomania and episodes with mixed features/mixed episodes in alternation with periods of normal (euthymic) mood or with subsyndromal symptoms over the life span. The spectrum of bipolar disorders includes the following disorders: bipolar I disorder (BD I), bipolar II disorder (BD-II), cyclothymic disorder and bipolar disorder not otherwise specified (BD-NOS). As the studies described in this thesis are based on DSM-IV based outcome measures and not the recently launched DSM-V, only DSM-IV criteria of BD will be discussed in this section. Table 1 shows the

DSM-IV definitions of the various episodes as they may occur in patients with BD (American Psychiatric Association., 1994). BD I is characterized by at least one manic episode and major- or less severe depressive episodes; but may be diagnosed after one manic episode only. BD II is characterized by the occurrence of one or more major depressive episodes and at least one hypomanic episode. Cyclothymic disorder is a chronic, fluctuating mood disturbance characterized by numerous hypomanic and depressive mood of which none meet the formal criteria for a full depressive or manic episode with a duration of minimal 2 years (or 12 months in children). BD-NOS is characterized by bipolar features but not meeting the criteria of any of the above mentioned disorders, e.g. very rapid alternation (over days) between manic and depressive symptoms, recurrent hypomanic episodes without intercurrent of depressive symptoms (Goodwin FK & Jamison KR, 2007; American Psychiatric Association., 1994). BD in children and adolescents is a much debated topic in the literature which goes beyond the DSM-IV and will therefore be discussed below.

Table 1 | Diagnostic criteria for mood episodes according to DSM-IV (American Psychiatric Association., 1994)

Major depressive episode*	
A period of at least 2 weeks with at least one core feature and four associated features and cause significant distress or impairment in social, occupational, or other important areas of functioning.	
Core feature	**Associated features**
– Depressed mood	– Change in appetite or weight
– In children and adolescents the mood may be irritable rather than sad	– Insomnia or hypersomnia
	– Psychomotor retardation or agitation
– Loss of interest or pleasure in nearly all activities	– Fatigue or loss of energy
	– Feelings of worthlessness or guilt
	– Difficulty thinking, concentrating or making decisions
	– Recurrent thoughts of death, suicidal ideation
Manic episode*	
A period of abnormal mood (core feature) including 3 or 4 (in case of irritable mood) associated features that lasts at least one week or less if hospitalization is required. The disturbance must be sufficiently severe to cause impairment in social, occupational, or other important areas of functioning or by the presence of psychotic features.	
Core feature	**Associated features**
– Abnormally and persistently elevated, expansive or irritable mood.	– Inflated self-esteem or grandiosity
	– Decreased need for sleep
	– Pressure of speech
	– Flight of ideas
	– Distractibility
	– Increased involvement in goal-directed activity or psychomotor agitation
	– Involvement in activities with painful consequences

Table 1 | *(Continued)*

Hypomanic episode*
Core and associated features as in Manic episode with a duration of at least 4 days. The symptoms are associated with a change in normal functioning, but do not cause marked impairment in social or occupational functioning.
Mixed episode*
Core and associated features as in Manic episode with a duration of at least 4 days. The symptoms are associated with a change in normal functioning, but do not cause marked impairment in social or occupational functioning.

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

Clinical characteristics of bipolar disorder

The prevalence of BD I is about 1-1.5% among adults. Taking into account the broader bipolar spectrum the prevalence ranges between 3-8.3% worldwide (Goodwin FK & Jamison KR, 2007). BD is, in contrast to unipolar depression, equally prevalent among sexes (Goodwin FK & Jamison KR, 2007). BD typically starts with a (mild) depressive episode followed by a (hypo)manic episodes years after (Drancourt et al., 2013; Goodwin FK & Jamison KR, 2007; Hillegers et al., 2004a). However, in retrospect most patients report the first discernable signs and symptoms years before the onset of the first mood episode (Malhi, Bargh, Coulston, Das, & Berk, 2014). The age of onset of BD is best classified in three categories, namely: early onset with a mean age of 17, an intermediate onset at age 27 and late onset with a mean age of 46 (Bellivier et al., 2011; Leboyer, Henry, Paillere-Martinot, & Bellivier, 2005). Especially early age of onset is associated with familial loading and worse outcome and comes along with more psychotic features, mixed episodes, increased prevalence of comorbid disorders, lower treatment response and more suicidality (Goodwin FK & Jamison KR, 2007).

Originally, it was thought that the prognosis of BD was favorable with good intermittent recovery in between episodes; however, only a third of the patients achieve the full level of premorbid functioning after recovery (Huxley & Baldessarini, 2007). Mean recurrence rates are about 40-50% over a 2 year period and 68-73% over a 4-5 year period (Gitlin, Swendsen, Heller, & Hammen, 1995; Simhandl, Konig, & Amann, 2014). The chance for recurrence is related to the number of previous episodes (Angst, Gamma, Sellaro, Lavori, & Zhang, 2003; Kessing, Hansen, Andersen, & Angst, 2004; Nolen et al., 2004; Simhandl et al., 2014). Mean time spent ill in BD patients is about 50% (Kupka et al., 2007).

About 65-71% of the BD patients have psychiatric comorbid conditions and 25-65% has multiple psychiatric conditions (Conus & McGorry, 2002; McElroy et al., 2001). The most common comorbid disorders are substance use disorders (24-42%) and anxiety disorders (15-42%) (Conus & McGorry, 2002; McElroy et al., 2001). Also, the risk for suicide among bipolar patients is high, about 25-50% of the patients attempt suicide at least once in their life (Valtonen et al., 2006), risk of actual suicides have been estimated to be around 8% in

men and 5% in women over a follow-up of 18-years (Nordentoft, Mortensen, & Pedersen, 2011) which is 20-30 times higher than the risk among the general population (Pompili et al., 2013; Schaffer, Sinyor, Reis, Goldstein, & Levitt, 2014). Apart from suicidality, morbidity and mortality in BD is also strongly related to the frequent comorbid medical conditions such as cardiovascular disease, thyroid dysfunction, diabetes and metabolic syndrome. Medical conditions may be consequence of lifestyle, adverse effects of medication, but also may point to shared etiology (Goodwin FK & Jamison KR, 2007).

Clinical staging

The clinical presentation of BD is heterogeneous, also within the larger subcategories of BD I, BD II and BD-NOS. Illness course, degree of intermittent recovery, treatment history, treatment responsiveness, and degree of functional and cognitive outcome, but also comorbidity and familial loading vary substantially among BD patients (Kupka, Hillegers, & Scott, 2015). In general there is agreement that clinical course, functional outcome, cognitive impairment and possible biological mechanisms worsen as BD progresses, however individual differences occur (Berk et al., 2014; Kapczinski et al., 2014). A better understanding of these individual differences may guide us towards more personalized treatment and ideally offers opportunities for early intervention. In recent years, clinical staging has become topic of interest. Clinical staging is a method widely used in other medical specialties, such as oncology. Clinical staging aims to indicate stage of disease, prognosis of disease and provide stage appropriate treatment (Berk et al., 2014; Kapczinski et al., 2014). The premises of staging include that the illness is progressive and renders a better treatment response and prognoses in the early stages (Berk et al., 2014; Kapczinski et al., 2014). In general, there is agreement for the progressive nature of BD and better treatment response in the early stages and thus BD opts for the use of a staging model (Berk et al., 2014; Kapczinski et al., 2014). In Table 2, one of the proposed models is depicted. This model represents several stages ranging from a general at risk stage into a persistent chronic course of the illness. Berk's (2014) proposed model focuses primarily on the clinical course of BD. Others have proposed models focusing more on functional impairment along psychiatric symptomatology (Kapczinski et al., 2009). The two models basically complement each other. The field of clinical staging is still in its infancy, but rapidly evolving. A limitation of the presented clinical staging models is that the majority of data is based on cross-sectional and retrospective studies in adults (Kapczinski et al., 2014). Moreover, the early stages of BD are only roughly defined. Studies among bipolar offspring may contribute to the refinement of clinical staging.

Prepubertal bipolar disorder and transatlantic controversies

BD in children and adolescents, especially prepubertal mania, has been a controversial topic for many years. The US NIMH Research Roundtable on Prepubertal BD in 2001 did agree upon the existence of a BD phenotype in children and adolescents. Prepubertal BD was divided in two phenoptypes: 1) a 'narrow' phenotype fitting the DSM-IV criteria for BD-I and

Table 2 | A potential clinical staging model for bipolar disorder Berk et al. (2014)*

Clinical stage	Definition	Potential interventions
0	Increased risk of severe mood disorder (e.g. family history, abuse, substance use) No specific current symptoms	Mental health literacy Self help
1a	Mild or non-specific symptoms of mood disorder	Formal mental health literacy Familial psycho-education Substance use reduction Cognitive behavioral therapy, supportive counseling
1b	Prodromal features: ultra high risk	1a plus therapy for episode: phase specific or mood stabilizer
2	First episode threshold mood disorder	1b plus case management, vocational rehabilitation, specific rehabilitation, specific psychotherapy
3a	Recurrence of subtreshold mood symptoms	2 and emphasis on maintenance medication and psychosocial strategies for full remission
3b	First threshold relapse	3a and relapse prevention strategies
3c	Multiple relapses	3b plus combination of mood stabilizers
4	Persistent unremitting illness	3c and clozapine and other tertiary therapies, social participation despite disability

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II and typically an episodic course, and 2) a 'broad' phenotype including BD-NOS including children not meeting the full DSM-IV criteria for BD but who suffer nonetheless from mood instability, are severely impaired and *may* have BD. Moreover, this broad phenotype is usually accompanied by high rates of comorbid disruptive disorders and ADHD (Carlson & Klein, 2014; Goodwin FK & Jamison KR, 2007; 2001). However, the concept of prepubertal BD raises many questions: How does mania presents during childhood? How to differentiate from ADHD and other disruptive behaviors? How to count overlapping criteria for these disorders? These issues may be interfering with research findings and are important to bear in mind (Carlson & Klein, 2014).

Ever since the roundtable, prepubertal BD has attained tremendous attention in the United States in research and clinics. Moreno et al. (2007) reported in US children and adolescents a 40-fold increase in outpatient visits with a diagnosis of BD in between 1994-2003. In contrast, European researchers and clinicians remained behind. European clinicians rarely diagnose BD in children or adolescents following line with the more restrictive guidelines of the UK National Institute for Health and Care Excellence (NICE) (National Institute for Health and Clinical Excelence, 2006). This guideline recommend restrictive use of BD I and a cautious use of BD II, and not to use the diagnosis BD-NOS in children and adolescents. This controversy is also mirrored in so called 'administrative' studies. In a

comparison of US and UK hospital discharges between 2000 and 2010, hospital discharge rates of prepubertal BD are 12.5 fold higher in the US than in the UK (James et al., 2014).

Epidemiological studies have shown that the prevalence of the narrow phenotype seems equal across continents with 1.8%; only the broader phenotype resulted in significantly higher rates in the US studies (6.7%) as compared to the rates of 2.3% elsewhere (Van Meter, Moreira, & Youngstrom, 2011). Despite the controversy, an interesting study has been done by Axelson et al. (2011). They followed 140 outpatient children and adolescents with the diagnosis BD-NOS. After on average 5 years of follow-up, 45% converted to BD I or BD II with a median time of conversion of 58 weeks. The strongest predictor for conversion was having a first or second degree family member with BD (59% conversion after 5 years). Thus, in patients with a family history BD-NOS may reflect an early course. Therefore, it may be concluded that BD-NOS may have prognostic value.

Retrospective adult patient studies show that there is a substantial proportion of the patients reporting a prepubertal onset. Also, in these adult studies differences in age of onset across continents are observed: in a study by the Stanley Foundation Bipolar Network 31% of US patients reported a childhood onset versus 6% of European (German and Dutch) patients (Post et al., 2014). This early age of onset was related to a longer treatment delay and in general a more pernicious course was reported in US patients. Moreover, US patients presented with more comorbid disorders, more rapid cycling and more comorbid alcohol- and drug abuse and more medical conditions (Post et al., 2014). Thus apart from the transatlantic differences in definitions and diagnostic habits and attitudes, also true transatlantic differences may exist.

POTENTIAL RISK MECHANISMS

The pathogenesis of BD is not well understood. Despite that the increased risk for BD for first degree family members with BD and twin studies suggest that 60-80% of the risk to develop BD is genetically determined, the genes predisposing for BD are largely unknown and do not follow a simple mendelian pattern (Craddock & Jones, 1999; Craddock & Sklar, 2013). The picture of genetics for BD is complex and assumes a complex interplay of multiple genes and gene mechanisms together with non-genetic environmental factors (Craddock & Sklar, 2013). Several potential candidates have been suggested to intervene in this complex gene-environment inter-play including mechanisms involved in circadian rhythm, neuronal development, immunological- and metabolic aspects and environmental stress including trauma and other stressful life events (e.g. Bender & Alloy, 2011a; Frey et al., 2013). In this section, we briefly introduce two potential risk mechanisms that were subject of our studies: alterations in the immune system and stressful life events.

Underlying mechanisms of bipolar disorder: a central role for the immune system?

As noted above, medical conditions frequently co-occur in BD patients. Some of these conditions are considered to be associated with life style and the adverse effect of medication prescribed for BD, but the etiology of the co-occurrence of these diseases is poorly understood and this comorbidity may also hint towards shared susceptibilities between BD and these medical conditions (Goodwin FK & Jamison KR, 2007). For instance, patients with BD show more abnormalities in thyroid dysfunction, independently of lithium use (Kupka et al., 2002). Thyroid dysfunction was also found to be more prevalent in teenage female bipolar offspring, as compared to control children, although independently of mood disorders or psychopathology in general (Hillegers et al., 2007), suggesting shared susceptibility. In recent years, there is a shift in thinking of the pathogenesis of BD as a multi-systemic disorder and it has been proposed that BD involves a cascade of genetic, immune, endocrine, metabolic and neurochemical changes or aberrancies (see Figure 1 for schematic depiction) (Berk et al., 2011a; Leboyer et al., 2012). One of the links and maybe the central link within this cascade may be an imbalance of the immune system (Leboyer et al., 2012).

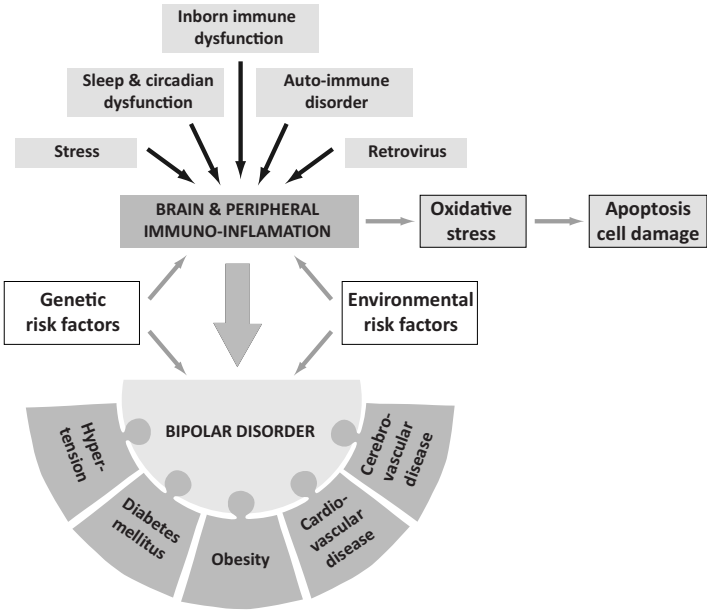

Figure 1 | Bipolar disorder viewed as a multisystem disorder with strong immune dysfunction underpinnings. Adapted from Leboyer et al. (2012)*

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In this thesis, we focus on alterations in the immune system. The association between inflammatory networks and mood disorders is not new. In the early 1990ies, the *Macrophage T cell theory of depression* was introduced (Smith, 1991; Smith & Maes, 1995). This theory, postulates an inflammatory-changed immune system to be a driving force behind unipolar depression and BD in which pro-inflammatory cytokines (excreted by pro-inflammatory activated monocytes, macrophages, dendritic cells and T cells) can pass the blood-brain barrier and then destabilize the brain by alternating neurotransmitter set points and hence causing mood disturbances (Smith, 1991). In the past two decades, several patient studies have shown that immune alterations, both pro- and anti-inflammatory, are associated with BD (Berk et al., 2011b; Beumer et al., 2012; Drexhage et al., 2010; Goldstein, Kemp, Soczynska, & McIntyre, 2009; Modabbernia, Taslimi, Brietzke, & Ashrafi, 2013; Munkholm, Vinberg, & Vedel, 2013; Padmos et al., 2008). A recent meta-analysis of 30 studies showed that patients with BD have increased levels of IL-4, IL-6, sIL2R, sIL-6R, TNF-alpha, sTNFR41 and IL1-Ra in comparison with controls; and also that some cytokines (TNF-alpha, sTNFR1, sIL-2r, IL-6 and IL-1RA) are state dependent, i.e. higher in a depressive or manic state than when euthymic (Modabbernia et al., 2013). In another study from our group, Padmos et al. (2008) found prove for altered gene expression in circulating monocytes of 19 genes involved in inflammation, trafficking, survival, and mitogen-activated protein kinase (MAPK) activation in BD patients compared to healthy controls. Apart from alterations in peripheral immune networks, alterations in neural networks have been suggested to be involved in the pathogenesis of BD. In particular alterations in the levels of Brain-Derived Neurotrophic Factor (BDNF) and the S100 calcium binding protein B (S100B) have been found (Berk et al., 2011b; Schroeter, Steiner, & Mueller, 2011). S100B is produced and secreted by astrocytes and increased levels of S100B reflect neuronal damage or survival depending on its concentration and is associated with neuropathology in neurodegenerative disease and brain-inflammatory diseases (Rothermundt, Peters, Prehn, & Arolt, 2003). In both unipolar depression and BD, increased levels of S100B have been consistently found in acute depressive and manic states (Andreazza et al., 2007; Schroeter et al., 2010). Also age was associated with altered levels of S100B: both young and older adults with mood disorders showed increased levels of S100B; however, the impact of S100B in mood disorders increases with age (Schroeter et al., 2011). BDNF is a neurotrophin involved in neurogenesis, synaptic plasticity, neural growth and cell survival. A meta-analysis of 13 studies (Fernandes et al., 2011) found decreased levels of BDNF in adult patients with BD during an acute episode of mania or depression, but not during euthymia. However, BDNF levels during euthymia were associated with age and length of illness. Decreased levels of BDNF have been associated with increased levels of oxidative stress in BD patients (Kapczinski et al., 2008).

To date, most reports on biological mechanisms in BD, are based on cross-sectional data and have focused mainly on adult patients with BD, i.e. often with already chronic BD using the appropriate pharmacological treatment. This is problematic since age, the illness itself and pharmacological treatment do have an impact on the association between BD and biological mechanisms, and thus has led to inconsistent findings (Goldstein et al.,

2009). So far, only few studies have focused on early stage BD or high risk populations. In the above mentioned gene-expression study by Padmos et al. (2008), the pro-inflammatory signature in circulating monocytes was also investigated – apart from in adult bipolar patients – in 54 participants of our Dutch Bipolar Offspring Study at a mean age of 18 years. The pro-inflammatory monocyte signature was present in bipolar offspring, including three participants who were not yet detected with any disorder at time of the study, but from who we know that they have developed a mood disorder during follow-up. These promising findings hinted towards a possible biomarker for BD. Another study by Goldstein et al. (2011) examined in a pilot study among 30 adolescent bipolar patients BDNF, IL-6 and high-sensitivity C-reactive protein (hsCRP). They found a positive association between mood symptoms and pro-inflammatory cytokines IL-6 and hsCRP, while there was a negative association between IL-6 and BDNF. Furthermore, Kauer-Sant Anna et al. (2009) examined serum TNF-α, IL-6, IL-10 and BDNF in early (0-3 years) and late stage (> 3 years) BD patients compared to healthy controls. Compared to healthy controls, TNF-α and IL-6 were increased in both early and late stage patients. IL-10 was only increased in the early stage. BDNF was decreased in late stage patients, but not altered in early stage patients. When comparing early versus late stage patients they found TNF-α to increase at the later stage, whilst BDNF and IL-6 decreased from early to late stage. Both observations suggest a connection between the immune and neuro-chemical networks associated with the stage of the disorder.

Taken together, these studies suggest a role for both peripheral immune networks and brain immune-neurotropic networks in the pathogenesis of BD. However, the precise role of alterations in the immune system and neurotropic networks in relation to BD remains to be elucidated. More specifically, we need to determine in which stage of BD these factors are of particular importance, or how these alterations fluctuate across stages (Berk et al., 2007; Berk et al., 2011b; Brietzke et al., 2012; McGorry et al., 2007). Prospective long-term studies of bipolar offspring may be valuable in unraveling the biological underpinnings of BD.

Environmental stress: life events and bipolar disorder

There is a large body of evidence that stressful life events associated with the onset of a first mood episode, and with the course of the illness, e.g. with recurrences and time to recovery (Bender & Alloy, 2011b; Brown & Harris, 1989; Hlastala et al., 2000; Malkoff-Schwartz et al., 1998; Koenders et al., 2014; Johnson, 2005). However, the precise role of stressful life events in the pathogenesis and course of BD remains poorly understood. The literature on stress in relation to mood disorders is extensive and complex and is hampered by methodological issues by design and illness characteristics. In this section, we aim to provide a brief description of present theoretical stress/life event models and in unipolar depression and bipolar disorder to put studies in this thesis in perspective. Most life event theories belong to the class of *diathesis stress models* based on the assumption that a stressor activates the *diathesis/predisposition* of an individual and consequently triggers the onset of psychopathology (Monroe & Simons, 1991).

Due to the recurrent and often progressive course of BD, several studies investigated whether the impact of life events is different in the early phase of the illness as compared to recurrences of mood episodes. The *kindling hypothesis* (Post, 1992a) or *stress sensitization model* premises that stressors/life events trigger mood episodes in the first couple of mood episodes, but as the illness progresses, mood episodes do occur more autonomously (Bender & Alloy, 2011b; Monroe & Harkness, 2005; Post, 1992b). Regardless the elegance of the proposed hypothesis, the interpretation of the model is multi-interpretable. Kindling may represent on the one hand a decoupling of stress and mood liability as the illness progresses, the *autonomy model*. On the other hand, it may represent a *sensitization model* in which the threshold for stress declines as a result of illness progression (Monroe & Harkness, 2005). Findings in BD on kindling thus far have been inconsistent (Bender & Alloy, 2011a). This may have to do with methodological differences between studies, but also the model of life events may not be conclusive (Bender & Alloy, 2011a; Monroe & Harkness, 2005). The inconsistencies thus far, emphasize the importance of life event research in prospective studies, including high risk samples such as bipolar offspring.

Others have found support for the *stress-generation hypothesis* which implies that especially events in which the subject has a personal contribution are predictive for depression, so called *dependent events.* These events involve mostly negative social or interpersonal content, contrasting *independent* or so called fateful events (Hammen, 1991; Hammen, 2005). In unipolar depression many studies support this hypothesis (Liu & Alloy, 2010), but for BD only a few studies have focused on this issue (Bender, Alloy, Sylvia, Urosevic, & Abramson, 2010; Koenders et al., 2014). As reviewed by Hammen (2005), evidence for the stress generation hypothesis currently holds four hypotheses for explanation: 1) the depression itself may cause increased interpersonal conflicts; 2) patients often live in highly stressful families; 3) patients with depression, or a genetic vulnerability, select 'high conflict' environments; 4) maladaptive family functioning, dysfunctional social skill training or personality traits such as temperament may mediate or moderate the association between dependent life events and mood recurrence and induce the elevated frequency of dependent life events.

Furthermore, as life events do not occur in an isolated environment, there is accumulating interest and need for more sophisticated multifactorial models including possible moderators and/or mediators such as developmental, biological, psychological and sociodemographic characteristics and the interplay with life events and mood episode onset (Hammen, 2005). However, research in BD reporting on more complex multifactorial life event models remain scarce to date. These models are presented in the literature as (*cognitive) diathesis stress model, vulnerability model* or *stress buffering hypothesis* (Cohen & Wills, 1985; Hammen, 2005).

In general, life event research in BD is challenging with both the polarity, the subtypes of BD, measurement issues related to life event research, the definition of stress, type of events and lack of large prospective BD patient studies (Johnson, 2005; Koenders et al., 2014). This together with the numerous theories on the association of life events and BD requires

further studies of life events and the onset of BD, for instance in high risk populations. To date, only few studies have investigated the role of life events in bipolar offspring. Overall, these studies found an increased number of life events and/or more severe life events in bipolar offspring (Duffy et al., 2007; Hillegers et al., 2004b; Ostiguy et al., 2009; Wals et al., 2005a; Petti et al., 2004). Yet, the literature on the more complex multifactorial life-event models in high risk populations is scarce. In this thesis, we investigated the effects of psychological aspects and social environment on the association of life events and onset of first mood episodes, as well as on the further course of the illness, i.e. recurrences.

BIPOLAR OFFSPRING STUDIES

The majority of bipolar offspring studies have focused on the clinical outcome of bipolar offspring to date. Table 3 and 4 provide an overview of the literature on the clinical outcome of all bipolar offspring studies performed between 1980 and March 2015. Only studies meeting the following criteria were selected: 1) assessment of psychopathology using (semi-)structured interviews, 2) provision of information on lifetime prevalence rates for mood and/or bipolar spectrum disorders according to DSM-III(-R) or DSM-IV(-TR) and 3) availability of the full text manuscript as accessed via PubMed/university library or upon personal request. Studies were divided in studies with a cross-sectional- (Table 3) and longitudinal design (Table 4). The 12-year follow-up of the Dutch Bipolar Offspring Study was excluded as this study is presented extensively in this thesis.

In total, 19 offspring studies with a cross-sectional design including 710 families and 1061 offspring fulfilled selection criteria. A recent study by Perich et al. (2015) was excluded as bipolar offspring with already existing BD were excluded from the study. The number of offspring per study ranged from 5-141. The age of the offspring was between 2 and 35. The majority of studies reported an age range between 5 and 18 years old. Only one study included subjects above age 21 (Waters & Marchenko-Bouer, 1980). In these studies the lifetime prevalence rates of bipolar spectrum disorders ranges from 0 to 38%, for BD I from 2 to 18% and 0 to 56% for any kind of mood pathology. Apart from the large variability in mood disorders, there is also a wide variation in the prevalence of externalizing disorders. A review by Duffy et al. (2011) suggested that methodological differences such as recruitment procedures and assessment across studies may underpin the large variations found across studies. Moreover, as written earlier, the controversies regarding how to define and diagnose BD among children or adolescents may also play a role. A limitation of cross-sectional studies is that prevalence of psychopathology are subject to recall bias, which is especially problematic in terms of more mild previous episodes and age of onset.

Table 3 | An overview of cross-sectional bipolar offspring studies: study characteristics and psychopathology outcome

	Parental characteristics					Offspring characteristics			Offspring Assessment						
Author (year)	***n***	**BD index Parent**	**BD Mother**	**Study source**	**Diagnosis Other parent**	***n***	**Mean age**	**Age range**	**Interview**	**Any BPS**	**Any mood**	**Any ADHD / DBD**	**Any axis I**	**DSM**	**Country of origin**
Waters and Marchekio-Bouer (1980)	16	BAD (NS)	50%	Outpatient clinic	No info	48	26.7	16-35	SADS-L	**15% BPS** BD I or II	42%	No info	52%	III	Canada
LaRoche et al. (1981)	10	BAD (NS)	50%	Outpatient clinic	No info	17	10.1	8-18	CPRS/CAS	0%	0%	0%	6%	III	Canada
Decina et al. (1983)	18	61% BD I 39% BD II	61%	Outpatient clinic	No info	31	11.0	7-14	Mental Health Assessment Form	0%	26%	6% ADHD ~6% DBD	52%	III	U.S.A.
Gershon et al. (1985)	19	100% BD I	29%	Inpatient clinic or NIMH study	Any: ~41.3%	29	No info	6-17	K-SADS-E	**~10% BPS** 3% BD I ~7% CYCL	41%	14% ADHD 17% DBD	72%	III	U.S.A.
Kashani et al. (1985)	5	BAD (NS)	NS	Inpatient clinic	No info	9	12.4	7-17	DICA & DICA-P	0%	22%	0% ADHD 22% DBD	No info	III	U.S.A.
Klein et al. (1985)	24	100% BD I	54%	Inpatient clinic	Any: 25%	37	17.9	15-21	SADS-L	**27% BPS** 3% BD II 24% CYCL	38%	11% DBD	43%	III	U.S.A.
Grigoriou-Serbanescu et al. (1989)	47	100% BD I	60%	Inpatient clinic	Any: 28% Mood: 4% SCZ-BD: 2%	72	12.92	10-17	K-SADS-E	**1% BPS**	10%	21% ADHD 14% DBD	61%	III	Roma-nia
Todd et al. (1996)	9	89% BD I 11% BD II	NS	Subsample NIMH study	Mood: 11%	16	11.1	6-17	DICA-R-P	**25% BPS** 19% BD I 6% BD II	44%	25% ADHD 25% DBD	No info	III	U.S.A.

Table 3 | *(Continued)*

Author (year)	Parental characteristics					Offspring characteristics			Offspring Assessment						
	n	BD index Parent	BD Mother	Study source	Diagnosis Other parent	*n*	Mean age	Age range	Interview	Any BPS	Any mood	Any ADHD / DBD	Any axis I	DSM	Country of origin
Chang et al. (2000)	37	BD I or BD II	81%	Outpatient clinic or local support groups	Mood: 49%	60	11.1	6-18	WASH-U-K-SADS	**15% BPS**	30%	28% ADHD 3% DBD	55%	IV	U.S.A.
Henin et al. (2005)	88	72% BD I 28% BD II	67%	Inpatient clinic	No info	117	13.6	4-18	K-SADS-E; SCID	**20% BPS**	42%	37% DBD or ADHD	63%	IV	U.S.A.
Hirshfeld – Becker et al. (2006)	23	52% BD I 48% BD II	52%	Clinical referrals and advertisement	BD: 4% Any: No info	34	7.1	> 5	K-SADS-E	**9% BPS** 6% BD I 3% BD II	15%	50% DBD or ADHD	No info	IV	U.S.A.
Jones et al. (2006)	20	95% BD I 5% BD II	75%	85% Self-help groups and 15% outpatient clinics	No info	25	16.2	13-19	SADS-L	**12% BPS** 8% BD I 4% CYCL	56%	No info	No info	IV	U.K.
Singh et al. (2007)	29	100% BD I	51%	In- and outpatient clinics	Mood: 28%	37	10.2	8-17	WASH-U-KSADS	**38% BPS** 16% BD I 11% BD II 8% CYCL 3% BDNOS	MDD 14% DYST 14%	31% ADHD 22% DBD	78%	IV	U.S.A.
Petresco et al. (2009)	53	79% BD I 16% BD II 5% BD-NOS	100%	Outpatient clinic	No info	43	11.2	6-18	K-SADS-PL	**2% BPS**	12%	12% ADHD 14% DBD	63%	IV	Brazil

Table 3 | *(Continued)*

Author (year)	Parental characteristics					Offspring characteristics			Offspring Assessment						
	n	BD index Parent	BD Mother	Study source	Diagnosis other parent	*n*	Mean age	Age range	Interview	Any BPS	Any mood	Any ADHD / DBD	Any axis I	DSM	Country of origin
Birmaher et al. (2010)	83	61% BD I 39% BD II	90%	60% Advertisement, 9% adult BD studies and 31% outpatient clinics	Any: 41% BD: 3.9%	121	3.8	2-5	K-SADS-PL	2% BD-NOS	3%	16% ADHD 12% DBD	26%	IV	U.S.A.
Nurnberger et al. (2011)	91	86% BD I 7% BD II 5% SCZBD	NS	5% In- and 95% outpatient clinics	No info	141	16.7	12-21	K-SADS-P & BP	**8.5% BPS** 4% BD I 3% BD II 1% BDNOS	23%	8% ADHD 11% DBD	60%	IV	U.S.A.
Zappitelli et al. (2011)	26	100% BD I	83%	Advertisement and outpatient clinics	Mood: 29% Any: 54%	35	12.5	6-17	K-SADS-PL	**9% BPS** 6% BD I 3% BDNOS	29%	40% ADHD 17% DBD	71%	IV	U.S.A.
Garcia-Amador et al. (2013)	36	70% BD I 30% BD II	55%	In- and out-patient clinics	Any: 50% MDD: 15% SCZ: 12%	50	12.17	6-17	K-SADS-PL	**4% BPS**	10%	18% ADHD 12% DBD	50%	IV	Spain
VandeLeur et al. (2012)	76	BD I, BD II or SCZBD	60%	In- and out-patient clinics	BD: 12% MDD: 26%	139	11.5	6-18	K-SADS-E	**3.5% BPS** 2% BD I/II 1% BDNOS	35%	8% ADHD 8% DBD	62%	IV	Switzer-land

BD = bipolar disorder; BAD = bipolar affective disorder as defined in the DSM-III; BPS = bipolar spectrum disorders, including any type of bipolar disorder, bipolar I disorder, bipolar II disorder, cyclothymia, bipolar disorder not otherwise specified, schizoaffective disorder bipolar type; BD I = bipolar I disorder; BD II = bipolar II disorder; CYCL = cyclothymia; BDNOS = bipolar disorder not otherwise specified; SCZBD = schizoaffective disorder bipolar type; MDD = major depressive disorder; DYST = dysthymic disorder; ADHD = attention deficit (hyperactivity) disorder; DBD = disruptive behavioral disorder: including oppositional defiant disorder and conduct disorders; SUD = substance use disorder; ~ = rough estimation based on information provided in article; NS = not specified.

Table 4 | An overview of prospective bipolar offspring studies: study characteristics and psychopathology outcome

Published work	Cohort characteristics				Parental characteristics			
	Years of follow-up	Follow-up interval; (# interviews)	Drop-out rate	Type of cohort	*n*	BD index parent	BD mother	Source
Nurnberger et al. (1988)	2	Baseline, 1-, 2-years (3)		F	32	BAD (NS) SCZBD	No info	Oupatient clinic, research studies and local clinicians
Zahn-Waxler et al. (1988; 1984)	4	Baseline, 3-, 4 years (3)	0%	F	7	BAD (NS)	57%	Inpatient
Hammen et al. (1987; 1990)	Up to 3	Every 6 months	15%	D	13	67% BD I 33 BD II	100%	Inpatient and outpatient clinics
Weintraub and Carlson (1987); Carlson and Weintraub (1993; 1987)	3	Baseline, 3 years (2)	15%	D	58	BAD (NS)	81%	Inpatient
Meyer et al. (2004; 1992); Radke-Yarrow et al. (1992)	23	Baseline, every 3-5 years (5)	12%	D/F	22	23% BD I 77% BD II	100%	Advertisement, parent groups and local clinicians
Hillegers et al. (2005) Reichart et al. (2004b); Wals et al. (2001)	5	Baseline, 1-, 5-years (3)	6%	F	80	74% BD I 26% BD II	60%	82% national patient association and 28% outpatient clinic
Egeland et al. (2012; 2003); Shaw et al. (2005)	16	Annually (16)	0%	D/F	15	100% BD I	43%	Genetic linkage research; Amish community
Nijar et al.(2004; 2014); Ellenbogen et al. (2004)	Up to 10	No info	18%	D	58	BAD (NS)	47%	Outpatient clinics, advocacy and support groups
Duffy et al. (1998; 2002; 2007; 2009b; 2010; 2014; 2011)	Up to 16	Annually (mean follow-up 6.3)	No info	D	113	41% BD I 43% BD II 4% SCZBD 10% RMDD (2011)	52%	Molecular studies from outpatient clinics; lithium and nonlithium responders
Axelson et al. (2015) Birmaher et al. (2009)	Mean follow-up 7 years	Mean follow-up 2.5 years	9%***	F	236	72% BD I 28% BD II	81%	53% Advertisement, 31% adult BD studies and 16% outpatient clinics

BD = bipolar disorder; BAD = bipolar affective disorder as defined in the DSM-III; BPS = bipolar spectrum disorders, including any type of bipolar disorder, bipolar I disorder, bipolar II disorder, cyclothymia, bipolar disorder not otherwise specified, schizoaffective disorder bipolar type; BD I = bipolar I disorder; BD II = bipolar II disorder; CYCL = cyclothymia; BD-NOS = bipolar disorder not otherwise specified; SCZBD = schizoaffective disorder bipolar type; MDD = major depressive disorder; DYST = dysthymic disorder; ADHD = attention deficit (hyperactivity) disorder; DBD = disruptive behavioral disorder: including oppositional defiant disorder (ODD) and conduct disorders (CD); SUD = substance use disorder; F = fixed population recruited

	Offspring characteristics			Offspring assessment						
Diagnosis other parent	***n***	**Mean age**	**Age range**	**Interview**	**Any BPS**	**Any mood**	**Any ADHD /DBD**	**Any axis I**	**DSM**	**Country of origin**
28% BAD or SCZBD	53	19.6	15-25**	SADS-L	2% BD I 2% BD II	9% major 34% minor	Childhood disorders: 15%	72%	III	U.S.A.
Mood: 71%	7	6	6	CAS	0% BPS	43% MDD	No info	86%	III	U.S.A.
No info	18	13.6	8-16**	K-SADS	0% BPS	61%	6% ADHD 17% DBD	72%	III	U.S.A.
No info	125	No info	> 18	Rating scales; SADS-L	5% BPS	No info	~30% ADHD ~28% DBD	53%	III	U.S.A.
Mood: 63%	32		18-23; 20-28	CAS; DICA-R; SCID	19% BPS 6% BD I 13% BD II	No info	NS for bipolar offspring	No info	III	U.S.A.
No info	132	20.8	16-26	K-SADS-PL; SCID	10% BPS 4% BD I 6% BD II	40%	6% ADHD 7% DBD	59%	IV	The Nether-lands
No info	115	No info	75% < 14**	CARE – interview	8% BD I	No info	No info	No info	IV	U.S.A
Mood: 33%	71	20.5	14-27	K-SADS-PL; SCID	3% BD I 3% BD II	8%	3% ADHD 1.3% DBD	65%	III/IV	Canada
None	229	22.6	7-25	K-SADS-PL; SADS-L	22% BPS 3% BD I 6% BD II 7%BDNOS 5% SCZBD 1% CYCL	61%	11% ADHD ~2% DBD	~71% (2011)	IV	Canada
Any: 49% BD: 4% MDD: 23	357***	18.1	6-18	K-SADS-PL; SCID	19% BPS 4% BD I 5% BD II 11%BDNOS	48%	31% ADHD 27% DBD 25% ODD 10% CD	74%	IV	U.S.A.

within a fixed enrollment period; F/D = fixed design, but new siblings in the study age-category were added or new families when parents with unipolar mood disorder made a switch to BD; D = a dynamic cohort, recruiting new families, no fixed enrollment period.~ = rough estimation based on information provided in article; NS = not specified. **Age range baseline, age range at most recent assessment not available. ***357 out of 391 were prospectively followed. Offspring lost to follow-up were included for analysis in this paper.

A total of 10 offspring studies with a longitudinal design were found (Table 4) including 634 families and 1139 offspring. The study by LaRoche et al. (1985; 1987) was excluded because the full text of the manuscript was not available. Moreover the study by Akiskal et al. (1985) was excluded because the subjects were referred for the study because of already existing psychopathology. Seven out of 10 studies (also) included offspring above 18 years, whilst six studies followed the offspring from childhood or adolescence onwards. The longest follow-up is 23 years in the study by Meyer et al. (2004). Two other studies followed offspring for about 16 years (Duffy et al., 2011; Egeland et al., 2012). Moreover, there is a large variation in dynamic cohorts (enrolment of new families or offspring is allowed during follow-up) and fixed cohorts (no enrolment of new subjects after the first assessment). In sum, lifetime prevalence rates of bipolar spectrum disorders range from 0 to 22%, for BD I between 2 and 6%. Prevalence of any kind mood disorders ranged from 8 to 61 and 53 to 86% for any psychopathology (for those studies providing information). Again a wide variation of externalizing like disorders was observed for those studies providing information on externalizing disorders. In this thesis, we present the follow-up data of the Dutch Bipolar Offspring Study (Wals, 2004; Reichart, 2005; Hillegers, 2007) with up to date a follow-up of 12 years. The Dutch bipolar offspring is to our knowledge the largest fixed bipolar offspring cohort worldwide with a follow-up into adulthood (i.e. no new offspring enrolled the study after the first assessment).

The Dutch Bipolar Offspring Study

The studies described in this thesis are from the Dutch Bipolar Offspring Study, a prospective fixed cohort study established in 1997 and with up to now a follow-up of 12-years. Below a description of the study sample is presented. Parts of this section are reprinted and adapted sections of previous PhD theses on the Dutch Bipolar Offspring Study (Wals, 2004; Reichart, 2005; Hillegers, 2007).

Main objective

The main objective to initiate the Dutch Bipolar Offspring Study, back in 1997, was to explore the early trajectories of BD in a high risk population with the ultimate goal to be able to detect BD in an early stage and to prevent or at least delay onset and/or diminish the severity of the illness (Reichart, 2005).

Study design

Inclusion criteria of the study

Families with at least one parent with bipolar I or II disorder having children in the age range 12-21 years old. A family was only included if all offspring within the age range 12-21 agreed to participate. Only adolescents without a severe physical disease or handicap and with an IQ of at least 70 were included. Written informed consent was obtained from all offspring and their parents (if younger than 18) at each assessment.

Recruitment

The Dutch Bipolar Offspring Study cohort is a fixed cohort, i.e. all families and offspring were recruited at baseline and no new families or siblings were recruited during the study. Families were recruited via the Dutch Patient Association for Manic Depressives and Relatives (Nederlandse Vereniging voor Manisch-Depressieven en Betrokkenen (VMDB)) and outpatient clinics of psychiatric hospitals. By the end of 1997 a survey was sent to all 1961 members of the Dutch patient association. This survey explained the aim of the study and included questions about their illness, family composition and age of the offspring. In total, the response rate was 36% (n = 712) containing 110 eligible families. Of these 110 families, 62 families with 102 offspring in the age range 12-21 agreed to participate. In addition, we contacted nine psychiatric hospitals with an assigned outpatient clinic for patients with BD in different regions widely spread over the Netherlands. The psychiatric hospitals identified 91 eligible families, whereof 24 families (26%) with 38 offspring were willing to participate. In total, this resulted 86 families and 140 offspring at baseline. All parents were outpatient at the time of recruitment. No control families were recruited for prospective follow-up.

The 140 offspring of 86 families were assessed for the baseline measurement (T1) between November 1997 and April 1999 (Wals et al., 2001). The second assessment (T2) was performed 14 months later, 132 offspring were reassessed (Reichart, Wals, & Hillegers, 2007), followed by a third assessment (T3) at five year follow-up (n = 129) (Hillegers et al., 2005). This thesis presents the fourth assessment (T4) performed 12-years after baseline. All study assessments were approved by the Medical Ethics Committee of the University Medical Center Utrecht. For an overview of the study flow please see Figure 2.

Assessment of psychopathology in offspring and parents

All psychiatric interviews were administered by intensively trained interviewers with graduate degrees in psychology or medicine. All interviews were evaluated with psychiatrists certified in child and adolescent as well as adult psychiatry in consensus meetings.

Parents

DSM-IV diagnoses of BD I and BD II were confirmed by face-to-face interviews with the patient, and if available the partner, using the International Diagnostic Checklist and further confirmed by the clinical diagnosis of the treating psychiatrist (Hiller, Zaudig, Mombour, & Bronisch, 1993). Lifetime diagnoses of mood, substance use, anxiety and psychosis of the biological co-parent were assessed using the Family History Research Diagnostic Criteria method (Andreasen, Endicott, Spitzer, & Winokur, 1977).

Offspring in the adolescent phase

At baseline and the second assessment, DSM-IV diagnoses were obtained by a face-to-face interview with both the child and the parent using the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL) (Kaufman

et al., 1997). The K-SADS-PL is an interviewer-oriented diagnostic interview designed to assess current (present in the past 2 months) and past DSM-IV symptoms resulting in diagnoses in children and adolescents, by interviewing the parent(s) and child separately. In addition to the K-SADS-derived diagnoses, we also screened for DSM-IV pervasive developmental disorders.

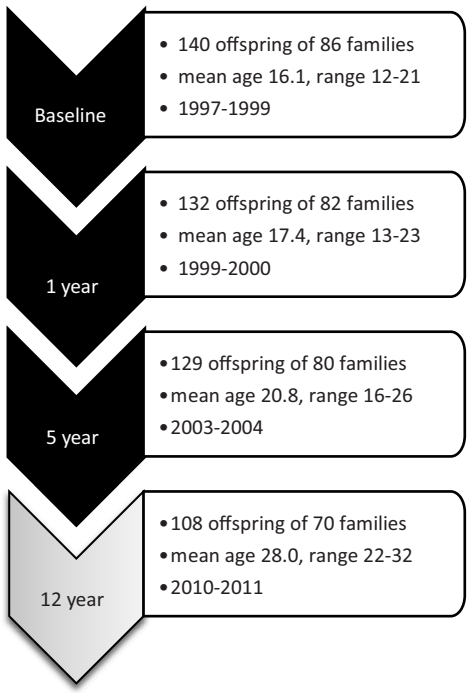

Figure 2 | Study flow of the Dutch Bipolar Offspring Study

Offspring in the young adulthood phase

Because of the increasing age of the offspring the K-SADS-PL was replaced by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID; First, Spitzer, Gibbon, & Williams, 1997) at five year follow-up questions regarding oppositional defiant disorder, conduct disorder, and tic disorders originating from the K-SADS-PL were applied. Lifetime DSM-IV diagnoses are based on all psychiatric interviews that took place during the study. Each psychiatric assessment evaluated current and past symptoms during the interim period. For all diagnoses, the age at onset and the duration of the episode were established. Because of the perceived uncertainty of the BD-NOS diagnosis (Goodwin & Jamison, 2007), we decided not to specifically assess for this diagnosis in our studies.

Description of the study sample at baseline

The characteristics of the study sample at the baseline measurement are shown in Table 5.

Table 5 | Demographics of the Dutch Bipolar Offspring Study at baseline

	N	%	Mean	SD	*p*
Parental characteristics					
Bipolar parent	86				
Bipolar mothers	52	60			0.06
Bipolar I disorder	64	74			
Number of hospitalizations			2.2	2.1	
Age 1st mood episode			26.1	9.8	
Married	65	76			
Age			45.4	4.8	
Non bipolar parent	86				
No psychiatric disorder	59	70			
Mood disorder	21	24			
Other psychiatric disorder	6	6			
Age			46.2	5.2	
Offspring characteristics	140				
Girls	68	49			0.80
Age girls			16.3	2.7	0.41
Age boys			16.0	2.7	
Socioeconomic status, range 1-9			4.8	2.1	
IQ			113	16	

RESULTS OF PREVIOUS STUDIES ON THE DUTCH BIPOLAR OFFSPRING STUDY

Based upon the first three assessments of the Dutch Bipolar Offspring Study, a total of fifteen peer-reviewed articles and three PhD theses were published. To put the findings of this thesis in perspective, we will first briefly address previous theses on the Dutch Bipolar Offspring Study.

The first thesis entitled "*Children of bipolar parents: prevalence of psychopathology and antecents of mood disorders*" written by Marjolein Wals (2004) was based on the first two assessments of the study. She addressed the following issues in her thesis:

1. Prevalence of psychopathology in children of a bipolar parent at the baseline assessment (Wals et al., 2001);

2. Determinants of mood disorders in bipolar offspring. Determinants examined were familial loading of mood and substance use disorders, birth weight, family problems and stressful life events (Wals et al., 2003; Wals et al., 2004);
3. Determinants of change in level of problem behavior between baseline and the 1-year follow-up among bipolar offspring (Wals et al., 2006);
4. The association of stressful life events and first or recurrent onset of mood disorders in children of bipolar parents during the one year follow-up (Wals et al., 2005b).

Regarding psychopathology, at the mean age of 16 years prevalence rates of psychopathology (44%) and of bipolar disorder (3%) were not highly elevated. Prevalence of mood disorders (29%) appeared to be moderately elevated (Wals et al., 2001). The study of determinants showed that familial loading of unipolar depression and substance use disorder, low birth weight and stressful life events were important determinants for mood disorders in bipolar offspring. Determinants contributed in different ways to the development of psychopathology. Low birth weight, familial loading of unipolar depression and substance use disorders were strong independent predictors for lifetime mood disorders in bipolar offspring (Wals et al., 2003; Wals et al., 2004). Familial loading of unipolar depression and substance use were also found to predict for future behavior and emotional problems, whereas low birth weight and family functioning did not (Wals et al., 2006).

The second thesis *"Being a child of a bipolar parent. Psychopathology, social function and family functioning"* was written by Catrien Reichart (2005) and addressed the following issues:

1. Prevalence of psychopathology in children of a bipolar parent at the second assessment after 1-year follow-up (Reichart et al., 2004b);
2. The course of affective symptomatology (between the first and third assessment) and determinants of age of onset of BD in bipolar offspring (Reichart, 2005);
3. The use of the General Behavior Inventory (GBI) in a population of adolescent offspring of parents with a bipolar disorder (Reichart et al., 2004a);
4. The use of the GBI as predictor of bipolar disorder in a population of adolescent offspring of parents with a bipolar disorder (Reichart et al., 2005);
5. Social functioning in bipolar offspring (Reichart et al., 2007b);
6. Subjective parental rearing styles among bipolar offspring (Reichart et al., 2007a).

Psychopathology at the 1-year follow-up at a mean age of 17 years was still not clearly elevated with prevalence of DSM-IV axis I disorders (49%) in comparison to the general population. The lifetime prevalence of mood disorders was moderately higher (33%) than the general population. The prevalence of bipolar spectrum disorders had increased from 3% at baseline to 4% (Reichart et al., 2004b). Onset and course of self-reported affective problems were found of predictive value for the development of mood disorders (Reichart et al., 2004a; Reichart, 2005). Early detection of BD was possible by the use of the GBI

(Reichart et al., 2005). Psychosocial functioning and subjective parental rearing prior illness onset was largely unimpaired or experienced as dysfunctional. Impairment seemed rather a result of mood disorders in the offspring (Reichart et al., 2007a; Reichart et al., 2007b).

The third thesis *"Developing bipolar disorder: a follow-up study among children of patients with bipolar disorder"* by Manon Hillegers (2007) addressed the following issues:

1. Five year prospective outcome of psychopathology in the adolescent offspring of bipolar parents (Hillegers et al., 2005);
2. Impact of stressful life events, familial loading and their interaction with mood disorders at 1-year follow-up (2007); and five year follow-up (2007);
3. Signs of higher prevalence of autoimmune thyroiditis in female bipolar offspring of bipolar parents (Hillegers et al., 2007).

After five years of follow-up, at the mean age of 21 years, the lifetime prevalence rates of psychopathology were now substantially increased in comparison to the general population (de Graaf, Ten Have, & van Dorsselaer, 2010). Lifetime prevalence rates were 40% for any mood disorder, 10% for BD, and 59% for DSM-IV axis-I disorders in general, compared to 19.5%, 2.4%, and 46.5% in young adults aged 25-35 in the general population respectively. However, the lifetime rate of BD was moderate in comparison to other offspring studies (see Table 3 and 4). In total, 12 out of the 13 offspring with BD started the illness with a depressive episode followed by a (hypo)manic episode on average 4.9 years later. A further increase in BD and unipolar depression was expected as the cohort would further mature into adulthood.

A strong association was found between stressful life events and first mood episode onset (Hillegers et al., 2004a; Hillegers, 2007). Familial loading of unipolar disorder was found to have an independent effect on first mood episode onset, but did not modify the association between stressful life events and mood episode onset.

In a study on autoimmune thyroiditis, a higher prevalence of autoimmune thyroiditis was found in female bipolar offspring (Hillegers et al., 2007). This increased prevalence was found to be independent from the presence of mood disorders or other psychopathology. This finding in combination with previous findings in patient- and a twin study from our group led to the hypothesis of a common shared genetic factor for thyroid autoimmunity and BD (Vonk, van der Schot, Kahn, Nolen, & Drexhage, 2007).

Another key paper on immunological aspects in bipolar offspring was written by Padmos et al. (2008) who studied the gene expression of 19 genes in circulating monocytes in bipolar patients and bipolar offspring originating from the Dutch Bipolar Offspring Study. This pro-inflammatory monocyte signature of 19 genes was present in BD patients compared to healthy controls, but was also present in bipolar offspring. More interestingly, 3 out of 3 offspring who developed a mood disorder during further follow-up were also positive on this monocyte signature. These findings hinted towards a possible vulnerability marker for mood disorders in bipolar offspring.

In sum, the series of studies performed on the Dutch Bipolar Offspring study has shown a gradual increase of psychopathology in general and more specifically in mood disorders. After five years of follow-up a further increase of mood disorders and BD was expected according to survival analysis and the moderate rates of BD in comparison to other studies. Several determinants were found to be associated with mood disorders in bipolar offspring. Determinants were found to contribute in different ways to the development of mood disorders.

AIMS AND OUTLINE OF THIS THESIS

The aim of this thesis is to expand our knowledge on the early trajectories and potential risk mechanisms of mood disorders among bipolar offspring with the ultimate goal to detect BD at an early stage and to prevent or at least delay onset and/or diminish the severity of the illness. In this thesis we present a series of studies based upon the 12-year follow-up of the Dutch Bipolar Offspring Study with a focus on the prevalence and early trajectories of mood disorders among bipolar offspring, cross-national differences across bipolar offspring studies and potential risk mechanisms.

- **Chapter 2** presents a cross-national comparison of the Dutch Bipolar Offspring Study (T1) and the Pittsburgh Bipolar offspring Study from the U.S.A. This study aims to explore and clarify cross-national differences between adolescent US and Dutch offspring within a similar age range (10-18 years) in terms of categorical and dimensional psychopathology taking into account demographic and parental characteristics.
- **Chapter 3** provides a detailed presentation of the development of lifetime DSM-IV axis I disorders, especially mood disorders, in the Dutch Bipolar Offspring Study during 12 years of follow-up.

In **chapter 4** and **5** potential risk mechanisms are explored.

- **Chapter 4** aims to elucidate the interplay of life events, psychological aspects and social support on mood episode onset and recurrences among bipolar offspring.
- **Chapter 5** concentrates on biological mechanisms previously associated with BD and aimed to evaluate neuro-immune changes in affected and unaffected bipolar offspring followed from early adolescence into adulthood.

In **chapter 6** and **7** we focus on clinical phenomenology in adolescent bipolar offspring.

- **Chapter 6** focuses on the early clinical phenomenology of mood disorders in bipolar offspring. Threshold and subthreshold symptomatology at adolescent age as rated by the clinician will be explored by comparing diagnostic outcome categories at the 12-years follow-up of the Dutch Bipolar Offspring Study.

- **Chapter 7** explores the utility of the *General Behavior Inventory* (GBI), a self-report measure, as screenings instrument among bipolar offspring. In this study, we aim to test the validity of both the full length GBI and its abbreviated counterpart the *Seven Up Seven Down* (7U7D) as screening instrument for mood disorders in a high risk population. Moreover, we aim to explore the predictive value of GBI and 7U7D scores in terms of early detection of mood disorders in bipolar offspring.

Finally, **Chapter 8** provides a summary of all above noted chapters followed by a general discussion, clinical implications and suggestions for future research.

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Chapter 2

Categorical and Dimensional Psychopathology in Dutch and US bipolar offspring: A preliminary cross-national comparison

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ABSTRACT

Background

Cross-national differences in the prevalence of bipolar disorder and other psychopathology in offspring of parents with bipolar disorder have been reported. The present study aims to explore and clarify cross-national differences in categorical and dimensional psychopathology between US and Dutch bipolar offspring.

Methods

We compared two existing bipolar offspring studies (age range 10-18 years): the US Pittsburgh BIOS study (*n*=224, data collection 2001-2007) and the Dutch Bipolar Offspring Study (*n*=136, data collection 1997-1999 and 2010-2012). Categorical psychopathology was ascertained through the Schedule for Affective Disorders and Schizophrenia for School Age Children and dimensional psychopathology through the Child Behavior Checklist completed by parents.

Results

Categorical psychopathology, particularly anxiety and behavioral disorders, was more common in the US sample (66% vs 44%, $p < .001$). There were no cross-national differences in prevalence of mood disorders, including bipolar I or II disorder. After controlling for demographic and parental characteristics, the effect of geographic origin diminished, but remained significant for “any psychopathology” and “mood disorders with comorbid conditions”. There were no significant cross-national differences in dimensional psychopathology.

Limitations

The present study should be considered preliminary as a measure of inter-site reliability was not available.

Conclusions

US and Dutch bipolar offspring share a similar liability for mood disorders. In categorical psychopathology, cross-national differences were observed, but these were partially explained by differences in sample characteristics. Differences on the categorical level were not confirmed in dimensional psychopathology. Potential explanations for the observed differences and suggestions for future research are discussed.

INTRODUCTION

Bipolar disorder (BD) is characterized by recurrent episodes of (hypo)mania and depression that affects on average 1.8% of youth across the world (Van Meter, Moreira, & Youngstrom, 2011). Whereas epidemiologic prevalence of BD I and II in youth is not different between US and non-US countries (Van Meter et al., 2011), clinical studies have shown increased prevalence of outpatient visits and hospital admission rates of BD in youth in the United States (US) as compared to most other countries (James et al., 2014; Soutullo et al., 2005; Holtmann et al., 2010; Kozloff et al., 2010). Comparisons between US and European adult patients with BD have also shown higher prevalence, younger age of onset, more severe illnesses, and increased parental history of bipolar disorder in the US (Bellivier et al., 2011; Post et al., 2008; Post et al., 2014b; Post et al., 2014c). However, these studies relied on retrospective self-report data of adult patients. Numerous studies have consistently shown that offspring of patients with BD are at increased risk to develop BD and other psychiatric disorders (Duffy et al., 2011; Duffy, 2010; DelBello & Geller, 2001). In these offspring samples, the prevalence of BD and other psychiatric disorders as well as the age of onset of mood disorders varies significantly across studies and countries (Duffy et al., 2011; DelBello & Geller, 2001). The discrepancies in bipolar offspring studies and the prevalence of BD in youth may reflect demographic (e.g. parental- or offspring characteristics) or methodological differences (e.g. recruitment method, instruments used, informant source, age at assessment) as well as cultural factors and differences in diagnostic practices (DelBello & Geller, 2001; Duffy et al., 2011; James et al., 2014; Soutullo et al., 2005; Carlson & Klein, 2014; Merikangas et al., 2011). Thus far, cross-national variability in psychopathology among bipolar offspring has not been studied.

The present study aimed to explore and clarify cross-national differences in categorical and dimensional psychopathology in bipolar offspring. Two large and well characterized bipolar offspring studies were compared, namely: the Pittsburgh Bipolar Offspring Study (BIOS) (Birmaher et al., 2009) and the Dutch Bipolar Offspring Study (DBOS) (Wals et al., 2001). Categorical and dimensional psychopathology was examined in offspring aged 10-18 years using the K-SADS-PL (Kaufman et al., 1997) and the Child Behavior Checklist (CBCL) (Achenbach, 1991) respectively. We hypothesized a priori that possible observed differences in categorical and dimensional psychopathology between US and Dutch bipolar offspring would be explained by demographic and methodological differences.

METHODS

Subjects

The US sample is based on the Pittsburgh Bipolar Offspring Study (BIOS) (Birmaher et al., 2009), a sample of 388 offspring, aged 6-18 years, of parents with a bipolar I or II disorder. Families were recruited through advertisements, psychiatric hospitals and outpatient clinics

for patients with BD. Study design and recruitment procedures have been described in detail elsewhere (Birmaher et al., 2009). The Dutch sample is based on two ongoing prospective bipolar offspring cohort studies: the Dutch Bipolar Offspring Study (DBOS) (Wals et al., 2001) and a new yet unpublished cohort: the Dutch Bipolar & Schizophrenia Offspring Study (DBSOS) (for detailed information see addendum 1). The DBOS recruited 140 offspring, aged 12-21 years old, of parents with BD I or II, from 86 families between 1997 and 1999 (Wals et al., 2001). The DBSOS is recruiting bipolar and schizophrenia offspring, aged 10-16 years; all available bipolar offspring (n = 33) recruited between 2010 and 2012 were included in the present study. Both Dutch studies recruited through the Dutch Association for Manic Depressives and Relatives and outpatient clinics for patients with BD in different regions of the Netherlands. The DBOS and DBSOS were combined in order to enlarge the Dutch sample and to optimize equality in age range between the US and Dutch sample (age 6-18 versus 10-21). Only offspring aged 10-18 years were selected to optimally compare the US and the Dutch samples. Exclusion criteria for both the US and two Dutch studies were a severe physical disease or handicap and an IQ < 70. Studies were approved by the institutional review board and written informed consent was obtained from parents and offspring (Wals et al., 2001). An overview of the sample selection is provided in Figure 1.

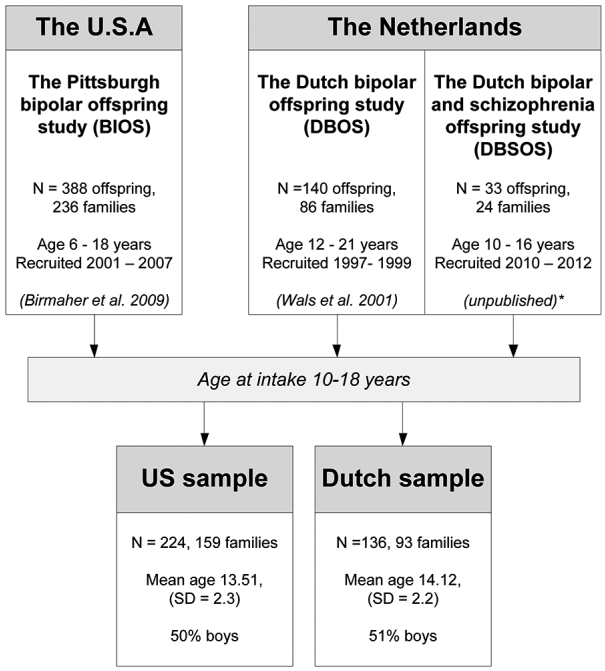

Figure 1 | Origin bipolar offspring studies.

Instruments

Parental psychopathology

In the US-sample, DSM-IV axis I disorders of all bipolar probands and 30% of the biological co-parents were ascertained through the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (First, Spitzer, Gibbon, & Williams, 1997). Diagnoses were confirmed during diagnostic consensus conferences with a psychiatrist. Psychopathology (i.e. depression, mania, psychotic disorders and substance use disorders) of the majority of biological co-parents (70%) was not evaluated directly, but assessed by the Family History Research Diagnostic Criteria method (FH-RDC) (Andreasen, Endicott, Spitzer, & Winokur, 1977) through the bipolar proband (Birmaher et al., 2009). In the DBOS, bipolar probands were directly evaluated using the International Diagnostic Checklists (IDCL) (Hiller, Zaudig, Mombour, & Bronisch, 1993) and diagnoses were confirmed by the treating psychiatrist or general practitioner. Biological co-parents were assessed by the FH-RDC (Andreasen et al., 1977) directly, by phone interviews or through the bipolar proband. For the DBSOS, both the bipolar proband and biological co-parent were directly psychiatrically evaluated using the SCID-I (Andreasen et al., 1977). For both the US- and Dutch sample parental age of onset of the first mood episode of BD was classified as before age 19, between 19-25 years old or 26 years and older.

Offspring psychopathology

In both the US and Dutch sample, all current (past 2 months) and past disorders in offspring were assessed using the Schedule for Affective Disorders and Schizophrenia for School Age Children Present and Lifetime Version (K-SADS-PL) (Kaufman et al., 1997). Children and their parents were interviewed separately. Diagnoses were established in accordance with DSM-IV criteria (American Psychiatric Association., 1994). Although both samples were evaluated using the K-SADS-PL, there were minor differences in the implementation of the K-SADS-PL mood section. With regard to bipolar disorder not otherwise specified (BP-NOS) and cyclothymia, the Dutch sample did not operationalize BP-NOS, but included cyclothymia. In contrast, the US sample did not assess cyclothymia, but the diagnosis for BP-NOS was ascertained using operationalized criteria applied in the Course and Outcome of Bipolar Youth (COBY) study (Birmaher et al., 2006). Although, BP-NOS and cyclothymia were not assessed in both studies with similar procedures, all these offspring had mood symptoms with a considerable burden and it was decided not to exclude these subjects from the analyses. For both samples, age at onset of first mood disorder was recorded and defined as the age when the subject first met the DSM-IV criteria for a mood disorder. Interviews were conducted by well-trained interviewers with a bachelor or graduate degree and clinical working experience. US interviewers were blind to parental diagnosis (Birmaher et al., 2009). In both samples, lifetime psychiatric disorders were diagnosed in consensus with psychiatrists certified in child and adolescent as well as adult psychiatry. The US study kappa's for all disorders were above 0.8. Kappa's were not calculated for the Dutch site, but all diagnoses were carefully discussed during consensus meetings reviewing

video recordings of the interviews. Studies were done in different languages, precluding assessment of inter-site reliability.

Dimensional psychopathology

Dimensional psychopathology was ascertained using the CBCL and completed by parents (Achenbach, 1991; Achenbach & Rescorla, 2001). Both the 1991 (Achenbach, 1991) (BIOS, DBOS) and 2001 (Achenbach et al., 2001) (DBSOS) version of the CBCL were administered, and only overlapping problem scores of both CBCL versions were used for calculations, according to the CBCL manual (Achenbach et al., 2001). Total problem scores, internalizing problem scores, externalizing problem scores (Achenbach, 1991; Achenbach et al., 2001) and the CBCL mania scale (Papachristou et al., 2013) scores were calculated. The CBCL measures behavioral and emotional problems within the last six months.

Socioeconomic Status (SES)

There are no reliable international standards to evaluate SES across countries and income between the US and the Dutch sample was measured differently. Thus, for this study, a proxy for SES the presence of an employed head of household was utilized.

Statistical analyses

Differences in demographic characteristics and categorical and dimensional psychopathology across the US- and Dutch sample were compared using t-, χ^2- and Fisher exact tests as appropriate. The age of onset of first mood disorder was compared between the two samples using Kaplan-Meier survival analysis and Log-rank tests. Demographic, clinical and methodological variables that differed significantly ($p < 0.05$) between the two samples were included in univariate single predictor regression models. Logistic regression models were used on the categorical level, linear models on the dimensional level. Accordingly, all variables in the univariate regression model with a coefficient significance of $p < 0.2$ were included in multiple (predictor) regression models. Age of onset of mood disorders across samples was further investigated using a cox-proportional hazard model. Goodness of fit for all models was determined by the Akaike Information Criterion (AIC). Smaller AIC values indicate best model fit. Missing values were treated as missing in the statistical analyses. Items or total scores with a missing value rate over 5% were excluded from the analyses. Analyses were conducted through the Statistical Package for Social Sciences, version 20.0.Results

RESULTS

Parental- and family characteristics

In total, 93 families from the Dutch sample and 159 families from the US sample were included (Figure 1). As shown in Table 1, compared to the Dutch sample, families from the US sample showed lower rates of employment. The bipolar proband in the US sample was more likely to be the mother, to have BD II, to have substance use disorders and to have a younger age of onset. With regard to the co-parent, prevalence of mood and substance use disorders was significantly higher in the US sample. In two US families and in one Dutch family, both parents were diagnosed with BD.

Bipolar offspring

In total 360 offspring subjects were selected for this study: 224 from the US and 136 from the Dutch sample. As illustrated in Figure 1 and Table 1, there were no between-group differences in gender or ethnic background. The Dutch offspring was significantly older and resided more often in families with both biological parents than the US offspring.

Categorical Disorders in the offspring

As shown in Table 2 prevalence of any lifetime psychiatric disorder was significantly higher in the US offspring than in the Dutch offspring (66% vs. 44%). Specifically higher rates of anxiety, ADHD and disruptive behavior disorders were observed in the US sample. Higher rates of psychopathology were also reflected in current psychopathology with 51% for US offspring and 29% in Dutch offspring. Interestingly, the US and Dutch sample did not differ in lifetime and current prevalence of any mood disorders. Also prevalence rates of BD I- and II were similar. Moreover, in the offspring affected with a mood disorder, we observed a significantly higher rate of comorbid disorders in the US sample; 80% (i.e. 54% anxiety-, 25% ADHD, 44% disruptive-, 3% pervasive developmental-, and 13% substance use disorders) versus 34% in the Dutch sample (i.e. 11% anxiety-, 9% ADHD, 9% disruptive-, and 9% pervasive developmental- disorders) (χ^2 (1) = 19.76, $p < 0.001$). As illustrated in the survival curve of Figure 2, age of onset of the first mood disorder was younger in the US offspring (mean age: 10.9 years, range 5-17) compared with the Dutch offspring (mean age: 12.8 years, range 6-18), χ^2 (1) = 3.97, $p < 0.05$).

Dimensional measurements (CBCL)

In contrast to the categorical K-SADS-PL findings, there were no significant between group differences in the parental ratings on the CBCL scales (Table 2). US offspring with a mood disorder as defined by the K-SADS-PL had significantly higher scores on the CBCL externalizing problem subscale compared to Dutch offspring with a mood disorder.

Table 1 | Demographic and Clinical characteristics US- and Dutch sample.

	US sample		Dutch sample		
	n	**%**	***n***	**%**	***p***
Offspring characteristics					
Bipolar offspring	224	100	136	100	
Sex, girls	113	50.4	66	48.5	0.72
Living with both biological parents	92	41.1	100	73.5	< 0.001
Caucasian	189	83.6	121	89.0	0.16
Mean age, *sd*	13.51	2.3	14.12	2.2	0.02
Family characteristics					
Families	159	100	93	100	
Employment	105	66.0	83	89.2	< 0.001
Bipolar parent					
Sex, female	124	78.0	55	59.1	0.001
Bipolar I disorder	107	67.3	75	80.6	0.02
Substance use disorder	104	65.4	14	15.1	< 0.001
Age of BP onset:					
- <19	80	50.3	24	25.8	< 0.001
- 19-25	41	25.8	31	33.3	
- >25	33	20.8	38	40.9	
Biological co-parent					
Mood disorder	37	23.3	16	17.2	0.06
Substance use disorder	43	27.0	3	3.2	< 0.001
Mania	2	1.3	1	1.1	1.00
Psychosis	0	0	1	1.1	0.423
Methodological characteristics					
Recruitment procedure					< 0.001
– advertisement	101	63.5	4	4.3	
– psychiatric clinic	58	36.5	35	37.6	
– patient advocacy groups	0	0	54	56.1	
Informant characteristics					
Categorical psychopathology, K-SADS-PL					
Single informant[a]	224	100%	78	57.4%	< 0.001
Mother[b]	197	88.7	128	94.1	0.08
Bipolar parent	168	75.7	102	75.0	0.89
Dimensional psychopathology, CBCL**					
Mother**	169	79.0	75	67.0	0.02
Bipolar parent	214	95.5	112	82.3	0.01

[a] One informant versus both parents. bMother versus father or significant other (*n* = 7). ** As the majority of CBCLs were completed by the bipolar proband; only CBCLs completed by the bipolar proband were selected for further analyses. In total, nine subjects in the US sample and one subject in the Dutch sample had a missing value rate over 5% and were excluded from the analyses.

Table 2 | Categorical psychopathology outcome as assigned by the clinician (K-SADS-PL) and dimensional ratings by the bipolar proband (CBCL).

Categorical Psychopathology	**US sample, *n* = 224**		**Dutch sample, *n* = 136**		
	n	**%**	***n***	**%**	***p***
Lifetime					
Any DSM-IV axis-I disorder	147	65.6	60	44.1	< 0.001
Any mood disorder	69	30.8	34	25.0	0.24
– bipolar I disorder	5	2.2	2	1.5	0.71
– bipolar II disorder	4	1.8	1	0.7	0.65
– BP-NOS	15	6.7	ND	ND	–
– cyclothymia	ND	ND	2	1.4	–
– major depressive disorder	30	13.4	6	4.4	0.006
– dysthymic disorder	5	2.2	7	5.1	0.14
– depression nos	18	8.0	17	12.5	0.17
Any psychotic disorder	1	0.4	0	0.0	1.0
Any anxiety disorder[a]	70	31.3	12	8.8	< 0.001
ADHD	50	22.3	11	8.1	< 0.001
Disruptive behavior disorders[b]	43	19.2	8	5.9	< 0.001
Autism spectrum disorders[c]	4	1.8	7	5.1	0.11
Substance use disorders	12	5.4	3	2.2	0.18
Other disorders[d]	51	22.8	17	12,5	0.02
Current					
Any DSM-IV axis-I disorder	115	51.3	40	29.4	< 0.001
Any mood disorder	44	19.6	18	13.2	0.12
Dimensional Psychopathology	**US sample, *n* = 214**		**Dutch sample, *n* = 112**		
	Mean	***SD***	**Mean**	***SD***	***p***
Total problems	32.66	25.1	27.49	20.7	0.06
Internalizing problems	10.44	8.8	8.82	8.2	0.11
Externalizing problems	9.58	8.5	8.11	6.4	0.08
Mania Scale	4.96	4.7	4.12	3.9	0.09
Offspring with mood disorders	***n* = 65**		***n* = 27**		
Total problems	49.11	29.0	42.63	23.2	0.31
Internalizing problems	15.57	11.1	14.44	9.0	0.64
Externalizing problems	15.00	9.7	10.81	7.6	0.05
Mania Scale	7.82	5.5	7.11	5.2	0.57

Lifetime and current categorical psychopathology. Current categorical psychopathology is defined as the past 2 months. [a] Any anxiety disorder includes: generalized anxiety disorder, separation anxiety disorder, social-, agora- and specific phobia's, posttraumatic stress disorder, panic disorder, obsessive-compulsive disorder, anxiety nos; [b] Disruptive behavior disorders includes: opposition defiant-, conduct-, tic- disorder and disruptive disorder nos; [c] Autism Spectrum disorders includes: Autism-,PDD-NOS or Asperger disorder; [d] Other disorders includes: lifetime: eating-, elimination-, adjustment- and somatization disorders. *Note:* ND = not determined; BP = bipolar disorder; NOS = not otherwise specified; ADHD = Attention Deficit Hyperactivity Disorder.

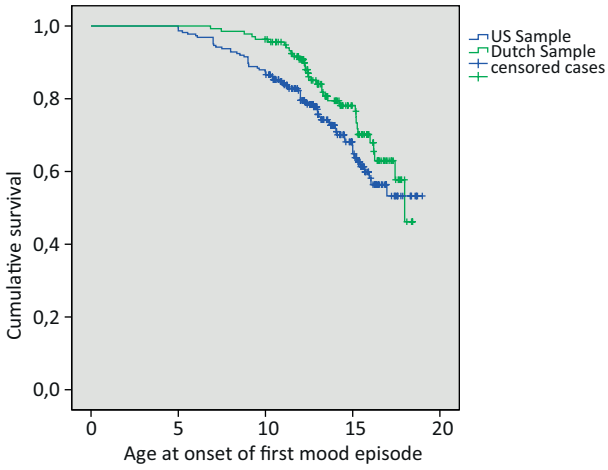

Figure 2 | Survival Curve Age of onset of the first mood episode in US and Dutch BD Offspring.

Regression analyses

Multiple regression analyses were carried out to evaluate whether the observed cross-national differences (referred to in the analyses as 'geographic origin') in categorical psychopathology outcome on any psychopathology, comorbid disorders in offspring with a mood disorder, and age of onset of mood disorders remained significant after controlling for methodological, parental, offspring, and environmental characteristics (Table 1). First separate univariate single predictor regression models were analyzed for each characteristic that differed significantly between the two samples (Table 1). All predictors with a coefficient significance of $p < 0.2$ (Table S1) were included in the multiple predictor regression models (Table 3). Because of high specificity of the features recruitment method and number of informants for sample of origin (see Table S1), these variables were excluded from the analyses. Yet, recruitment method and number of informants did not reveal significant differences for any psychopathology, comorbidity in mood disorders or age of onset within samples (data not shown). The final set of predictors was hierarchically organized starting with 'geographic origin', with parental, offspring and environmental characteristics consecutively added stepwise to the multiple regression models. Final models were selected using the AIC-goodness of fit index. The impact of 'geographic origin' decreased in all three models as subsequent determinants were added to the model. Geographic origin only lost significance in the age of onset model. These models suggest, that cross-national variation in categorical psychopathology was partially explained by differences across samples including: age of the offspring at study entry and maternal BD. Dimensional psychopathology did not differ between the US and Dutch sample; therefore, no multiple regression analyses were performed on the dimensional level.

Table 3 | Stepwise multiple regression analyses: categorical outcome

	Any psychopathology, n = 318				Mood disorders & comorbidity, n = 91				Age of onset mood disorder, n = 330[b]			
Predictors ↓ Model →	**1**	**2**	**3[a]**	**4**	**1[a]**	**2**	**3**	**4**	**1**	**2**	**3[a]**	**4**
Step 1: Geographic Origin (US)	**2.39*** **	**1.92***	**2.17** **	**2.06***	**7.84*** **	**4.21***	**4.22***	**3.74***	**1.53***	**1.48**	**1.43**	**1.23**
Step 2: Parental characteristics												
– Bipolar parent (mother)		1.46	1.72*	1.68		1.16	1.12	1.14		1.60	1.54	1.38
– Bipolar disorder (type I)		0.76	0.73	0.72		-	-	-		-	-	-
– Age of BP onset (< 18 years)												
– 19-25 years		0.64	0.61	0.62		1.37	1.41	1.43		-	-	-
– >=26 years		1.00	0.94	0.93		0.79	0.81	0.78		-	-	-
– SUD bipolar parent (yes)		-	-	-		1.90	1.90	1.76		-	-	-
– SUD co-parent (yes)		1.60	1.52	1.46		2.40	2.41	2.69		-	-	-
Step 3: Age Offspring (per year)			1.19**	1.19**			0.98	0.99			0.91	0.92
Step 4: Environmental char.												
Employment (not employed)				1.56				1.66				1.32
Not living with both biological parents				0.96				0.93				1.30
Model fit index: AIC	*425.4*	*424.9*	*416.2[a]*	*418.2*	*105.5[a]*	*111.8*	*113.8*	*117.2*	*1038.3*	*1036.2*	*1035.9[a]*	*1036.1*

Stepwise procedure multiple regression analyses. Values per predictor represent odds ratio's or hazard ratio (age of onset mood disorder). When no values presented, predictors were not included in the model (see also Table S1 online). With regard to the reference category: US origin means that the odds presented are increased in comparison to Dutch origin etc. [a] Model with best model fit according to Akaike's Information Criterion (AIC); [b] Because of the PH assumption of the cox-regression analyses, only offspring aged < 17.4 years were selected for further analyses. *p-value <= 0.05, ** p < .01, *** p < 0.001. *Note:* BP= bipolar disorder, SUD = Substance use disorder. AIC = Akaike Information Criterion.

DISCUSSION

This is the first study to compare two cross-national bipolar offspring samples, aged 10-18 years, using similar instruments to assess categorical and dimensional psychopathology. US and Dutch bipolar offspring showed a similar liability for mood disorders, including similar prevalence of BD-I and -II. However, based on the K-SADS-PL, US offspring showed higher rates of categorical psychopathology and more comorbid psychopathology in mood affected offspring. Cross-national variation was partially explained by differences in sample characteristics, including both parental and offspring characteristics. In contrast to the categorical differences between the US and Dutch sample, there were no differences in dimensional parent-reported offspring psychopathology.

The finding that bipolar offspring from the US or the Netherlands have a similar prevalence of BD-I and -II is in line with previous epidemiologic cross-national comparison studies (Weissman et al., 1996; Van Meter et al., 2011). Moreover, this study suggests that the liability for mood disorders in general was similar across samples. Nevertheless, mood disorders in US offspring appeared to be more severe as evidenced by higher rates of comorbid disorders. A more severe course and earlier onset of mood disorders has previously been observed retrospectively in US versus European adult BD patients (Post et al., 2014a). In our study, age of onset of mood disorders did not remain a significant predictor after controlling for other characteristics. However, the young age of the sample implies early-onset in all participants in our studies, which may have constrained variability. Among offspring with a mood disorder, the observed higher rates of comorbidities in bipolar offspring were best explained by. After controlling for demographic characteristics, the observed cross-national differences remained significantly different. Other unmeasured variables may have contributed to the noted differences between the two samples. For example, adult bipolar studies have shown that US patients experienced more stressors, both prior to and during the course of their illness, than European patients (Post et al., 2014b). Overall, we found, in line with previous offspring studies, higher rates of categorical psychopathology in US offspring (Duffy et al., 2011).

Interestingly, in contrast to the differences in categorical psychopathology, there were no significant differences in dimensional psychopathology as reported by the bipolar proband parent between the US and Dutch bipolar offspring. Although the reason for this difference is not clear, it is possible that trained interviewers using the K-SADS-PL were able to more accurately ascertain psychopathology. Previous studies have shown that CBCL scores and the K-SADS-PL based DSM-IV diagnoses significantly correlate, but that both approaches do not converge completely (Rishel, Greeno, Marcus, Shear, & Anderson, 2005; Kasius, Ferdinand, van den Berg, & Verhulst, 1997). Moreover, the K-SADS-PL evaluated both current and lifetime psychopathology, while the CBCL only ascertained psychopathology for the prior 6 months before parents completed this questionnaire. However, cross-national differences were mirrored in the K-SADS-PL current psychopathology. Also, cross-national differences in prevailing attitudes and beliefs regarding psychiatric diagnoses in youth may

be involved, this may impact how clinical information is expressed by individuals, parents and/or interpreted by the clinician (Draguns & Tanaka-Matsumi, 2003; Reichart & Nolen, 2004).

Findings of this study must be interpreted in the context of the following limitations. First, inter-site reliability was not obtained; this reliability measure could have served to potentially illuminate reasons for cross-national differences in scoring diagnostic interviews. Second, as noted in the methods section, BP-NOS and cyclothymia were not similarly assessed in both studies. These disorders were included in the analyses as part of mood disorders in general rather than a separate analysis for BD. Future studies could benefit from including more specifically defined BP-NOS criteria such as those used in the COBY study (Birmaher et al., 2006) and the new subcategories of bipolar spectrum disorders in the DSM-5 (American Psychiatric Association., 2014). Finally, some possibly important methodological (e.g. recruitment, informant) predictors could not be taken into account as the variation in these predictors were too sample specific. Also other possible important, environmental (e.g. life stressors, early traumas) and demographic variables (e.g. socio-economic status) were not taken into account as they were not available for both samples, or due to absence of reliable international standards. Other than true cross-national differences, these characteristics may also have contributed to the noted variation in psychopathology outcome between the two studies. Despite the limitations of the study, this study is the first attempt to disentangle cross-national variation in bipolar offspring studies using similar instruments, multiple informants and an adolescent age range. Future studies are warranted, and present findings provide important heuristics to guide the hypotheses and designs of future studies.

In conclusion, we found cross-national differences in the prevalence of categorical psychopathology in adolescent bipolar offspring, but not in the prevalence of bipolar or other mood disorders, nor in parent-reported dimensional psychopathology. Potential explanations for cross-national variation and the discrepancy in categorical versus dimensional ratings were discussed. Despite the preliminary character of this study, present findings suggest that cross-national differences may exist, but these differences appear to be in part accounted for by differences in parental- and demographic characteristics.

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SUPPLEMENTAL MATERIAL

ADDENDUM 1. THE DUTCH BIPOLAR AND SCHIZOPHRENIA OFFSPRING STUDY (DBSOS)

The Dutch Bipolar and Schizophrenia Offspring Study (DBSOS) is a longitudinal cohort study established in 2010 at the University Medical Center Utrecht, Utrecht, The Netherlands. The design of the DBSOS is based on the Dutch Bipolar Offspring Study (DBOS) (Wals et al. 2001), yet this study also includes offspring of patients with schizophrenia and control families. It is aimed to perform follow-up assessments every 3 years. The cohort has a dynamic nature with ongoing inclusion of new subjects. Clinical-, neurocognitive-, neuroimaging- and other biological measures are assessed at each follow-up. Bipolar families were recruited through the Dutch Association for Manic Depressives and Relatives and psychiatric hospitals with an assigned outpatient clinic for patients with bipolar disorder in different regions of the Netherlands. Both parents were assessed for DSM IV Axis I diagnoses in face-to-face interviews using the SCID-I and diagnoses were confirmed by the treating clinician if available. Inclusion criteria for the DBSOS are children with at least one parent with bipolar disorder I or II, children with at least one parent with schizophrenia or schizoaffective disorder and control children with healthy parents, within an age range of 10-16 years. Exclusion criteria were an IQ < 70 and no knowledge of the Dutch language. All available offspring of parents with bipolar disorder I or II from the DBSOS, recruited between 2010 and 2012, were included in the present study. The study is approved by the Medical Ethics Committee of the University Medical Center Utrecht.

Table S1 | **Table S1. Univariate regression analyses for each single predictor: categorical outcome.**

	Any Psychopathology		Mood disorders with comorbidity		Age of onset mood disorders	
Predictors	**b**	***p***	**b**	***p***	**b**	***p***
Geographic Origin (US origin)	0.98	**<.001***	2.11	**<.001***	0.43	**0.04***
Parental characteristics						
– Bipolar parent (mother)	0.59	**0.01***	0.77	**0.11***	0.50	**0.04***
– Bipolar disorder (type I)	-0.33	**0.17***	0.17	0.70	-0.09	0.68
– Age of BP onset(<18)						
– 19-25	-0.67	0.01*	-0.22	0.68	-0.19	0.45
– >=26	-0.29	0.29	-0.86	**0.08***	-0.15	0.53
– SUD bipolar parent (yes)	0.23	0.29	1.76	**<.001***	0.13	0.51
– Mood disorder co-parent (yes)	0.03	0.91	-0.61	0.23	-0.23	0.39
– SUD co-parent (yes)	1.01	**0.002***	1.57	**0.02***	0.30	0.23
Offspring characteristics						
– Age per year (older)	0.09	**0.05***	-0.12	**0.18***	-0.12	**<0.05***
Environmental characteristics						
– Employment (not employed)	0.59	**0.02***	0.99	**0.05***	0.50	**0.02***
– Not living with both biological parents	0.43	**0.05***	0.88	**0.04***	0.52	**0.01***
Methodological characteristics						
– Recruitment procedure (patient advocacy groups)						
– advertisement	0.91	**0.001***	2.51	**<.001***	0.47	**0.08***
– psychiatric clinic	0.77	**0.01***	1.71	**0.006***	0.32	0.26
– Single informant (both parents)	-0.28	0.33	-1.14	**0.04***	0.40	**0.16***

Univariate single predictor regression analyses. With regard to the reference category: US origin means that the odds presented are increased in comparison to the NL origin; bipolar mother as compared to a father with BP etc. All predictors with a significance level of p < .2 were selected for further stepwise multiple regression analyses. *p < .200. *Note:* BP = bipolar disorder, SUD = Substance use disorder.

Chapter 3

The Dutch Bipolar Offspring Study: 12-year follow-up

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ABSTRACT

Objective

Offspring of bipolar parents have a genetically increased risk of developing mood disorders. In a longitudinal study, the authors followed a bipolar offspring cohort from adolescence into adulthood to determine the onset, prevalence, and early course of mood disorders and other psychopathology.

Method

The Dutch Bipolar Offspring Study is a fixed cohort initiated in 1997 (N = 140; age range at baseline, 12-21 years). Bipolar offspring were psychiatrically evaluated at baseline and at 1-, 5-, and 12-year follow-ups. Of the original sample, 77% (N = 108) were followed for the full 12 years.

Results

Overall, 72% of the bipolar offspring developed a lifetime DSM-IV axis I disorder, 54% a mood disorder, and 13% bipolar spectrum disorders. Only 3% met DSM-IV criteria for bipolar I disorder. In 88% of the offspring with a bipolar spectrum disorder, the illness started with a depressive episode. In total, 24% of offspring with a unipolar mood disorder developed a bipolar spectrum disorder over time. Mood disorders were often recurrent (31%), were complex (comorbidity rate, 67%), and started before age 25.

Conclusions

Even after 12 years of follow-up, from adolescence into adulthood, bipolar I disorder was rare among bipolar offspring. Nevertheless, the risk of developing severe and recurrent mood disorders and other psychopathology was high. Future follow-up of this and other adult bipolar offspring cohorts is essential to determine whether recurrent mood disorders in bipolar offspring reflect the early stages of bipolar disorder.

INTRODUCTION

Given that bipolar disorder is strongly genetically determined, children of patients with bipolar disorder (bipolar offspring) constitute an at-risk population that can provide us with better insight into the development and early course of bipolar disorder. In 1997, Lapalme et al. showed in a meta-analysis (n = 2973) that bipolar offspring have 2.7 times the risk of developping a mental disorder and 4 times the risk of developping a mood disorder compared with children of healthy parents. More recently, two review articles on bipolar offspring reported elevated, but varying prevalence rates of bipolar disorder (ranging from 3 to 27%), mood disorders (ranging from 5 to 67%), and non-mood disorders (ranging from 5 to 52%) (DelBello & Geller, 2001; Duffy et al., 2011). However, these studies could not fully address the development and early course of bipolar disorder and other mood disorders because they used either a cross-sectional design or a longitudinal design without follow-up into adulthood (Lapalme, Hodgins, & LaRoche, 1997; Birmaher et al., 2009; Birmaher et al., 2010; Chang, Steiner, & Ketter, 2000; DelBello & Geller, 2001; Duffy et al., 2011; Hillegers et al., 2005; Maziade et al., 2008; Nurnberger, Jr. et al., 2011; Reichart et al., 2004; Singh et al., 2007; Wals et al., 2001). We report here on one of the largest prospective bipolar offspring studies with a follow-up into adulthood: the 12-year follow up of the Dutch Bipolar Offspring Study (Hillegers et al., 2005; Reichart et al., 2004; Wals et al., 2001).

To date, only four bipolar offspring cohort studies have prospectively followed bipolar offspring for more than a decade. The first study, a U.S. study conducted by Meyer et al. (2004), has had the longest follow-up to date, although it has a small sample. The study started in 1979 with 76 mothers with a mood disorder, including 25 mothers with bipolar I or II disorder with 48 bipolar offspring (ages 1.5-7 years at baseline), and 45 healthy community subjects. At the young adult follow-up assessment 23 years later, 19% of 32 bipolar offspring who were still in the study had developed bipolar disorder; of these, 6% were diagnosed with bipolar I disorder and 13% with bipolar II disorder. The second study is the bipolar offspring cohort from the Amish population followed by Egeland et al. for 16 years (Egeland et al., 2003; Egeland et al., 2012). This sample included 115 bipolar offspring (ranging from age 13 to beyond age 30) from 15 families with a parent with bipolar I disorder and focused on prodromal symptoms of bipolar I disorder. After 16 years of follow-up, 7% of offspring had developed bipolar I disorder. In addition, bipolar offspring more often showed potentially prodromal characteristics compared to offspring of healthy families (39.2% and 5.9% respectively). The third study is the study of Duffy et al. (1998) in Canada, started in 1995 with 36 children (ages 10 to 25 years) from 23 families (with bipolar I and II disorders). Over the past 15 years, Duffy et al. expanded their cohort to 220 children (ages 8 to 25 years) with a maximum follow-up of 15 years. At a mean age of almost 25 years, 71.4% of the bipolar offspring had received a DSM-IV axis I diagnosis: 55% had developed a mood disorder, including 16.3% a bipolar spectrum disorder (2.7% bipolar I, 5.9% bipolar II, 5.5% bipolar-NOS, 1.8% schizoaffective-bipolar type) (Duffy, Alda, Kutcher, Fusee, & Grof, 1998; Duffy, Alda, Hajek, & Grof, 2009; Duffy et al., 2011). Despite different methods, the main

finding of these studies is the same: low rates of bipolar I diagnoses compared with other mood disorders and psychopathology in general.

The fourth study, which we present here, is the Dutch Bipolar Offspring Study; a fixed sample of 140 bipolar offspring from 86 families (bipolar I and II) followed from adolescence into adulthood to a mean age of 28 years (Hillegers et al., 2005; Reichart et al., 2004; Wals et al., 2001). At the 5-year follow-up (mean age 21 years), we found lifetime prevalence rates of 40% for any mood disorder, 10% for bipolar disorder (3.9% bipolar I, 6.1% bipolar II) and 59% for psychopathology in general. Furthermore, in all participants with bipolar disorder, the illness started with a depressive episode. Based on survival analysis we predicted a further increase in bipolar disorder and unipolar depression in the coming years while the cohort would further mature to adulthood (Hillegers et al., 2005). In the present study, we sought to provide a thorough description of the onset and early developmental trajectories of mood disorders and other psychopathology in bipolar offspring.

METHODS

Population and procedure

The study design and recruitment procedure of the Dutch Bipolar Offspring Study have been described in detail by Wals et al. (2001). In short, 140 offspring (ages 12-21 years) from 86 families were recruited in the years 1997-1999 (T1). Participants were recruited via the Dutch Association for Manic Depressives and Relatives (62 families; 102 children) and through outpatient clinics in nine psychiatric hospitals (24 families; 38 children). All bipolar parents were outpatients at the time of recruitment. DSM-IV diagnoses of bipolar I and II disorder were confirmed by a face-to-face interview using the International Diagnostic Checklist (Hiller, Zaudig, Mombour, & Bronisch, 1993) and further confirmed by the clinical diagnosis of the treating psychiatrist (Wals et al., 2001). Lifetime diagnoses of the biological co-parent were assessed by using the Family History Research Diagnostic Criteria (FHRDC) method (Andreasen, Endicott, Spitzer, & Winokur, 1977). At the second measurement (at 1 year) 132 offspring were reassessed (Reichart et al., 2004) and at the third measurement (at 5 years) 129 offspring (Hillegers et al., 2005). At the latest assessment, 108 offspring from the original cohort agreed to participate once again, resulting in a retention rate of 77.1%. The demographic characteristics of the study population and dropouts are summarized in Table 1. The Medical Ethics Committee of the University Medical Center Utrecht approved the study. Written informed consent was obtained from both the offspring and their parents.

Instruments

Over the past 12 years the psychiatric interviews were administered by four of the authors (E.M., M.H., M.W. and C.R.) and six intensively trained interviewers with graduate degrees in psychology. Subsequently, all outcomes were evaluated with psychiatrists certified in child- and adolescent- as well as adult psychiatry (C.R. and M.H.) to reach consensus onfinal

Table 1 | Demographic characteristics of offspring in the Dutch Bipolar Offspring Study at 12 years

	Participants in 12-year follow-up		Drop-outs		
	N	**%**	**N**	**%**	***p***[a]
Bipolar offspring	108	77.1	32	22.9	
Males	58	53.7	14	43.8	
Females	50	46.3	18	56.3	0.322
	Mean	**SD**	**Mean**	**SD**	
Age at intake	16.5	2.00	16.45	2.8	0.399
	N	**%**	**N**	**%**	
Any lifetime disorder at T3	64	59.3	16	50	0.353
Family composition[b]					
Bipolar Parent	70		23		
Bipolar mothers	41	58.6	15	65.2	
Bipolar fathers	29	41.4	8	34.8	0.572
Bipolar I	52	74.3	18	78.3	
Bipolar II	18	25.7	5	21.7	0.701
Non bipolar proband[c]	72		24		
bipolar disorder	–	–	1	4.2	
unipolar mood disorder	11	15.3	4	16.7	
psychosis	1	1.4	–	–	
substance use disorders	2	2.8	2	8.3	
no diagnosis	58	80.5	17	70.8	0.318
Married	45	62.5	17	70.8	
Divorce	27	37.5	7	29.2	0.460
	Mean	**SD**	**Mean**	**SD**	
Parents' socioeconomic status at baseline[d]	4.97	2.08	4.87	2.44	0.846

[a] For continuous measures the Mann-Whitney test was used; for categorical measures the Pearson Chi-square test.
[b] A total of 16 complete families left the study; seven families have left the study partly.
[c] Three bipolar parents have children from a previous marriage participating; therefore, 89 nonbipolar parents are presented here.
[d] Socioeconomic status was measured on scale from 1 to 9, as described in Wals et al. (2001)

diagnoses. At baseline and at 1 year, DSM-IV diagnoses were obtained by a face-to-face interview with both the child and the parent by using the Schedule of Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL) (Kaufman et al., 1997). In cases of disagreement between child and parent about the presence of a symptom, greater weight was given to parent's reports of observed behavior and the children's reports of subjective experiences (Kaufman et al., 1997). We also screened for

pervasive developmental disorders (Wals et al., 2001). After offspring reached age 18, the K-SADS-PL was replaced by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) (First, Spitzer, Gibbon, & Williams, 1997). As discussed previously (Hillegers et al., 2005), the two interviews share many similarities; however, there are some important differences to note: the K-SADS-PL uses more informants, compared to only one informant in the SCID and the SCID does not include all DSM-IV diagnoses. Therefore, the questionnaires for Attention Deficit Hyperactivity Disorder (ADHD), Oppositional Defiant Disorder, Conduct Disorder and Tic Disorders originating from the K-SADS-PL were applied as well.

Lifetime DSM-IV diagnoses at 12 years are based on the four psychiatric interviews that took place over the past 12 years. Each psychiatric assessment evaluated current and past symptoms during the interim period. For all diagnoses the age of onset and duration of the episode were established. For depression not otherwise specified we included only 'minor depressive disorder' and 'recurrent brief depressive disorder'. Also, because of the perceived uncertainty of the bipolar disorder not otherwise specified diagnosis (due to lack of instruments) (Goodwin FK & Jamison KR, 2007), we decided not to specifically assess for this diagnosis in our studies.

Statistical Analysis

We first assessed the numbers and percentages of subjects with bipolar spectrum disorders, any other mood disorder, and other non-mood disorders, including age of onset. Next, we performed two standard Kaplan-Meier survival analyses. Kaplan-Meier survival analyses give an estimation of the probability of remaining well for a given point in time. In the first analysis, the age of onset of offspring with a lifetime mood disorder was recorded as event; offspring without a lifetime mood disorder at the end of the follow-up period were recorded as censored. For the second Kaplan-Meier survival analysis, the duration between the first mood episode and the first (hypo)manic episode was recorded as event; offspring without a bipolar spectrum disorder at the end of the follow-up period were recorded as censored.

RESULTS

A total of 108 offspring (58 of them male; mean age, 28 years, SD = 2.82) participated in the 12-year assessment. Table 2 presents the prevalence of lifetime psychopathology at baseline and at 12 years. Over the 12 years of follow-up, the prevalence of mood disorders doubled, with the result that now more than half of the cohort is positive for a lifetime mood disorder, including 13% bipolar spectrum disorders. None of the bipolar offspring developed a primary psychotic disorder without affective symptoms. Overall, more than 70% of the cohort met the criteria for at least one lifetime DSM-IV axis I disorder.

Table 3 summarizes the clinical characteristics of the 17 participants from 15 families who developed a bipolar spectrum disorder during the past 12 years. Twelve (80%) of the 15 bipolar parents had a bipolar I disorder, which is not statistically different from

Table 2 | Prevalence of current and lifetime DSM-IV diagnoses in bipolar offspring at baseline (n = 140) and 12-year follow-up (n = 108)

Psychopathology	T1		T4		T4	
	Lifetime Diagnosis at Baseline		*Lifetime Diagnosis at 12 years*		*Current[a] Diagnosis at 12-years*	
	N	%	N	%	N	%
Any mood disorder	38	27	58	54	22	20
Major depressive disorder	8	6	18	17	6	6
Dysthymic disorder	8	6	9	8	2	2
Depressive disorder NOS	15	11	22	20	0	0
Bipolar Spectrum disorders	6	0	14	13	14	13
Bipolar disorder (BD I, BD II)	4	3	12	11	12	11
Schizoaffective disorder	–	–	1	1	1	1
Cyclothymia	2	1	1	1	1	1
Adjustment disorder – Mood	1	1	4	4	0	0
Psychosis	–	–	–	–	–	–
Anxiety disorders	15	11	27	25	9	8
Disruptive behavioral disorders	8	6	8	7	2	2
Attention deficit disorder	7	5	5	5	3	3
Substance use disorder	9	6	25	23	8	7
Other disorders[b]	22	16	25	23	5	5
Any disorder	61	44	78	72	49	45

[a] Current diagnosis is defined as psychopathology in the past month. A current diagnosis of bipolar disorder does not imply a current episode.

[b] Includes enuresis, encopresis, pervasive developmental disorder, tic disorder, body dysmorphic disorder, and eating disorders.

the distribution in the overall group of parents (74%). In 88% of the subjects with bipolar spectrum disorder, the illness began with a depression; in two offspring, the illness started with cyclothymia. The mean age at onset of the first mood episode was 14.6 years (*SD* = 4.65; range 8.6-23.7), and onset of the first manic or hypomanic episode followed on average 5.3 years later (*SD* = 4.10; range 0-13.6; see also Figure 1a). We found no significant difference between the age of hypomania onset (median = 17.3*)* versus mania onset (median = 20.2*)*. Five participants (29%) had their first depressive episode before age 12 (i.e. prepubertal onset). None of the subjects had a prepubertal hypomanic or manic episode. Two participants were diagnosed with ADHD. Nine subjects (53%) had a comorbid anxiety disorder; in four of them, the anxiety disorder was present before, or close to, the onset of their first mood episode. All 17 offspring with a bipolar spectrum disorder received psychiatric treatment (pharmacologic 71%, counseling 100%) currently or in the past; six offspring had been hospitalized at least once. With regard to pharmacological

treatment, only one participant switched into hypomania after starting treatment with an antidepressant. One participant received a stimulant because of comorbid ADHD (before the onset of bipolar II disorder). For more detail on the characteristics of this group, see supplemental material, Table S1.

Apart from being at risk for bipolar spectrum disorders, bipolar offspring are at substantial risk for developing mood disorders in general. More than half of the cohort (54%) developed a lifetime mood disorder by a mean age of 28 years. The average age at onset of the first mood episode was 17.2 years (*SD* = 5.33, range 6.8-28.4). Of the 58 bipolar offspring with a lifetime mood disorder, 14 (24%) developed a bipolar spectrum disorder during follow-up, and 19 (33%) had a recurrent unipolar depression; taken together, 33 (31%) of the bipolar offspring had a recurrent mood disorder. Among participants with a lifetime mood disorder (n = 58), the lifetime prevalence of psychopathology is much more complex: 67% had a comorbid lifetime disorder, including 34% with an anxiety disorder, 19% with a substance use disorder, 7% with a disruptive behavior disorder, 3% with ADHD and 34% with other disorders (as defined in Table 2). When sorting for bipolar spectrum- and unipolar mood disorders, comorbid disorders were present in 64% versus 68% of the subjects respectively. In total, 71% of the subjects with a lifetime mood disorder have contacted mental healthcare services between T3 and T4; including 33% of the offspring receiving pharmacological treatment. In order to provide a better insight into the developmental course towards the onset of mood disorders we depicted the transition over the four measurements in Figure 2.

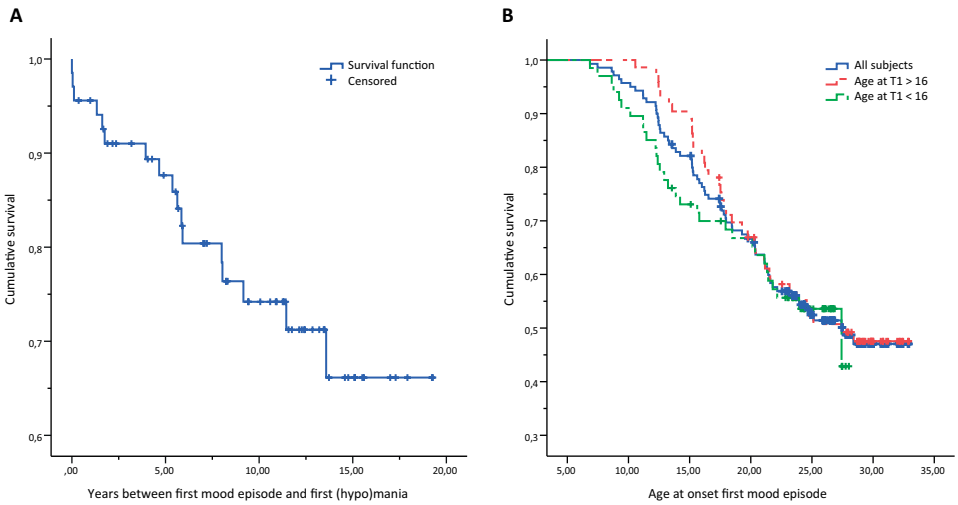

Figure 1 | Survival function of the development of first mood disorders in the Dutch Bipolar Offspring Study.

In panel A, the survival function is based on offspring developing their first manic or hypomanic episode (N = 17), and censored cases are those who left the study with a lifetime unipolar mood disorder but without developing bipolar disorder (either as a dropout [N = 7] or at the end of the study [N = 44]). In panel B, the survival function is based on offspring who developed their first mood episode (N = 68), and censored cases are those who left the study without a lifetime mood disorder (either as a dropout [N = 22] or at the end of the study [N = 50]).

Table 3 | Clinical characteristics of the 17 bipolar offspring who developed a bipolar spectrum disorder

Gender	Type of BD	Index mood episode	Age at index mood episode	Age at first (hypo) manic episode	Age of onset comorbid anxiety disorder	Age of onset comorbid substance abuse	Hospitalization[a]
Female	Bipolar II	Major depression	13	19	–	–	–
Female	Bipolar II	Depression not otherwise specified	8	16	16	–	–
Male	Bipolar II	Dysthymia	10	16	10	–	–
Female	Bipolar II	Major depression	20	21[b]	25	–	–
Female	Bipolar II	Depression not otherwise specified	19	24[b]	21	–	–
Female	Bipolar II	Depression not otherwise specified	16	25	–	–	–
Male	Bipolar I	Major depression	17	17	22	–	MM
Male	Cyclothymia	Cyclothymia	22	22	–	–	–
Male	Bipolar II	Depression not otherwise specified	23	31	25	19	–
Male	Bipolar I	Major depression	10	18	–	16	M
Male	Bipolar I	Major depression	15	15	–	–	M
Female	Bipolar II	Dysthymia	11	16	11	–	–
Female	Schizoaffective disorder, bipolar type	Depression not otherwise specified	12	13	–	–	MM
Male	Bipolar II	Cyclothymia	12	16	22	–	–
Male	Bipolar I	Depression not otherwise specified	15	16	–	–	M
Male	Bipolar II	Dysthymia	8	20[b,c]	–	–	D
Male	Bipolar II	Dysthymia	11	25[b]	2	18	–

[a] Episode at first hospitalization: D = depression; M = mania; MM = mixed mania.
[b] Use of antidepressants before onset of first hypomanic episode.
[c] Use of stimulants before onset of first manic/hypomanic episode.

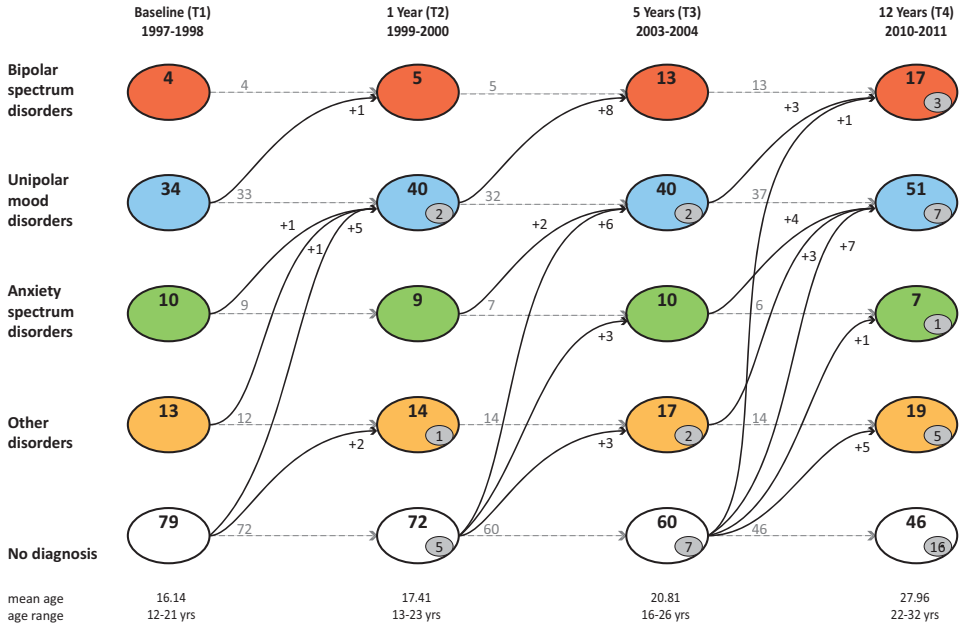

Figure 2 | Transition to mood disorders in the Dutch Bipolar Offspring Study, a 12-year follow-up (n = 140)

Numbers in gray circles indicate the number of offspring in this category who left the study; a participant who left the study with a lifetime diagnosis at baseline, at 1 year, or at 5 years would remain in this category at follow-up and would be added to the gray circle. The mean age at baseline was 16.1 years (range = 12-21); at the 1-year follow-up, 17.4 years (range = 13-23); at the 5-year follow-up, 20.8 years (range = 16-26); and at the 12-year follow-up, 28.0 years (range = 22-32).
Other disorders include any DSM-IV axis I disorder other than bipolar, unipolar mood, or anxiety disorders.

Because the prevalence of first-onset mood disorders increased significantly over the 12-year follow-up period, we performed a Kaplan-Meier survival analysis to check whether a further increase of first onset mood disorders in the future can be expected in the future (see Figure 1b). In contrast to the 5-year assessment, the slope of the Kaplan-Meier survival function appears now to level out after the age of 25. In total, only four out of 52 offspring over the age of 25 years old have developed a first onset mood disorder (data not shown).

DISCUSSION

Our aim in this study was to provide data on the onset and developmental trajectories of mood disorders and other psychopathology in bipolar offspring. In summary, at a mean age of 28 more than half of the cohort developed a mood disorder, including 13% with bipolar spectrum disorders (3% bipolar I, 8% bipolar II, 1% schizoaffective disorder – bipolar type and 1% cyclothymia) and 41% with a unipolar depressive disorder (major depressive disorder,

dysthymia, depression NOS or adjustment disorder – mood). None of the bipolar offspring developed a psychotic disorder without affective symptoms. In almost all participants with bipolar spectrum disorders, the illness started with a depressive episode. Among offspring with lifetime unipolar depression, 24% had a manic or hypomanic episode during follow-up on average 5.1 years after their first unipolar mood episode. None of the offspring had a prepubertal onset of mania of hypomania. The risk of developing a first mood episode was the highest up to age 25; only four participants developed a first mood episode after this age. Finally, we found that unipolar mood disorders in bipolar offspring were often recurrent (33%) and prone to be complex (68% with comorbid disorders), and that 71% offspring with a mood disorder received treatment from mental health services. Overall, 72% of the cohort developed a lifetime DSM-IV axis I disorder in 12-years of follow-up.

Our study has some limitations. First, it is not a population-based study: participants were recruited through the Dutch Association for Manic Depressives and Relatives and bipolar outpatient-clinics across the country, suggesting a selection of better informed and treatment seeking bipolar parents. Second, we had no control group of children of parents without bipolar disorder; however, we could compare our results with data from a comparable age group in the Netherlands Mental Health Survey and Incidence Study (NEMESIS-2), a recently published Dutch population study (de Graaf, Ten Have, & van Dorsselaer, 2010a; de Graaf, Ten Have, & van Dorsselaer, 2010b; de Graaf, Ten Have, van Gool, & van Dorsselaer, 2011). In that study, 1.123 subjects in the age range of 25-34 years were psychiatrically evaluated using the Composite International Diagnostic Interview 3.0 (CIDI 3.0) (Haro et al., 2006). Lifetime prevalence was 46.5% for any psychiatric disorder and 19.5% for any disorder, including 2.4% for bipolar disorder (without further specification). Although the diagnostic instruments were not identical, data from the NEMESIS-2 confirm that the lifetime prevalence of mood disorders, bipolar disorder and psychiatric disorders in general are considerably higher in our bipolar offspring cohort compared to the Dutch general population. A third limitation is that at baseline, offspring were already between 12 and 21 years old; therefore, data on prepubertal and early adolescent disorders or episodes may be affected by a recall bias. In additional analyses (see supplemental material, Table S2), we divided our cohort into an early adolescence group (ages 12-16) and a late adolescence group (ages 16-21) at baseline and examined whether data on prevalence rates of psychopathology (per category) at baseline and at 12 years and age of onset of the first mood episode were affected by recall bias. We found no evidence for different rates of psychopathology. However, as depicted in Figure 1b the age at baseline likely affected the age of onset in mood disorders as reported by the offspring and their parents. This supports the notion that diagnoses of internalizing disorders may be more affected by recall bias, since these diagnosis are mainly based on information from offspring (Tillman et al., 2004). Fourth, not specifically assessing for bipolar disorder not otherwise specified in this study may have affected our findings. However, of the four prospective studies that we mentioned earlier, only the Canadian offspring study (Duffy, Alda, Hajek, Sherry, & Grof, 2010) used the bipolar disorder not otherwise specified diagnosis, and the lifetime prevalence of bipolar

spectrum disorders was also comparable to the three other studies. Despite limitations, the strengths of this study are the long follow-up and high retention rate (77%) of 108 bipolar offspring from adolescence into adulthood.

With regard to both age distribution and psychopathology outcome, our results compare best to those of the prospective Canadian bipolar offspring study from Duffy et al. (2009; 2011). Cumulatively, their sample consists of 220 offspring with a mean age of 24.6 years (range = 8-30) and a mean follow-up of 9.2 years (*SD* = 4.16, range = 1-15); 21.4% have been followed for the full 15 years (Duffy & Doucette, 2012; Duffy, Alda, Crawford, Milin, & Grof, 2007; Duffy et al., 2010) Despite some methodological differences, prevalence rates in their study are remarkably similar: bipolar spectrum disorders, 16% versus 13%, respectively; mood disorders, 55% versus 54%, respectively and any axis-I disorder, 71% versus 72% for the Canadian and Dutch study respectively. Moreover, in both studies, bipolar spectrum disorders began in the majority of the bipolar offspring with a depressive episode (86% versus 88%, respectively) (Duffy et al., 2010). These similarities in prevalence rates appear to be at least partly the result of using the same assessment methods and including bipolar families with comparable socioeconomic status. In addition, the Dutch and Canadian health care systems provide easily accessible basic mental health care (Ministry of Health, 2011; 2011). Therefore, no sample selection occurred as a result of study participation in exchange for receiving mental health care.

Apart from these convergent findings, there are also some divergent findings worth mentioning between this and other bipolar offspring studies. Compared with the Duffy et al. study (2010), the onset of comorbid anxiety disorders in bipolar spectrum disorders was much later in our study (mean age, 10 years versus 17 years, respectively). As described earlier, age at baseline may significantly affect age at onset, Duffy et al. recruited younger offspring, and may therefore have detected (mild) anxiety disorders already at an earlier stage. In general, we observed much higher rates of comorbid anxiety in bipolar spectrum disorders (28% compared with 52%). Also, whereas some bipolar offspring studies have reported elevated rates of ADHD and disruptive disorders (Birmaher et al., 2009; Birmaher et al., 2010; Chang et al., 2000; Singh et al., 2007), we observed close to normal rates of ADHD and disruptive disorders in our study, as did Duffy et al. (2011). Again, age at intake may be involved. We may have missed some of these diagnoses because of the age-dependent decline of ADHD symptoms, especially since symptoms of hyperactivity and impulsivity are less overt during adolescence (Faraone, Biederman, & Mick, 2006). Another possible factor could be the parental characteristics of these cohorts: all studies reporting high rates of ADHD and disruptive disorders in bipolar offspring also show high rates of ADHD in the parental cohort (Birmaher et al., 2009; Birmaher et al., 2010; Chang et al., 2000; Singh et al., 2007). Furthermore, we found prevalence rates of substance use disorders close to prevalence rates in the Dutch general population (23 versus 25%, respectively) (de Graaf et al., 2010b). A possible explanation lies in the recruitment bias of our participating families. Most of these families (and their offspring) are members of the patient association, often aware and well informed about the risks of substance use. Also, the relatively high socio-

economic status of our cohort may explain the low prevalence of substance use disorders (van Oers, Bongers, van de Goor, & Garretsen, 1999).

In the end, one of the most remarkable findings of this and the three other longitudinal studies of bipolar offspring with a follow-up into adulthood is that although the prevalence of mood disorders and other psychopathology in this population is high, the prevalence of bipolar I disorder is low compared to other forms of bipolar disorder (Duffy et al., 2011; Egeland et al., 2012; Meyer et al., 2004). At the same time, the lifetime prevalence rate of recurrent mood disorders in our cohort is 31%. This finding points to the discussion of Kraepelin's broad concept of manic depressive illness, which included all recurrent mood disorders (Kraepelin, 1921). It is tempting to speculate that the genetic vulnerability comprises mainly the risk for mood instability and recurrences rather than the risk to develop full-blown mania. On the other hand, the long delay between the first unipolar mood episode and the onset of the first manic or hypomanic episode as found in this study may also suggest that the recurrent unipolar mood disorders in this study rather reflect the early stages of future bipolar disorder. These findings are in concordance with findings from a prospective study in adults by Angst et al. (2005), and this possibility is also proposed in several theoretical staging models (Berk, Hallam, & McGorry, 2007; Kupka & Hillegers, 2012). Apart from the meaning of recurrent depression in the concept of bipolar disorder, clinically it is important to realize that the depressive course in bipolar spectrum disorders is especially associated with a high burden of illness (Judd et al., 2003). Furthermore, it is worth mentioning that although there is emerging evidence for shared genetic susceptibility and etiology between bipolar disorder and schizophrenia (Craddock & Owen, 2010), none of the bipolar offspring – in both the Dutch and Canadian study – developed a primary psychotic disorder (Duffy et al., 2011).

In conclusion, after a 12 year follow-up of a large fixed bipolar offspring cohort, we found, like the three other existing prospective bipolar offspring studies (+10 year follow-up), low rates of bipolar I disorders in adult bipolar offspring. Nevertheless, in all bipolar offspring studies high rates of psychopathology and (recurrent) mood disorders have been observed (Lapalme et al., 1997; DelBello & Geller, 2001; Duffy et al., 2011; Nurnberger, Jr. et al., 2011; Duffy et al., 2009; Egeland et al., 2012; Meyer et al., 2004). Therefore, early intervention appears indicated to enhance normal development and prevent the onset of mood disorders in bipolar offspring. Future follow-up of this and the other adult bipolar offspring cohorts is essential to determine whether recurrent mood disorders in bipolar offspring reflect the early stages of bipolar disorder.

SUPPLEMENTAL MATERIAL

Table S1 | Clinical characteristics of subjects with bipolar spectrum disorder.

Bipolar parent			Offspring								
Gender[a]	Type of BD[b]	Age at first (hypo) manic episode	Gender[a]	Type of BD[b]	Index mood episode[c]	Age at index mood episode	Age at first (hypo) manic episode[d]	Age of onset comorbid anxiety disorder	Lifetime comorbid substance abuse (age of onset)	Hospitalization[e]	Medication current[f]	Medication past
F	BD I	30	F	BD II	MDD	13	19	–	–	–	–	–
F	BD I	30	F	BD II	Dep NOS	8	16	16	–	–	–	Benzo
F	BD II	17	M	BD II	Dysthymia	10	16	10	–	–	*	–
M	BD I	42	F	BD II	MDD	20	21[AD]	25	–	–	AP	AE; Benzo
F	BD I	32	F	BD II	Dep NOS	19	24[AD]	21	–	–	*	AD
F	BD I	18	F	BD II	Dep NOS	16	25	–	–	–	–	–
F	BD I	18	M	BD I	MDD	17	17	22	–	MM	Li; AD	AP; Benzo
M	BD II	40	M	CYCL	CYCL	22	22	–	–	–	AD	–
M	BD I	43	M	BD II	Dep NOS	23	31	25	19	–	–	–
F	BD I	17	M	BD I	MDD	10	18	–	16	M	–	Li
F	BD I	46	M	BD I	MDD	15	15	–	–	M	Li	–
F	BD I	43	F	BD II	Dysthymia	11	16	11	–	–	–	–
F	BD I	18	F	SCH-BD	Dep NOS	12	13	–	–	MM	AP; Benzo	–
M	BD I	32	M	BD II	CYCL	12	16	22	–	–	Li	–
M	BD I	32	M	BD I	Depr NOS	15	16	–	–	M	Li; AD	Val
M	BD II	37	M	BD II	Dysthymia	8	20[AD-S]	–	–	D	Stimulant	AD
F	BD I	28	M	BD II	Dysthymia	11	25[AD]	2	18	–	–	AD

[a] F = female; M = male; [b] BD I = bipolar I disorder; BD II = bipolar II disorder; CYCL = cyclothymia; SCH-BD = schizoaffective disorder-bipolar type ; [c] CYCL = cyclothymia; MDD = Major depressive disorder; Dep NOS = Depression Not Otherwise Specified; [d] AD = use of antidepressants before onset of first hypomanic episode; S = Use of stimulants before onset of first (hypo)manic epsisode; [e] Episode first hospitalization: D = depression, M = mania, MM = mixed mania; [f] Li = lithium, AD = antidepressant, AP = antipsychotic, Val = valproate, AE = anti-epileptic, Benzo = benzodiazepine, S = stimulant.

* Subjects dropped out from the study

Table S2 | The effect of age at intake at the prevalence of psychopathology

Psychopathology	**T1 < 16**	**T1 > 16**		**T4 < 16**	**T4 > 16**	
	n = 67	**n = 73**	***p****	**n = 54**	**n = 54**	***p****
Any mood disorder	22%	32%	0.257	50%	57%	0.563
Major depressive disorder	4%	7%	0.721	19%	15%	0.797
Dysthymic disorder	9%	4%	0.311	11%	6%	0.489
Depressive disorder NOS	7%	12%	0.406	13%	28%	0.093
Bipolar Spectrum disorders	1%	7%	0.211	11%	15%	0.776
Bipolar disorder (BD I, BD II)	1%	4%	0.621	7%	15%	0.359
Schizoaffective disorder	0%	0%	1.000	2%	0%	1.000
Cyclothymia	0%	3%	0.497	2%	0%	1.000
Adjustment disorder – Mood	1%	0%	0.479	4%	4%	1.000
Psychosis	0%	0%	1.000	0%	0%	1.000
Anxiety disorders	7%	14%	0.282	17%	33%	0.740
Disruptive behavioral disorders	1%	10%	0.065	7%	7%	1.000
Attention deficit disorder	4%	5%	0.710	7%	2%	0.363
Substance abuse disorder	0%	12%	0,003	22%	22%	1.000
Other disorders**	13%	18%	0.497	19%	28%	0.362
Any disorder	31%	55%	0.006	67%	78%	0.283

* Pearson χ^2 test was applied, or when expected frequencies were less than 5 we applied the the Fisher Exact test.
** Consists of enuresis, encopresis, pervasive developmental disorder, tic disorder, body dysmorphic disorder, and eating disorder

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Chapter 4

The role of life events and psychological factors in the onset of first and recurrent mood episodes in bipolar offspring: results from the Dutch Bipolar Offspring Study

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ABSTRACT

Background

Life events are an established risk factor for the onset and recurrence of unipolar and bipolar mood episodes, especially in the presence of genetic vulnerability. The dynamic interplay between life events and psychological context, however, is less studied. In this study, we investigated the impact of life events on the onset and recurrence of mood episodes in bipolar offspring, as well as the effects of temperament, coping, and parenting style on this association.

Methods

Bipolar offspring (n = 108) were followed longitudinally from adolescence to adulthood. Mood disorders were assessed with: the Kiddie Schedule of Affective Disorders and Schizophrenia – Present and Lifetime Version or the Structured Clinical Interview for DSM-IV Axis-I disorders; life events with the Life Events and Difficulties Schedule; and psychological measures using the Utrecht Coping List, Temperament and Character Inventory and short-EMBU (memories and upbringing instrument). Anderson Gill Models (an extension of the cox-proportional hazard model) were utilized.

Results

Life events were associated with an increased risk for first and, although less pronounced, subsequent mood episodes. There was a large confounding effect for the number of previous mood episodes; findings suggest a possible kindling effect. Passive coping style increased the risk of mood episode onset and recurrent episodes, but also altered the effect of life events on mood disorders. Harm avoidance temperament was associated with mood episode recurrence.

Conclusions

Life events are especially a risk factor in the onset of mood disorders, though less so in recurrent episodes. Psychological features (passive coping and harm avoidant temperament) contribute to the risk of an episode occurring, and also have a confounding effect on the association between life events and mood episodes. These findings create potential early intervention strategies for bipolar offspring.

INTRODUCTION

Bipolar disorder (BD) is characterised by episodes of depression and (hypo)mania, alternated with periods of euthymia. Typically, BD presents with a (mild) depressive episode, whereas the first (hypo)manic episode appears years later (Duffy, Alda, Hajek, & Grof, 2009; Mesman, Nolen, Reichart, Wals, & Hillegers, 2013). On average, this typical early course leads to a 10 year diagnostic delay (Drancourt et al., 2013; Altamura et al., 2010; Suppes et al., 2001). Presently, the most reliable predictor for BD remains a positive family history for BD (Gottesman, Laursen, Bertelsen, & Mortensen, 2010; Craddock & Jones, 1999). Several studies have consistently shown that children of patients with BD (bipolar offspring) have an increased risk for bipolar spectrum disorders, as well as (recurrent) unipolar mood disorders (Lapalme, Hodgins, & LaRoche, 1997; Duffy et al., 2011; Mesman et al., 2013).

Apart from a positive family history, stressful life events are associated with the onset of first as well as subsequent mood episodes in BD (Bender & Alloy, 2011; Brown & Harris, 1989a; Hlastala et al., 2000; Malkoff-Schwartz et al., 1998; Koenders et al., 2014; Johnson, 2005). However, the understanding of the precise role of stressful life events in the pathogenesis and the course of BD, remains quite poor. There is also evidence that life events are particularly influential with regard to the first number of mood episodes, yet become less so as subsequent episodes emerge; also known as the 'kindling hypothesis' (Bender & Alloy, 2011; Monroe & Harkness, 2005; Post, 1992). However, the results of studies like these are inconsistent. Evidence for the kindling hypothesis would emphasise the importance of studying the role of life events in populations at risk of developing BD prior to the onset of the first episode, such as bipolar offspring.

Presently, only a few studies have investigated the role of life events in bipolar offspring. Overall, these studies identified an increased number of life events and/or more severe life events in bipolar offspring (Duffy et al., 2007; Hillegers et al., 2004; Ostiguy et al., 2009; Wals et al., 2005; Petti et al., 2004). Two studies reported on life events in the Dutch Bipolar Offspring Study. Wals et al. (2005) found an increased number of life events preceding the year of mood episode onset, but this effect faded when controlling for prodromal mood symptoms in that same year. However, this study only took into account life events in the year preceding the onset of the first mood episode. While a single life event may only have a moderate effect on mood susceptibility, it is likely that especially the accumulation of events gradually increase mood susceptibility (Kessing, Agerbo, & Mortensen, 2004). It is, therefore, particularly interesting to follow the course of life events across the life cycle in relation to the onset of mood episodes. The second Dutch Bipolar Offspring Study found an association between life events and the onset of the first mood episode in 140 bipolar offspring age 5 up to 16, while the adverse effects of life events gradually subsided by 25% per year (Hillegers et al., 2004).

Studies in unipolar depression have found that the interplay between psychosocial factors and life events is also important. Life events are not equally stressful to everyone and their effect depends on several factors, such as temperament, coping, cognitive styles

and social support; the so called stress-buffering hypothesis (Cohen & Wills, 1985; Compas, Connor-Smith, Saltzman, Thomsen, & Wadsworth, 2001; Compas, Connor-Smith, & Jaser, 2004; Swendsen, Hammen, Heller, & Gitlin, 1995a). Two studies found a relation between maladaptive cognitive styles and increased reactivity to life events in bipolar patients (Alloy, Reilly-Harrington, Fresco, Whitehouse, & Zechmeister, 1999; Reilly-Harrington, Alloy, Fresco, & Whitehouse, 1999; Swendsen et al., 1995a). One study in bipolar offspring (Duffy et al., 2007) reported an increased number of recent life events in bipolar offspring with psychopathology, while emotionality was positively correlated with recent life events and psychopathology. Moreover, emotionality contributed to the risk of psychopathology, whereas life events only functioned as a mediator. However, a limitation of this study was that life events were not assessed longitudinally, and both life events and temperament measures were only assessed after the onset of the illness.

This study investigates the association of stressful life events on the onset of first and recurrent mood episodes, in the same Dutch Bipolar Offspring Study as reported above (Wals et al., 2005; Hillegers et al., 2004), now followed up 12 years to a mean age of 28 years. Furthermore, we investigated the effects of psychological factors such as temperament, coping and parental rearing styles on this association.

METHOD

Sample

All data are derived from the Dutch Bipolar Offspring Study, a longitudinal fixed cohort study established in 1997 (Wals et al., 2001; Reichart et al., 2004; Hillegers et al., 2005; Mesman et al., 2013). A detailed description of the study design and recruitment procedure has been described elsewhere (Wals et al., 2001). In short, 140 offspring (ages 12-21) from 86 families with one bipolar parent (74% bipolar I; 26% bipolar II) were recruited from 1997-1999 and followed for a period of 12 years. A family was only included if all offspring within the age range 12-21 agreed to participate. Exclusion criteria were a severe physical illness or handicap or an IQ below 70. Participants were recruited through the Dutch patient association (62 families; 102 children) and through outpatient clinics in nine psychiatric hospitals (24 families; 38 children). Bipolar offspring were assessed at baseline and at one-, five-, and 12-year follow-up (Wals et al., 2001; Reichart et al., 2004; Hillegers et al., 2005; Mesman et al., 2013). In total, 108 (77%) subjects were followed for the full 12-years. The study was approved by the Medical Ethical Review Committee of the University Medical Center Utrecht. Written informed consent was obtained from both offspring and parents after a complete description of the study.

Instruments

Mood disorders

Offspring were psychiatrically evaluated at each assessment; at baseline and during the one-year follow-up DSM-IV diagnoses were obtained through direct interviews with both child and parent(s), using the *Kiddie Schedule of Affective Disorders and Schizophrenia Present and Lifetime Version* (K-SADS-PL) (Kaufman et al., 1997). From the five-year follow-up onwards, the K-SADS-PL was replaced by the *Structured Clinical Interview for DSM-IV Axis I Disorders* (SCID-I) (First, Spitzer, Gibbon, & Williams, 1997). Lifetime DSM-IV diagnoses are based on all four interviews. For a detailed overview of the psychopathology after 12-year follow-up, see Mesman et al. (2013). In the current study, the presence of mood disorders was extrapolated by identifying a lifetime history of DSM-IV major depressive disorder, dysthymia, cyclothymia, bipolar I- or II disorder, depression NOS or adjustment disorder with depressed mood. For depression NOS only 'minor depressive disorder' and 'recurrent brief depressive disorder' were included. Moreover, because of the perceived uncertainty of the bipolar disorder not otherwise specified (BD-NOS) diagnosis (Goodwin & Jamison, 2007), BD-NOS was not specifically assessed. Recurrent mood disorder was defined as any consecutive mood episode/disorder after the first episode (e.g. depression NOS and subsequent major depressive disorder). For all diagnoses, both onset-age and episode(s) duration were documented.

Stressful life events

Life events were assessed with *the investigator-based Bedford College Life Events and Difficulties Schedule* (LEDS), a semi-structured interview assessing life events and long-term difficulties (Brown & Harris, 1978; Brown & Harris, 1989a), adjusted for adolescents (Monck & Dobbs, 1985). The present study focussed solely on life events. The LEDS collects detailed information about the event itself, the timing of its occurrence (date) and relevant contextual information for each event. Based on the contextual information, the threat for each event is rated via standardized rating procedures. The threat score represents the severity of the event, ranging from mild (1) to severe (4). The contextual threat is conceptualized as: "What most people would be expected to feel about an event in a particular set of circumstances and biography, taking no account of what the respondent says either about his or her reaction or about any psychiatric or physical symptoms that followed it" (Brown & Harris, 1989b). Severe events could be negative as well as positive, for example: moving to another country can be a very positive, but at the same a time stressful, life event. No distinction was made between positive and negative life events. Because of the retrospective nature of the data, only severe events (threat score 3 or 4) that had occurred after age 4 were included for analyses. For all severe life events we defined whether the event was related to the respondents' psychopathology and whether the event was dependent on the respondents own behaviour. Several studies support the reliability and validity of the LEDS in adults exhibiting a variety of psychiatric symptoms (Brown & Harris, 1978; Brown & Harris, 1989a; Ormel, Oldehinkel, & Brilman, 2001). The LEDS interviews were administered at each

assessment. The interviews covered life events from early childhood (after age 4) up to baseline assessment and for the interim periods at the follow-up assessments. Life events were rated on a yearly basis. All interviewers and raters were trained by MH, who herself was trained by Brown and Harris who developed the LEDS. The events were rated from written transcripts by two independent raters who had not been involved in the interview, and were unaware of the respondent's psychiatric status. A panel consisting of five raters, including SK, EM and MH, reached consensus on the events that raised rating problems.

Temperament

Temperament was examined using the Dutch adaption of the short version of the *Temperament and Character Inventory* (TCI) (105-items) (Cloninger, Przybeck, Svrakic, & Wetzel, 1994; Duijsens & Spinhoven, 2001; Duijsens, Spinhoven, Verschuur, & Eurelings-Bontekoe, 1999; Cloninger, 1994). The TCI is based on the neurobiological model of Cloninger (Cloninger, 1994), measuring four temperament dimensions (*novelty seeking*, *harm avoidance, reward dependence* and *persistence*) and three character dimensions (*self-directness, cooperativeness* and *self-transcendence*). Temperament reflects the developmentally stable personality components from infancy through adulthood, and character is thought of as the part of the personality that gradually matures throughout life (Cloninger, 1994). To maintain a certain stable personality measurement, only temperament scales were used for further study. Each dimension contains 15 items with a true/false-scoring. The Dutch adaption of the TCI shows modest to good reliability in terms of internal consistency with Cronbach ranging from 0.69 (reward dependence) up to 0 0.89 (harm avoidance) and good test-retest reliability (0.71 to 0.90) (Duijsens & Spinhoven, 2001).

Coping

Coping was assessed with *the Utrecht Coping List* (UCL), a self-report questionnaire of 47-items that measures 7 coping styles (Scheurs, van de Willege, Tellegen, & Brosschot, 1993). The items describe possible reactions to problem situations or unpleasant events, and are answered on a 4-point response scale ranging from rarely to never. The seven coping styles include *active tackling* (6 items), i.e. the individual actively approaches the problem situation and is goal-oriented; *palliative response* (8 items), i.e. distraction, engaging in other activities and trying to relax; *avoidance and passive expectancy* (8 items), i.e. avoidance of the problem situation and waiting to see what happens; *seeking social support* (6 items), i.e. sharing feelings of discomfort and seeking support and understanding from others; *passive reacting* (7 items), i.e. being completely overwhelmed by the situation, pessimistic and withdrawn; *expression of emotion* (3 items), i.e. venting emotions of discomfort such as anger and irritation; and *reassuring thoughts* (5 items), i.e. realizing worse things can happen and positive reframing of the situation. The UCL has moderate to good internal consistency with Cronbach α ranging from 0.64 to 0.82 and reasonable test-retest reliability 0.52 to 0.78 (Scheurs et al., 1993).

Parental rearing

The respondents' subjective experience of parental rearing (both father and mother) was assessed by use of the short-EMBU (Swedish acronym for Egna Minnen Beträffande Uppfostran [My memories of upbringing]; s-EMBU) at the 5-years follow-up (Arrindell, Emmelkamp, Brilman, & Monsma, 1983; Arrindell et al., 2001; Perris, Jacobsson, Lindstrom, von, & Perris, 1980). The s-EMBU is a 23-item with 4-point Likert type response scale and examines three parenting rearing styles: *emotional warmth* (6 items)*, protection* (9 items)*,* and *rejection* (7 items). *Emotional warmth* refers to affectionate, stimulating and praising behaviour in the parent; *protection* refers to fear and anxiety for the subject's safety, and intrusive and overinvolved behaviour of the parent; and *rejection* refers to punitive behaviour, shaming, favouring a sibling, rejection through criticism, rejection of the subject and abusive behaviour. All were found to have good internal reliability with Cronbach $\alpha>0.70$ (Arrindell et al., 2001). The correlation of parenting styles of mothers and fathers were moderate to high in this study (emotional warmth, $r = 0.58$, protection, $r = 0.68$ and rejection $r = 0.72$). For further analyses these scores were combined to a mean total score per parenting style.

Temperament, coping and subjective parental rearing styles were all assessed during the 5-year follow-up of the study.

Data Analysis

Time dependent life event load

In order to study the impact of life events at the onset of first and subsequent episodes, a time dependent life event load (LEL) for each year of follow-up was calculated, representing the sum of all severe life events (threat scores 3 & 4). The cumulative life event load (CLEL) at a particular point in time (year Y) was calculated as the sum of the life event load in year Y and all preceding years. For the impact of life events on the onset of a *first* mood episode, we calculated a CLEL for the year before its onset. For the impact of *recurrent* episodes the CLEL load started at zero after each episode. Subsequently, the CLEL in the year preceding recurrence was used for analysis. Overall, we calculated three different types of life event measures: cumulative load (CLEL); cumulative load excluding events related to psychopathology of the respondent (CLEL-NoPsy); and cumulative load including only independent events (CLEL-Ind). Taking into account a possible decay effect of life events over time, a time-specific life event load was subjected to an exponential decay function (Wainwright & Surtees, 2002). We tested four models: model I tested a purely cumulative effect of life events (= CLEL); model II the decay function implied a 25% loss of CLEL per year; model III the decay function implied a 50% loss of CLEL per year; and model IV the decay function implied a 75% loss of CLEL per year. The decay-function that yielded the best model fit (-2* log likelihood) was subsequently used for all further analysis.

Statistical analyses

The impact of life events and the onset and recurrence of mood disorders was studied using an extension of the standard cox-proportional hazard model for recurrent events, the Andersen-Gill model (A-G model). The A-G model accommodates censored data and time dependent covariates (Fleming & Harrington, 1991; Therneau & Grambsch, 2000). Data for the A-G model was structured in such a way that each individual risk interval was defined by variables describing the start and end times of each year of age. An event variable was coded "1" for episode and "0" for no episode. Time from age 5 to first mood episode was used or, when no episode occurred, the time until the last interview was used to test the influence of life events on mood episode onset. To test the impact of life events on recurrent episodes, the time until the last interview was included regardless of whether one or more episodes occurred. The A-G approach follows the usual assumption of the Cox model, whereby the hazard or risk ratio is proportional over time, and more specifically, that the risk of developing a mood episode is unaffected by earlier episodes. Time dependent covariates, such as the CLEL or the number of previous episodes, may be used to relax the latter assumption. The hazard ratio represents the proportionate change in the 'episode' rate due to a unit change in the respective covariate, in this case the CLEL. Subsequently, temperament, coping styles, subjective parental rearing style, plus the number of episodes were added as covariates in the A-G model. Our aim was to examine whether these variables affected the risk of mood episode onset and/or recurrence, and the impact of life events. A confounding effect was considered present if inclusion of these variables substantially (by at least 10%) changed the coefficient for life event load. If a significant confounding effect of any of these three psychological factors was present in the onset model, the interaction between the significant factor and life events was tested. This was realised by incorporating an interaction function into the A-G model. Finally, the presence of a kindling effect was tested by the interaction between the number of previous episodes and the CLEL between episodes. Analyses were performed under the statistical programming platform R (R Development Core Team, 2008).

RESULTS

The general characteristics of the study population are shown in Table 1. In total, 68 (54%) of the 140 offspring were diagnosed with a lifetime mood disorder, of which 38 had a history of one or more recurrent episodes, including 16 (24%) with bipolar spectrum disorder. Of the offspring with a recurrent mood disorder, the median number of recurrent episodes was 4 (range 2-36). Descriptives of CLEL, temperament-, coping- and subjective parenting styles are shown in Table 1. In order to take into account a temporal decay effect of life events impact, life event data was fitted to four different models with decay function 0%, 25%, 50% and 75% (model I-IV respectively) (Table 2). According to the log-likelihood, the decay function of 75% (model IV) was in most agreement with the observed data for the

Table 1 | Descriptive characteristics

	Bipolar offspring N = 140	
Mean age at first assessment, years (range)	16.1	(12-21)
	N	**%**
Gender, boys	72	51
Mood affected offspring	68	49
First mood episode:		
Major depressive episode	21	
Dysthymia	10	
Cyclothymia	3	
Depression NOS	31	
Adjustment disorder, depressive type	3	
Mean age of onset of first mood episode (range)	16.8	(7-28)
Offspring with recurrent episodes	36	26
Median # of episodes (range)	4	(2-36)
Offspring with a current mood episode at one of the 4 interviews	38	27
Non mood disorders[a]	26	19
No disorder[b]	46	33
	Mean	**(SD)**
Life event load		
CLEL	36.2	(20.4)
CLEL-Ind	25.6	(14.5)
CLEL-NoPsy	23.1	(14.9)
Temperament		
Novelty seeking	8.3	(2.6)
Harm avoidance	5.8	(3.2)
Reward dependence	9.2	(2.6)
Persistence	7.7	(3.0)
Coping style		
Active tackling	17.8	(3.2)
Palliative response	17.2	(3.8)
Avoidance and passive expectancy	15.8	(2.9)
Seeking social support	14.3	(3.2)
Passive reacting	10.6	(2.5)
Expression of emotion	6.2	(1.4)
Reassuring thoughts	11.7	(2.9)

Table 1 | *(Continued)*

	Bipolar offspring *n* = 140	
Emotional warmth	17.6	(2.9)
Protection	16.9	(3.2)
Rejection	8.6	(1.8)

CLEL = cumulative life event load including all events under model III (50% decay model); CLEL-Ind = cumulative life event load including only independent events; CLEL-NoPsy = cumulative life event load excluding events related to psychopathology.
[a] Including all subjects without a lifetime mood disorder or dropping out from the study without developing a mood disorder, but with other non-mood pathology. Including anxiety, attention-deficit hyperactivity disorder, disruptive behaviour, substance abuse, enuresis, encopresis, pervasive developmental disorder, tic, obsessive-compulsive disorder and eating disorders.
[b] Offspring without a lifetime DSM-IV axis I disorder before the end of/leaving the study.

Table 2 | Relative risk of an episode using four models of decay onset and lifetime

	Life event load onset			Life event load lifetime		
Model	**Coefficient**	**Exp coef**	**-2 Log-likelihood**	**Coefficient**	**Exp coef**	**-2 Log likelihood**
I (cumulative)	0.005	1.01	-287.1	0.020	1.02	-836.9
II (25% decay)	0.049	1.05	-286.0	0.087	1.09	-825.0
III (50% decay)	0.127	1.14	-284.9	0.181	1.20	-824.7[a]
IV (75% decay)	0.348	1.42	-283.9[a]	0.415	1.51	-826.0

Exp coef = Exponentiated linear coefficients and 95% confidence interval
[a] Lowest absolute log-likelihood of fitted model

first mood episode, and for recurrent mood episodes the decay function of 50% (model III). Since the difference between the log-likelihoods of the fitted models was minimal, all further analyses were performed under model III. Figure 1A/B displays the difference in course of CLEL and the CLEL according to model III for mood affected offspring versus unaffected offspring per year.

First mood episode onset

As shown in Table 3, the CLEL up to the first mood episode was associated with a positive coefficient of 0.127 (HR = 1.14) indicating the increased relative risk for mood episode onset per increase per unit of CLEL. Next, we looked at the different types of life events, namely: CLEL including only independent events (CLEL-Ind), excluding events related to psychopathology of the respondent (CLEL-NoPsy). The coefficient of CLEL-Ind was 0.177 (HR = 1.19) and was also positively associated with mood episode onset per increase in unit CLEL. A coefficient of 0.104 (HR = 1.11) was found for CL-NoPsy, and did not reach significance, suggesting that life events triggering mood disorder onset also includes events already associated with previous non-mood disorders.

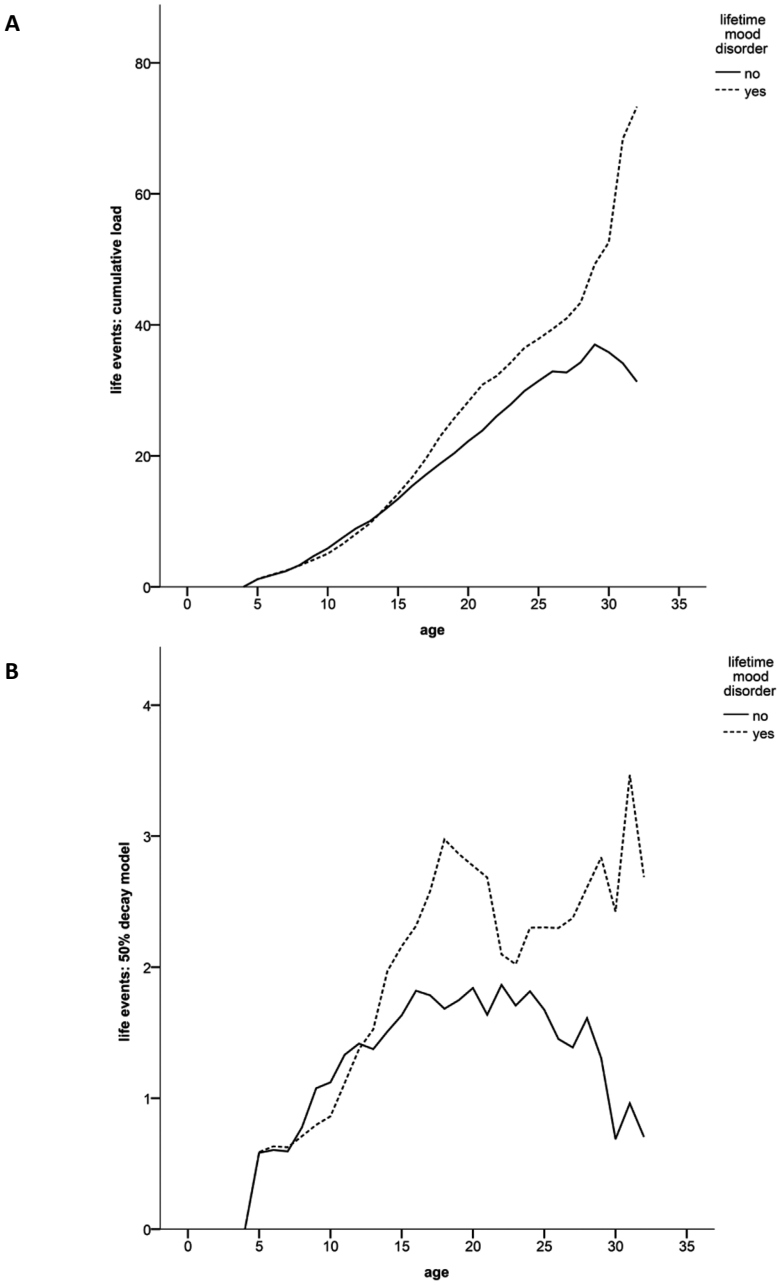

Figure 1 | (**A**) Course of cumulative life event load by age (years) for mood affected and unaffected offspring. (**B**) Course of cumulative life event load by age (years) according to decay model III for mood affected and unaffected offspring (bottom)

Table 3 | Influence of different types of life event load under model III (50% decay) on mood episodes

Type of Cumulative Load[a]	Coefficient	Exp coef[a]	SE (coef)	Robust SE[b]	z	*p*
Mood episode onset						
CLEL	0.127	1.14	0.052	0.056	2.26	< 0.05
CLEL-Ind	0.177	1.19	0.082	0.081	2.19	< 0.05
CLEL-NoPsy	0.104	1.11	0.098	0.090	1.15	0.25
Recurrent mood episodes						
CLEL	0.112	1.12	0.022	0.031	3.67	< 0.001
CLEL-Ind	0.106	1.11	0.026	0.0298	3.54	< 0.001
CLEL-NoPsy	0.123	1.13	0.0323	0.039	3.16	< 0.05
Recurrent mood episodes and previous episodes						
CLEL	0.078	1.08	0.024	0.036	2.18	< 0.05
Previous episodes[c]	0.181	1.20	0.014	0.029	6.31	< 0.001
Recurrent mood episodes; interaction with previous episodes						
CLEL	0.105	1.11	0.027	0.031	3.38	< 0.001
Previous episodes[c]	0.204	1.22	0.018	0.035	5.81	< 0.001
CLEL x Previous episodes[d]	-0.007	.993	0.004	0.003	-1.91	0.056

SE = Standard error; CLEL = cumulative life event load including all events under model III (50% decay model); CLEL-Ind = cumulative life event load including only independent events; CLEL-NoPsy = cumulative life event load excluding events related to psychopathology.

[a] Exponentiated coefficients, representing the hazard ratio

[b] Robust SE (standard error), corrected for the dependency of multiple times to event within the same subject

[c] Expresses the relative risk per each episode

[d] Interaction term

Looking at psychological features and social support, only harm avoidant temperament, passive reacting coping style, and a rejecting parenting style were significantly associated with first mood episode onset (Table 4). Yet, only passive reacting coping style altered the coefficient of CLEL by more than 10% from 0.127 (HR = 1.14) to 0.196 (HR = 1.22), suggesting that having more passive reacting coping style features, enhances the risk of mood episode onset, whereas the impact of CLEL decreases, suggesting a confounding effect. All other coefficients for psychosocial factors did not reach significance (for an overview of all temperament, coping and parental rearing styles see Table S1, available online). Passive reacting coping style was the only factor that had a confounding effect, therefore we tested the interaction with life events. The interaction coefficient did not reach significance (p=0.37). This indicates that passive reactive coping style does not influence the impact of life events on mood episode onset.

Table 4 | Influence of life event load, psychological and social factors on mood episode onset

		Coefficient	Exp coef[a]	*p*
Mood episode onset				
Baseline model	CLEL	0.127	1.14	< 0.05
Temperament	CLEL	0.127	1.14	< 0.05
	Harm avoidance	0.099	1.10	< 0.05
Coping	CLEL	0.196*	1.22	< 0.05
	Passive reacting	0.209	1.23	< 0.001
Parental rearing	CLEL	0.124	1.13	< 0.05
	Rejection	0.252	1.29	< 0.001
Recurrent mood episodes				
Baseline model	CLEL	0.078	1.08	< 0.05
	Previous episodes[b]	0.181	1.20	< 0.001
Temperament	CLEL	0.059**	1.06	0.08
	Previous episodes[b]	0.167	1.18	< 0.001
	Harm avoidance	0.084	1.09	< 0.05
Coping	CLEL	0.057**	1.06	0.12
	Previous episodes[b]	0.169	1.18	< 0.001
	Passive reacting	0.162	1.18	< 0.001
Parental rearing	CLEL	0.069**	1.07	< 0.05
	Previous episodes[b]	0.171	1.19	< 0.001
	Rejection	0.151	1.16	< 0.001
	CLEL	0.066**	1.07	0.056
	Previous episodes[b]	0.182	1.20	< .001
	Protection	0.073	1.08	< 0.05

CLEL = Cumulative life event load including all severe events under model III (50% decay model); previous episodes, number of previous episodes.

[a] Exponentiated coefficients, representing the hazard ratio

[b] Expresses the relative risk per each episode.

*main effect is significant & coefficient for life events changes > 10%; < 0.114 or > 0.140

**main effect is significant &coefficient for life events changes > 10%; < 0.0702 or > 0.0858

Recurrent Mood episodes

For recurrent mood episodes a coefficient of 0.112 (HR = 1.12, $p < 0.001$) for CLEL on the risk of mood episodes was found. Also, CLEL-Ind and CLEL-NoPsy showed significant and positive coefficients (CLEL-Ind 0.106, HR = 1.11, $p < 0.001$ and CLEL-NoPsy 0.123, HR = 1.13, $p = < 0.05$), indicating that all types of life event load are associated with an increased risk of recurrent episodes. In Table 3 provides the results of the final A-G model of LEL, as modelled for recurrent episodes. Adding the number of previous episodes in the model decreased the coefficient for life events by more than 10% with a positive and significant coefficient for previous episodes, indicating that the number of previous episodes is a significant contributor to the risk of recurrent episodes. In addition, a greater number of previous episodes is associated with a lower CLEL preceding episode onset; since the amount of time

between the episodes decreases, so does the CLEL preceding the episode. The interaction term for CLEL and number of prior episodes effect did not reach significance, indicating that the effect of CLEL on the risk of recurrence does not change with subsequent episodes, as suggested by the kindling hypothesis. However, significance reached trend level and the influence of life events on first episode was higher compared with the influence of life events after the first episode; suggesting a shift in the effect of life events between first and subsequent episodes and thus a possible kindling effect.

Apart from the CLEL and number of previous episodes, harm avoidant temperament, passive reacting coping style and a rejecting and protective parenting style were significantly associated with the risk for recurrent episodes and altered the impact of CLEL (Table 4). Including these factors into the model, in addition to the number of previous episodes, lowers the impact of life events on mood episode recurrence. The change of the coefficient of life events was largest for harm avoidant temperament and passive reactive coping style. Furthermore, for these two factors the coefficient for life events not only decreased, but also became non-significant. The coefficients of these two factors were positive, indicating that the presence of a more pronounced harm avoidant temperament and/or passive reactive coping style increases the risk of recurrent episodes. Adding these four psychosocial factors decreased the coefficient of life events, though not reduced to zero, indicating that, although not significant, life events are still present as a risk factor for recurrent episodes. For an overview of the effects of the other psychological and social factors, see Table S2 online.

DISCUSSION

To our knowledge, this is the first long-term follow-up study investigating the impact of life events and psychological variables on the onset and course of psychopathology in bipolar offspring. In this study, bipolar offspring were followed for 12 years, from early adolescence (N = 140) to adulthood (N = 108). In total, 68 offspring developed a mood disorder, of which 36 a recurrent mood disorder. The results illustrate that the effect of life events is especially a risk factor in the early stage of mood disorders, and that this effect is enhanced by passive reactive coping styles in bipolar offspring. After the first episode, the number of previous episodes became an important predictor for new episodes, with a shift in the effect of life events between first and subsequent episodes; supporting the kindling hypothesis. Moreover, psychological factors, such as harm avoidant temperament and passive reactive coping style, increase the risk of subsequent episodes.

That life events are associated with mood episode onset in bipolar offspring confirms findings in other offspring studies (Duffy et al. 2007; Ostiguy et al. 2009; Petti et al. 2004). The impact of life events was the strongest with regard to the first episode, becoming less so with recurrent episodes. Although we found no interaction between previous episodes and CLEL, the impact of life events becoming less evident corresponds with a possible kindling

effect. Thus far, the kindling effect has consistently been reported in unipolar depression, but irregularly in BD (Dienes, Hammen, Henry, Cohen, & Daley, 2006; Swendsen, Hammen, Heller, & Gitlin, 1995b; Hammen & Gitlin, 1997).

Previous research has suggested that especially dependent life events (e.g. life events related to the individual's own behaviour) are important in light of mood episode onset (Hammen, 1991). In line with others (Reilly-Harrington et al., 1999; Grandin, Alloy, & Abramson, 2007; Ostiguy et al., 2009), we found that differentiating between dependent and independent life events did not change our findings; suggesting that no specific type of life event contributes to increased mood liability, but rather the full range of severe life events.

Regarding the psychological factors we found that a more passive reactive coping style, defined as being overwhelmed by situations, pessimism, and withdrawal, was associated with mood episode onset. This finding is in line with previous research, where especially the disengaging coping styles are related to an increased risk of internalizing symptoms (Compas et al., 2001). Adding passive reacting coping style enhanced the association between life events and mood episode onset. Although this confounding effect is suggestive evidence for the stress-buffering theory (Cohen & Wills, 1985; Compas et al., 2001; Compas et al., 2004; Swendsen et al., 1995a) , the interaction between life events and passive reacting coping style yielded no significant results and therefore no conclusive evidence for this theory. For recurrent episodes, especially harm avoidant temperament and passive reactive coping style were important predictors: while the association between life events and recurrent episodes was less pronounced, it did not become redundant. Parental rearing styles were not found to have an additional effect on the association between life events and mood episode onset. In summary, our study suggests that life events play an important role in the early stages of mood episode onset, yet psychological factors such as a negative temperament and/or passive reactive coping style may be of more significance for recurrent mood disorder susceptibility.

Strengths in our study are that life events were recorded over the life course within relatively short retrospective time frames, limiting the effect of recall bias. Furthermore, a natural decay effect of life events was taken into account, aiming to model the natural processes of life events. Moreover, life events were recorded using the LEDS of Brown and Harris; the suggested golden standard in life event research (Dohrenwend, 2006). Nevertheless, the findings of this study should be interpreted in the light of several limitations. The first limitation of the study is that temperament, coping, and parental rearing styles were administered at the third assessment (mean age 21). Although the present study shows that harm avoidant temperament and passive reacting coping style are associated with the susceptibility for mood episodes in a high risk population, the direction of the impact of these factors remains partly intangible. Temperament has been suggested to be relatively stable over time and across situations, but there are also suggestions that temperament can be changed by previous mood episodes (e.g. Compas et al., 2004). Secondly, due to the small sample size of subjects with BD, it was not possible

to run separate analyses for depressive or hypomanic episodes. Thirdly, the present study concerns a high risk population, limiting generalisation for other populations. However, studies have shown that the impact of life events is especially significant within the context of familial risk for mood disorders (e.g. Kessler, 1997; Zimmermann et al., 2008).

More studies are needed to further disentangle the interplay of life events, psychological factors, impact of social support and mood susceptibility. These studies could benefit by incorporating not only early assessment of psychological factors, in order to determine directions of associations, but also considering more diverse populations, and including healthy controls and larger sample sizes. In the meantime, our findings suggest that early intervention on stress-reduction in terms enhancement of coping skills through training, cognitive behavioural therapy or EMDR in case of more severe trauma, might potentially prove beneficial in preventing onset and recurrences op mood episodes in high risk populations. In conclusion, our study shows that both life events and psychological factors play an important role in bipolar offspring regarding their susceptibility to develop first as well as recurrent mood episodes. These findings provide potential for early intervention.

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SUPPLEMENTAL MATERIAL

Table S1 | Confounding effects of psychological and social factors on life events and mood episode onset

		Coefficient	Exp coef[a]	*p*
Baseline	CL	0.127	1.14	< 0.05
Temperament				
	CL	0.124	1.13	< 0.05
	Novelty seeking	0.071	1.07	0.24
	CL	0.127	1.14	< 0.05
	Harm avoidance	0.099	1.10	< 0.05
	CL	0.133	1.14	< 0.05
	Reward dependence	0.071	1.07	0.20
	CL	0.126	1.13	< 0.05
	Persistence	0.033	1.03	0.46
Coping				
	CL	0.215	1.24	< 0.05
	Active tackling	-0.065	0.93	0.09
	CL	0.215	1.24	< 0.05
	Palliative response	0.051	1.05	0.15
	CL	0.221	1.24	< 0.05
	Avoidance and passive expectancy	-0.013	0.986	0.76
	CL	0.209	1.23	< 0.05
	Seeking social support	0.041	1.04	0.28
	CL	0.196*	1.22	< 0.05
	Passive reacting	0.209	1.23	< 0.001
	CL	0.215	1.24	< 0.05
	Expression of emotion	0.13	1.14	0.16
	CL	0.222	1.25	< 0.05
	Reassuring thoughts	-0.037	0.964	0.40
Parental rearing				
	CL	0.124	1.13	< 0.05
	Rejection	0.252	1.29	< 0.001
	CL	0.126	1.13	< 0.05
	Emotional warmth	-0.121	0.886	< 0.05
	CL	0.121	1.13	< 0.05
	Protection	0.021	1.02	0.60

CL = cumulative life event load including all severe events under model III (50% decay model).

[a] Exponentiated coefficients, represent the hazard ratio

* main effect is significant & coefficient for life events changes > 10%; < 0.114 or > 0.140

Table S2 | Confounding effects of psychological and social factors on life events and mood episodes recurrence

		Coefficient	Exp coef[a]	*p*
Baseline model	CL	0.078	1.08	< 0.05
	Previous episodes	0.181	1.20	< 0.001
Temperament				
	CL	0.077	1.08	< 0.05
	Previous episodes	0.195	1.22	< 0.001
	Novelty seeking	0.060	1.06	0.30
	CL	0.059*	1.06	0.08
	Previous episodes	0.167	1.18	< 0.001
	Harm avoidance	0.084	1.09	< 0.05
	CL	0.078	1.08	< 0.05
	Previous episodes	0.178	1.20	< 0.001
	Reward dependence	0.028	1.03	0.60
	CL	0.081	1.08	< 0.05
	Previous episodes	0.183	1.20	< 0.001
	Persistence	0.059	1.06	0.11
Coping				
	CL	0.085	1.08	< 0.05
	Previous episodes	0.181	1.19	< 0.001
	Active tackling	- 0.027	0.97	0.43
	CL	0.082	1.09	< 0.05
	Previous episodes	0.176	1.19	< 0.001
	Palliative response	0.022	1.02	0.47
	CL	0.085	1.09	< 0.05
	Previous episodes	0.177	1.19	< 0.001
	Avoidance and passive expectancy	-0.006	0.99	.86
	CL	0.081	1.08	< 0.05
	Previous episodes	0.177	1.19	< 0.001
	Seeking social support	0.044	1.05	0.31
	CL	0.057*	1.06	0.12
	Previous episodes	0.169	1.18	< 0.001
	Passive reacting	0.162	1.18	< 0.001
	CL	0.079	1.08	< 0.05
	Previous episodes	0.179	1.20	< 0.001
	Expression of emotion	0.153	1.17	0.11
	CL	0.086	1.09	< 0.05
	Previous episodes	0.178	1.20	< 0.001
	Reassuring thoughts	-0.02	0.98	0.63

Table S2 | *(Continued)*

		Coefficient	Exp coef[a]	*p*
Parental rearing				
	CL	0.069*	1.07	< 0.05
	Previous episodes	0.171	1.19	< 0.001
	Rejection	0.151	1.16	< 0.001
	CL	0.071	1.07	0.056
	Previous episodes	0.185	1.20	< .001
	Emotional warmth	-0.062	0.93	0.16
	CL	0.066*	1.07	0.056
	Previous episodes	0.182	1.20	< 0.001
	Protection	0.073	1.08	< 0.05

CL = cumulative load including all severe events under the 50% decay model between episodes; previous episodes, number of previous episoded

[a] Exponentiated coefficients, represent the hazard ratio

* Main effect is significant & coefficient for life events changes > 10%; < 0.0702 or > 0.0858

Chapter 5

Monocyte activation, brain-derived neurotrophic factor (BDNF), and S100B in bipolar offspring: a follow-up study from adolescence into adulthood

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ABSTRACT

Objectives

There is increasing evidence that both immune and neurochemical alterations are involved in the pathogenesis of bipolar disorder; however, their precise role remains unclear. In this study, we aimed to evaluate neuro-immune changes in a prospective study on children of patients with bipolar disorder.

Methods

Bipolar offspring, originating from the prospective Dutch Bipolar Offspring Study (n = 140), were evaluated cross-sectionally within a longitudinal context in adolescence, young adulthood and adulthood. We examined the expression of 44 inflammation-related genes in monocytes, and the cytokines pentraxin 3 (PTX3), chemokine ligand 2 (CCL2) and interleukin-1β and brain-derived neurotrophic factor (BDNF) and s100 calcium binding protein B (S100B) in the serum of bipolar offspring and healthy controls.

Results

During adolescence, bipolar offspring showed an increased inflammatory gene expression in monocytes, high serum PTX3 levels, but normal CCL2 levels. BDNF levels were decreased, while S100B levels were normal. During young adulthood monocyte activation remained, although to a lesser degree. Serum PTX3 levels remained high, and signs of monocyte migration became apparent through increased CCL2 levels. BDNF and S100B levels were not measured. In adulthood, circulating monocytes had lost their activation state, but CCL2 levels remained increased. Both BDNF and S100B were now increased. Abnormalities were independent of psychopathology state at all stages.

Conclusions

This study suggests an aberrant neuro-immune state in bipolar offspring, which followed a dynamic course from adolescence into adulthood and was present irrespective of lifetime- or future mood disorders. We therefore assume that the aberrant neuro-immune state rather reflects a general state of vulnerability for mood disorders than being of direct predictive value.

INTRODUCTION

Bipolar disorder is characterized by recurrent episodes of (hypo)mania and depression in alternation with periods of euthymia. There is accumulating evidence that the pathogenesis of bipolar disorder involves both immune and neurochemical changes (Andreazza et al., 2007; Beumer et al., 2012; Drexhage et al., 2010; Fernandes et al., 2011; Goldstein, Kemp, Soczynska, & McIntyre, 2009; Goldstein et al., 2011; Kauer-Sant'Anna et al., 2009; Modabbernia, Taslimi, Brietzke, & Ashrafi, 2013; Munkholm, Vinberg, & Vedel, 2013; Padmos et al., 2008; Schroeter et al., 2010). To date, most of these studies have focused on adult patients with already existing bipolar disorder and intensive pharmacological treatment. As suggested in clinical staging models, stage-related biological changes may be especially helpful in a better understanding of the early course of bipolar disorder and the development of new (preventive) treatment strategies (Berk et al., 2007; Berk et al., 2011; Brietzke et al., 2012; McGorry et al., 2007). Children of patients with bipolar disorder (bipolar offspring) are at increased risk to develop bipolar spectrum and other mood disorders (Mesman, Nolen, Reichart, Wals, & Hillegers, 2013; Lapalme, Hodgins, & LaRoche, 1997; Duffy et al., 2011). Hence, studies of bipolar offspring are valuable in unraveling the biological underpinnings of bipolar disorder, especially when studied in longitudinal design.

In this study, we aimed to evaluate neuro-immune aspects, which are known to be altered in bipolar disorder, in the Dutch Bipolar Offspring Study, one of the world's largest prospective bipolar offspring studies following bipolar offspring from adolescence into adulthood in the Netherlands (Hillegers et al., 2005; Mesman et al., 2013; Reichart et al., 2004; Wals et al., 2001). Bipolar offspring were cross-sectionally evaluated within a longitudinal context in adolescence (mean age 16), young adulthood (mean age 21) and adulthood (mean age 28). We investigated the expression in circulating monocytes of 44 inflammation-related genes previously selected by us and examined in patients with bipolar disorder (Padmos et al., 2008; Heul-Nieuwenhuijsen et al., 2010; Drexhage et al., 2010; Bergink et al., 2012). In addition, we measured serum levels of pentraxin 3 (PTX3), interleukin-1β (IL-1β) and chemokine ligand 2 (CCL2), monocyte products previously found to be increased in bipolar disorder (Padmos et al., 2008; Drexhage et al., 2010). And finally, we measured serum brain-derived neurotrophic factor (BDNF) and S100 calcium binding protein (S100B), a neurotrophic factor and an astrocyte activation marker frequently associated with mood disorders (Andreazza et al., 2007; Fernandes et al., 2011; Kauer-Sant'Anna et al., 2009). We took into account whether the offspring had a lifetime mood disorder, would develop a 'future' mood disorder (i.e. during follow-up), had a lifetime diagnosis of a non-mood disorder, or had not developed any disorder into adulthood. To our knowledge, this is the first study, to explore the dynamic course of biological mechanisms in bipolar offspring longitudinally.

Materials and Methods

Population and procedure

The Medical Ethical Review Committee of the University Medical Center Utrecht approved the study. Written informed consent was obtained from all subjects and their parents after a complete description of the study was given.

Bipolar Offspring

Bipolar offspring described herein belong to an ongoing prospective bipolar offspring cohort in the Netherlands (Wals et al., 2001; Reichart et al., 2004; Hillegers et al., 2005; Mesman et al., 2013). The study design and recruitment procedure of the Dutch Bipolar Offspring Study have been described in detail by Wals et al. (2001). In short, 140 offspring (mean age 16, range 12-21 years) from 86 families with one parent diagnosed with bipolar disorder (74% BD, type I; 26% BD, type II) were recruited in the years 1997-1999 and followed for 12 years. Subjects were assessed at four time points: baseline, 1-, 5-, and 12-year follow-up (for an overview see Table 1). As illustrated in Table 1, baseline and 1-year follow-up assessments were considered as the adolescent phase; the 5-year follow-up as the young adulthood phase and the 12-year follow-up as the adulthood phase. In total, 108 (77%) subjects were followed for the full 12-years. Psychiatric status of the offspring was evaluated at each time point according to DSM-IV Axis I criteria by using the K-SADS-PL (First, Spitzer, Gibbon, & Williams, 1997) or after the age of 18 by the use of the SCID-I (Kaufman et al., 1997). A full description of lifetime psychopathology and demographic characteristics at the 12-year follow-up has been given elsewhere (Mesman et al., 2013).

Healthy controls

Healthy controls were recruited cross-sectional at the various stages of the study from high schools (adolescent phase, recruited in 2001-2002), laboratory/medical staff and from control groups used in other studies (young adulthood phase recruited in majority between 2001-2005), and from university students (adulthood phase, recruited concurrent with the 12-year follow-up of the offspring study: 2010-2011). The inclusion criteria for healthy controls were the absence of (self-reported) psychiatric disorders and immune and/or endocrine disease in both the subject and their first degree family members.

Both bipolar offspring and healthy controls were excluded from analyses in cases of clinical evidence of acute infections 14 days prior to blood withdrawal, illicit drug use within 24 hours, or pregnancy.

Blood collection and preparation

Blood was drawn between 8.00 a.m. and noon. No fasting instructions were provided. Blood was collected into clotting tubes for serum preparation and in sodium-heparin tubes for immune cell preparation in the University Medical Center Utrecht. Consecutively, samples were transported to the Erasmus Medical Center in Rotterdam for preparation. On site, all

serum samples were stored at -80°C. Samples from the baseline assessment were stored at -20°C. From the heparinized blood, peripheral mononuclear cell (PBMC) suspensions were prepared by low-density gradient centrifugation, as described previously in detail (Knijff et al., 2006). Samples were prepared within eight hours of sampling to avoid activation of the monocytes (erythrophagia). PBMC's were frozen at 10% dimethylsulfoxide (DMSO) and stored in liquid nitrogen. This enabled us to run samples from bipolar offspring- and healthy controls in the same series of experiments. Care was taken to compare offspring and control PBMC samples that had been stored frozen for an identical periods of time.

Table 1 | General characteristics of the Dutch Bipolar Offspring Study

Dutch Bipolar Offspring Study	**T1**		**T2**		**T3**		**T4**	
Phase	Adolescence		Adolescence		Young Adulthood		Adulthood	
Follow-up	Baseline		1-years		5-years		12-years	
Year of assessment	1997-1998		1999-2000		2003-2004		2010-2011	
	n	*%*	**n**	*%*	**n**	**%**	**n**	**%**
Demographic characteristics								
Offspring	140	*100*	132	*94*	129	*92*	108	*77*
Males	72	*51*	71	*53*	69	*53*	58	*54*
Age, years, mean (range)	16.1 (12-21)		17.4 (13-23)		20.8 (16-26)		28 (22-32)	
Families	86	*100*	82	*95*	80	*93*	70	*81*
Bipolar mothers	52	*60*	49	*60*	48	*60*	41	*59*
Bipolar I disorder	64	*74*	59	*72*	59	*74*	52	*74*
Lifetime DSM-IV axis I disorders								
Any disorder	61	*44*	65	*49*	76	*59*	78	*72*
Any mood disorder	38	*27*	43	*33*	51	*40*	58	*54*
Bipolar disorder[a]	4	*3*	5	*4*	13	*10*	12	*11*
Current mood disorders[b]	19	*14*	21	*14*	9	*7*	16	*15*
Current psychotropic medication	NA	NA	3	*2*	4	*3*	6	*6*

NA = not applicable

[a] bipolar disorder type I or II.

[b] Symptoms/episode present in the past two months for T1 and T2; mood disorder present in the past month for T3 and T4. This difference is due to a change in the diagnostic instrument.

Gene expression in circulating monocytes

To evaluate mRNA expression in circulating monocytes, we used the 44 genes previously selected as abnormally expressed in bipolar disorder (Drexhage et al., 2010; Padmos et al., 2008), schizophrenia (Drexhage et al., 2010), major depressive disorder (Weigelt et al.,

2011), postpartum psychosis (Bergink et al., 2012), autoimmune thyroid disorder (Heul-Nieuwenhuijsen et al., 2010), as well as 4 interferon-inducible genes and the 2 transcripts of the active and inactive isoforms of the glucocorticoid receptors (GR-α, GR-β respectively) (Bergink et al., 2012). As previously described in Bergink et al. (2012), genes were clustered in 4 clusters: Cluster 1, including mostly genes involved in pro-inflammatory processes; Cluster 2 including genes involved in chemotaxis, motility, metabolic and cell adhesion processes; Cluster 3, an interferon-induced gene cluster; and Cluster 4, containing the two glucocorticoid-receptor transcripts GR-α and GR-β (Table 2).

The CD14 positive monocytes were isolated from frozen PBMCs by magnetic cell sorting system (Miltenyi Biotec, Cologne, Germany). The purity of monocytes was > 95% [determined by morphological screening after Trypan Blue staining and FACS)]. The RNA was isolated from purified monocytes with RNAeasy columns according to the manufacturer's instructions (Qiagen, Gaithersburg, Maryland) (Staal et al., 2004). One microgram RNA was reverse-transcribed with the High Capacity Complementary DNA Kit (Applied Biosystems, Nieuwerkerk a/d Ijssel, The Netherlands) for 120 min at 37°C, whereas reverse transcriptase polymerase chain reaction (RT-qPCR) was performed with a preloaded Taqman Low Density Array (TLDA) for real-time amplification and relative messenger RNA qualification (Applied Biosystems, Foster City, California). A TLDA is an array of 384 reaction wells for two-step RT-qPCR. Each complementary DNA sample (40 µL) was added to 50 µL of 2x TaqMan universal PCR master mix (Applied Biosystems), and 10 µL RNase free water was added to obtain a total volume of 100 µL. After gentle mixing and centrifugation, the sample was transferred on a TLDA card. The card was sealed, and PCR amplification was performed with an Applied Biosystems Prism 7900HT sequence detection system (equipped with a TLDA upgrade). Thermal cycler conditions were: two min at 50°C, 10 min at 94.5°C, 30 sec at 97°C, and one min at 59.7°C for 40 cycles. Due to limitations of the technique, not all TLDA cards could be determined in one run. Hence, we aimed to include bipolar offspring and healthy controls from the same time point in each run. The quantitative value obtained from Q-PCR is a cycle threshold (Ct) calculated with the comparative threshold cycle method (Schmittgen & Livak, 2008). The fold change values between different groups were determined from the normalized Ct values (Ct gene – Ct housekeeping gene (ABL)), using the ΔΔCt method (User Bulletin, Applied Biosystems, Foster City, California). The median fold change of healthy controls was set to 1. Data are expressed relative to this control-value. Values > 1 mean that bipolar offspring have higher expression than controls and vice versa.

Cytokines, BDNF and S100B

Serum levels of CCL2 and IL-1β were measured using the Cytometric Bead Array kit (Bender MedSystems, Burlingame, California) according to the manufacturer's protocol. Serum PTX3 levels were determined via an in house ELISA (M7M). Serum BDNF levels were assessed using the BDNF Quantikine ELISA kit (R&D Systems) according to manufacturer's instructions. S100B levels were measured in an electrochemiluminescence immunoassay (S100 kit, Roche Elecsys®, Roche Diagnostics GmbH., Mannheim, Germany).

Data Analysis

At each phase (adolescence, young adulthood and adulthood, respectively) between- and within-group analyses were performed for all biological parameters. Between-group analyses tested differences between bipolar offspring and healthy controls in general. Within-group analyses were performed to reveal differences between affected, future affected and unaffected bipolar offspring. Psychopathology categories were defined as (i) lifetime mood disorder; (ii) future mood disorder; (iii) lifetime non-mood disorder; and (iv) no disorder. A lifetime mood disorder was defined as a current or previous mood disorder at time of assessment, including both severe (bipolar spectrum disorders and major depressive disorder) and minor mood disorders (e.g. depression not otherwise specified). Future mood disorder was defined as development of a mood disorder during follow-up. Both the mood- and future mood disorder category could contain offspring having a comorbid past, present or future non-mood disorder. A subject was classified as having a lifetime non-mood disorder when he/she reached the end of the study without developing a mood disorder, but was diagnosed with a current, previous or future (during follow-up) non-mood disorder. The category no disorder applied to all offspring not developing any major DSM-IV axis I disorder up to the last assessment. Subjects dropping out before the end of the study without having developed a mood disorder were included in the between-group analyses, but excluded from the within-group analyses, because of the uncertainty of their lifetime diagnoses. The number of subjects in the within-group and the between-group analyses could vary per experiment and assessment, and is thus reported in the text, tables and figure legends.

Statistical Analysis

Statistical Analyses were performed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp, Armonk, NY, USA). For sample characteristics, chi-square tests were used to evaluate categorical data; independent *t*-tests were performed for continuous data. Kolmogorov-Smirnov tests and normality plots were used to test for normal distribution; Levene's test was used to test for the assumption of homogeneity. Since the majority of biological parameters were non-normally distributed, data were log-transformed (log_{10}). Despite careful selection of healthy controls, gender and age differences occurred in most experiments. Generalized linear model (GLM) analyses were used to detect group differences and allowed us to adjust for age and gender. Level of significance was set at .05 unless otherwise specified. Gene expression analyses were corrected for multiple comparison by use of a Bonferonni-correction.

Table 2 | Gene expression in circulating monocytes of bipolar offspring relatively expressed to healthy controls.

	Adolescence		Young Adulthood		Adulthood	
	Median FC	***p***[b]	**Median FC**	***p***[b]	**Median FC**	***p***[b]
Cluster 1						
IL1A	595.23	< .001	1.30	0.003	0.45	0.32
IL1B	93.12	< .001	1.66	0.01	0.63	0.05
CCL20	688.25	< .001	2.19	0.03	0.46	0.43
IL6	990.54	< .001	2.28	0.08	0.83	0.21
PTX3	22.57	< .001	1.30	0.58	0.68	0.08
IRAK2	129.14	< .001	2.50	< .001	0.38	0.003
TNF	38.29	< .001	0.77	0.003	0.94	0.56
BCL2A1	22.53	< .001	1.55	0.03	0.97	0.67
CXCL2	49.09	< .001	2.01	0.08	0.74	0.01
PTGS2	18.43	< .001	0.96	< .001	0.58	0.04
ADM	10.66	< .001	2.53	< .001	1.05	0.23
BTG3	16.60	< .001	1.94	< .001	0.87	0.06
SERPINB2	123.88	< .001	1.37	0.08	0.84	0.48
PDE4B	7.07	< .001	1.42	0.02	0.64	0.07
TNFAIP3	8.47	< .001	1.26	0.001	0.70	0.47
ATF3	3.16	< .001	1.23	0.01	0.96	0.67
CDC42	6.11	< .001	2.32	< .001	1.08	0.38
MAFF	29.01	< .001	2.62	< .001	0.80	0.14
DUSP2	4.66	< .001	1.50	0.49	0.82	0.12
EREG	53.09	< .001	3.42	0.34	0.95	0.04
Cluster 2						
CCL7	489.31	< .001	13.59	0.02	0.41	0.42
FCAR	3.66	< .001	1.34	< .001	–	NA
PTPN7	2.49	< .001	2.04	< .001	0.81	0.08
THBD	6.24	< .001	1.50	0.001	1.06	0.89
RGCC	16.44	< .001	4.66	< .001	0.65	0.26
STX1A	8.89	< .001	6.59	0.003	0.70	0.04
EMP1	3.21	< .001	3.65	< .001	0.64	0.07
NAB2	3.21	<.001	3.73	< .001	0.79	0.24
MAPK6	6.65	< .001	1.37	0.001	1.03	0.92
DHRS3	2.81	< .001	1.34	0.02	0.89	0.61
MXD1	3.82	< .001	1.57	0.04	1.01	0.72
IL1R1	4.11	< .001	1.38	0.02	1.00	0.42
CCL2	6.79	< .001	1.71	0.007	0.68	0.95

Table 2 | *(Continued)*

	Adolescence[a]		Young Adulthood		Adulthood	
	Median FC	***p***[b]	**Median FC**	***p***[b]	**Median FC**	***p***[b]
Cluster 2						
EGR3	5.77	< .001	2.08	0.002	0.55	0.082
CD9	2.10	0.03	1.84	0.18	1.04	0.99
FABP5	3.43	< .001	0.98	0.29	1.12	0.23
Interferon cluster						
IFI44	1.43	0.001	1.07	0.19	1.26	0.02
IFI44L	1.00	0.20	0.82	0.56	–	NA
IFIT3	6.60	< .001	0.65	0.32	1.50	0.03
HSPA1A	0.95	0.668	0.50	< .001	1.10	0.29
ADAM17	1.10	0.041	0.89	0.07	–	NA
IFI27	1.30	0.283	1.02	0.87	1.66	0.24
Glucocorticoid Cluster						
NR3C1: GR-alpha	1.1406	0.024	0.9155	0.54	1.0847	0.05
NR3C1: GR-beta	2.0528	< .001	1.5836	< .001	1.1727	0.42

Monocyte gene expression arrays of bipolar offspring were available in adolescence (1-year follow-up, mean age of 17 years, n = 24, 67% male, age range 13-22), young adulthood (5-year follow-up, 21 years, n = 97, 55% male, age range 16-26) and adulthood (12-year follow-up, 28 years, n = 95, 57% male, age range 22-32). For each phase healthy controls were selected: adolescence: n = 33, 67% male, mean age 14 (range 12-16); young adulthood: n = 31, 45% male, mean age 21 (range 17-27); and adulthood: n = 45, 53% male, mean age 26 (range 22-32). The quantitative value obtained from Q-PCR is a cycle threshold (Ct). The fold change (FC) values between different groups were determined from the normalized Ct values (Ct gene – Ct housekeeping gene (ABL)), via the ΔΔCt method (User Bulletin, Applied Biosystems, Foster City, California). The median fold change of healthy controls (HC) set to 1. Data are expressed relative to this HC-value. Values > 1: bipolar offspring have a higher expression than HC. Values < 1: bipolar offspring have a lower expression than HC. NA means the particular gene expression was not determined. Level of significance was set at .001 (Bonferroni correction: p .05/44 genes = .001).

[a] 17 out of 24 bipolar offspring at T2, originated from the same sample used in Padmos et al. (Padmos et al., 2008).

[b] P-values are adjusted for age and gender.

See appendix for the list of gene definitions.

RESULTS

Between-group analyses

Adolescence

In Table 2 the expression levels of the 44 immune activation genes in circulating monocytes are presented. In the adolescent phase, almost all (88.6%, 39 out of 44) genes were over-expressed in the monocytes of bipolar offspring as compared to healthy controls. Over-expression occurred in Cluster 1 and Cluster 2 genes. With regard to GR gene expression, it appeared that the inactive isoform (GR-β), but not the active isoform (GR-α) of the GR

showed significantly higher expression in the monocytes of bipolar offspring, suggesting steroid resistance at the level of the monocyte. In Figure 1a, we depict the gene expression in an alternative way, as the percentage of genes over-expressed in circulating monocytes, reflecting a clear difference with healthy controls (Mann-whitney $U = 761$, $p < 0.001$, effect size $r = 0.79$).

With regard to the tested pro-inflammatory cytokines, we found increased serum levels of PTX3 in bipolar offspring (median = 162 pg/ml, n = 124 and median = 126 pg/ml, n = 62 at the mean ages 16 and 17 years respectively) compared to healthy controls (median = 93 pg/ml, n = 74 and median = 52 pg/ml, n = 41 at the mean ages of 14 and 20 years respectively) (ages 16/14 $\beta = 0.180$, $p < 0.001$, and $\beta = 0.238$, $p < 0.001$ af ages 17/20). With regard to serum levels of IL-1β, a difference was not found between bipolar offspring (median = 10 pg/ml, n = 123) and healthy controls (median = 7.56 pg/ml, n = 50), $\beta = 0.017$, $p = 0.772$. Also, CCL2 levels were not statistically increased in bipolar offspring ($\beta = 0.046$, $p = 0.121$, see Figure 2a).

Regarding neurotrophin BDNF, we found decreased levels of BDNF in bipolar offspring compared to healthy controls, ($\beta = -0.101$, $p < 0.001$; Figure 3a), suggesting decreased neuronal growth, synaptic plasticity and/or neuronal survival processes during adolescence. Levels of serum S100B, secreted by activated astrocytes, were not altered in bipolar offspring in comparison to healthy controls, ($\beta = -7.475^{E005}$, $p = 0.678$; Figure 4a).

Young adulthood

In the phase of young adulthood, the higher expression of immune genes in monocytes of offspring in comparison to healthy controls became less pronounced: 16 (36.4%) out of the 44 genes investigated showed significantly higher expression (Table 2). The decrease in over-expressed genes in monocytes can also be seen in Figure 1a (in the alternative depiction). However, the difference compared with healthy controls was still significant with a moderate effect size, $U = 2207$, $p < 0.001$, $r = 0.38$. Despite the decrease in immune activation of the monocytes, the GR-β gene still showed higher expression in the monocytes (Table 2).

The serum level of the pro-inflammatory factor PTX3, remained significantly increased in bipolar offspring (median = 137 pg/ml, n = 103) during young adulthood compared with healthy controls (median = 52 pg/ml, n = 41) ($\beta = 0.238$, $p = 0.001$). Also, the levels of CCL2 were now significantly increased in offsprin ($\beta = 0.166$, $p < 0.00$; Figure 2a). Again, levels of IL-1β did not show a significant difference between bipolar offspring (median = 9.27 pg/ml, n = 105) and healthy controls (median = 7.26, n = 32) ($\beta = 0.073$, $p = 0.198$).

Unfortunately BDNF and S100B could not be examined during young adulthood, since we had run out of good quality serum for this test.

Adulthood

In adulthood, the over-expression of inflammatory genes in the circulating monocytes of bipolar offspring had disappeared completely, as depicted in Table 2 and Figure 1a. Also, the GR-β gene expression had become normal in monocytes of bipolar offspring.

With regard to the pro-inflammatory serum compounds, PTX3 levels could unfortunately not be examined in the adult phase, since the antibodies used in the in house assay were not available anymore. As during adolescence and young adulthood, we did not find a difference in serum IL-1β levels between bipolar offspring (median = 0.00, n = 89) and healthy controls (median = 0.00, n = 49) (β = -0.019, p = 0.732 . Serum CCL2 levels in bipolar offspring remained significantly higher than CCL2 levels in healthy controls (β = 0.190, p < 0.01; Figure 2a), particularly in female offspring (β = 0.315, p = 0.005).

As shown in Figure 3a, lower levels of BDNF were observed in bipolar offspring in adolescence in comparison to healthy controls; however, during adulthood the reverse pattern was observed: due to a stronger reduction of BDNF levels in healthy controls, higher levels of BDNF were found now in bipolar offspring than in healthy controls (β = 0.049, p = 0.019), suggesting increased growth/repair activity in the brain of offspring. Levels of S100B were significantly increased in adult offspring compared to healthy controls, (β = 0.006, p = 0.03 (Figure 4a).

Within-group analyses

Within-group analyses were performed to determine whether the described parameters would be useful in distinguishing bipolar offspring with a lifetime mood disorder, a future mood disorder, a lifetime non-mood disorder or no disorder. Data for monocyte gene expression are presented in Figure 1b (see Supplementary Tables 1a-c for expression levels of individual genes per group). Figure 1b shows that we did not find such within group differences for monocyte gene expression in bipolar offspring. Also, interestingly the no disorder group showed high over-expression of immune activation genes in circulating monocytes; bipolar offspring with a lifetime non-mood disorder showed the lowest monocyte gene over-expression data, while the future mood disorder group showed the highest gene over-expression data. Yet, group sizes were small (n = 7, n = 4 and n = 3 respectively) and, as indicated above, within group statistical significances were not reached. Also in young adulthood and adulthood, we did not find within-group differences for monocyte gene expression (Figure 1b, Supplementary Tables 1a-c).

In terms of serum levels of pro-inflammatory cytokines of PTX3 and CCL2, evidence was not found for within-group differences regarding psychopathology status (PTX3 adolescence: mean age of 16 years, mean age 17 years and young adulthood (p = 0.932, p = 0.798 and p = 0.178 respectively); for CCL2 see Figure 2c).

During adolescence, serum BDNF was decreased in bipolar offspring, while serum S100B was normal. Overall within-group differences in both BDNF and S100B were not statistically significant in the adolescent phase (Figure 3b and 4b). In adulthood, serum BDNF and S100B levels were increased, for serum S100B particularly in the group of mood disorders (Figure 4b); however, within group differences were not found in serum levels of S100B or BDNF.

We also performed analyses of the various measured parameters in individualisme with current mood disorders, but were unable to detect any significant differences within bipolar offspring (for analyses see supplementary Table 2).

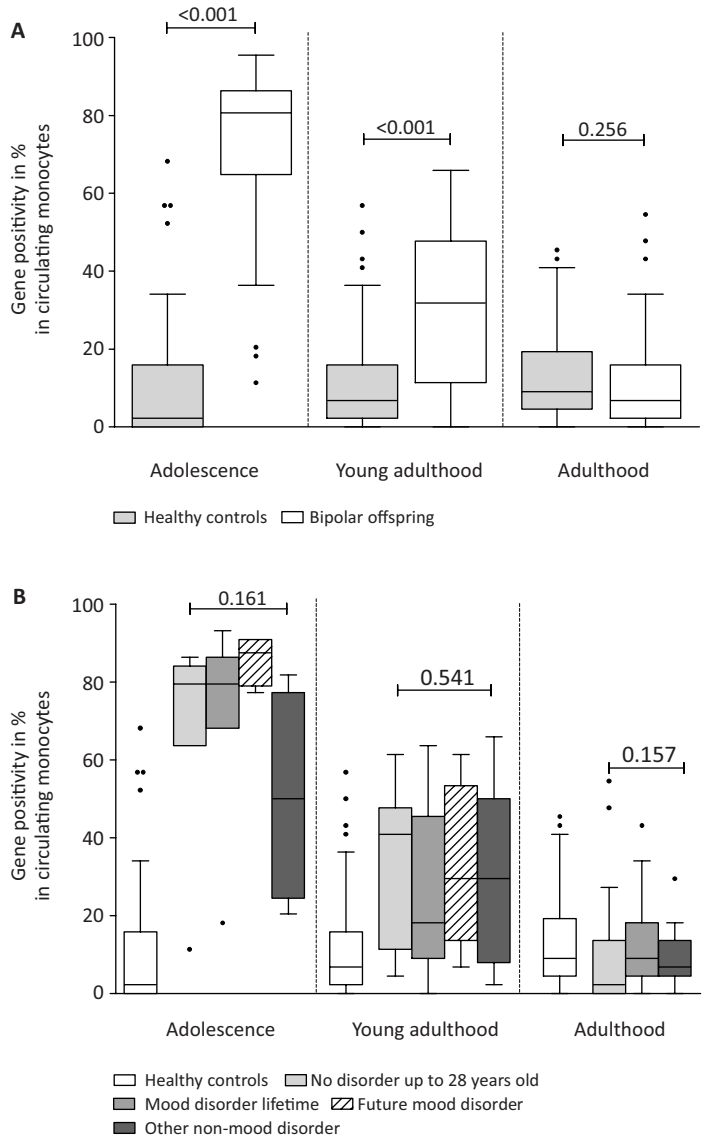

Figure 1 | Course of gene positivity in circulating monocytes in bipolar offspring and healthy controls. (**A**) Between-group analyses:Tukey box-plots of percentage of genes defined positive from the total gene array (44 genes). Group differences were tested by non-parametric Mann-Whitney tests. (**B**) Within-group analyses: Tukey box-plots of within group analyses in bipolar offspring: a lifetime mood disorder (adolescence, n = 7; young adulthood, n = 37; adulthood, n = 54), a future mood disorder as diagnosed at follow-up (adolescence, n = 4; young adulthood 1, n = 13; adulthood = not applicable), lifetime non-mood disorder (adolescence, n = 4; young adulthood, n = 13; adulthood, n = 17) or no disorder (adolescence, n = 7; young adulthood, n = 23; adulthood, n = 27). A Kruskal-Wallis test was performed to detect within-group differences in bipolar offspring.

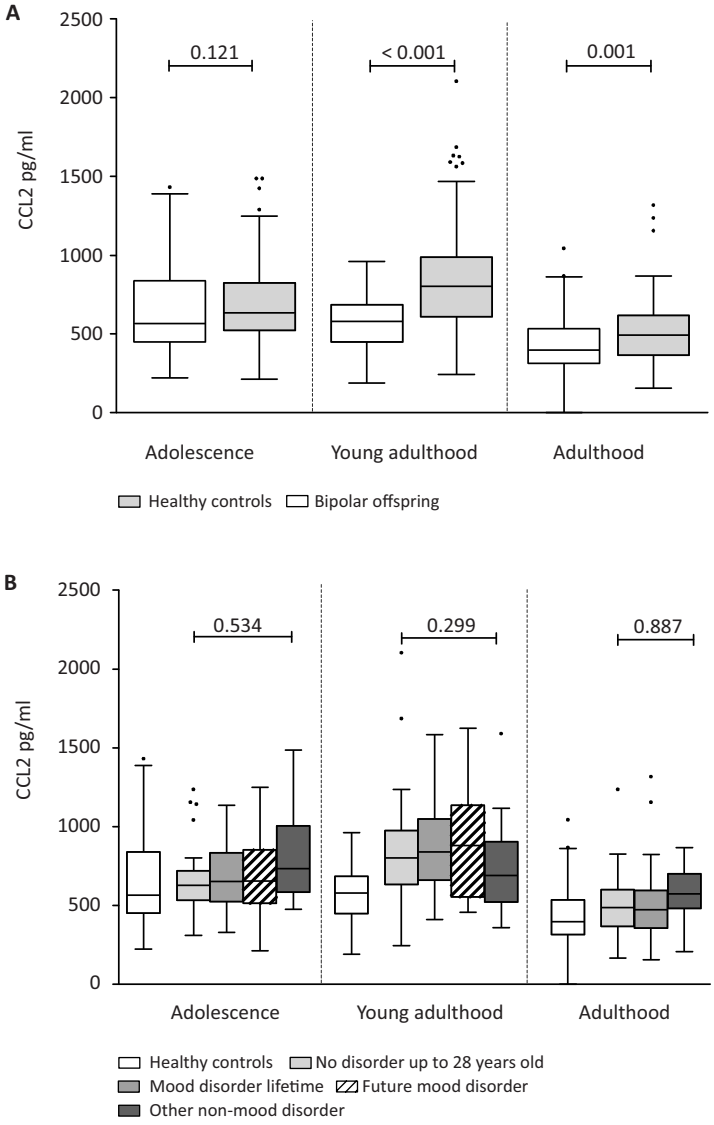

Figure 2 | Serum CCL2 pg/ml levels in bipolar offspring versus healthy controls. (**A**) Between-group analyses: Tukey box-plots of serum CCL2 levels of bipolar offspring and healthy controls. Demographic characteristics per time point: bipolar offspring adolescence: mean age 16, n = 122, 52% male; young adulthood: mean age 21, n = 105, 58% male; adulthood: mean age 28, n = 88, 56% male. Healthy controls adolescence: mean age 14, n = 50, 66% male, young adulthood: mean age 20, n = 32, 75% male; adulthood: mean age 26, n = 49, 47% male. (**B**) Within-group analyses: Tukey box-plots of serum CCL2 levels and within group analyses in bipolar offspring per time point: a lifetime mood disorder (n = 33, n = 41 and n = 47 respectively), a future mood disorder as diagnosed at follow-up (n = 26, n = 14 respectively), lifetime non-mood disorder (n = 17, n = 14 and n = 14 respectively) or no disorder (n = 29, n = 23 and n = 27). P-values are adjusted for age and gender.

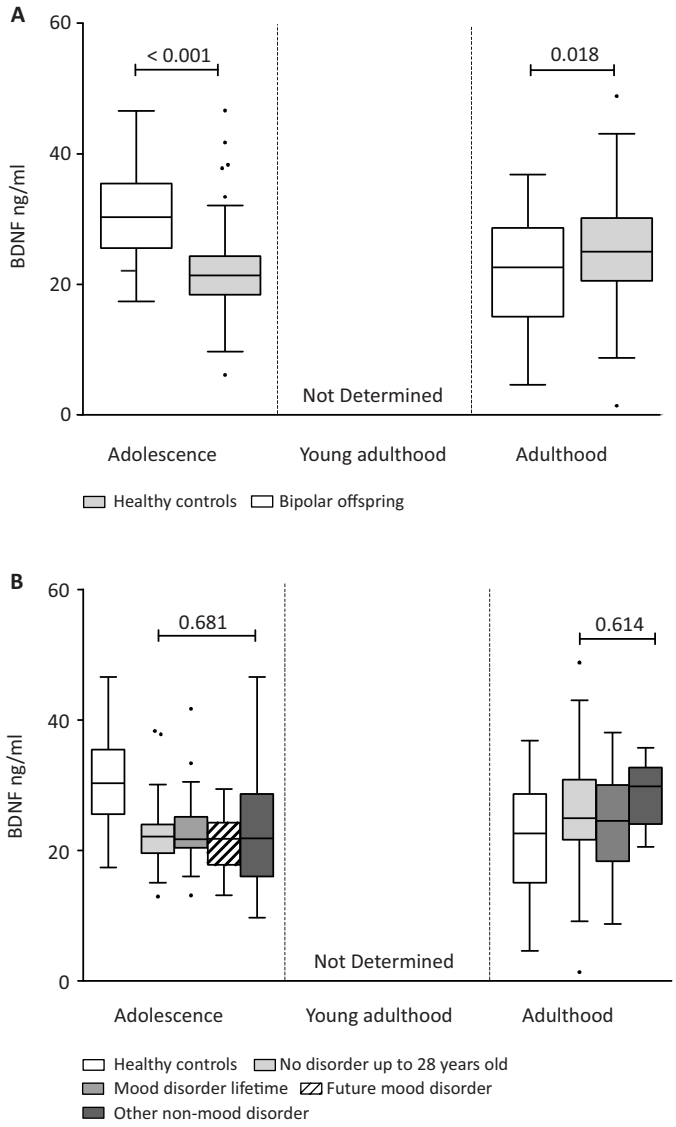

Figure 3 | Serum BDNF levels in Bipolar offspring versus healthy controls. (**A**) Between-group analyses: Tukey box-plots of serum BDNF levels of bipolar offspring and healthy controls. Demographic characteristics per time point: bipolar offspring adolescence: mean age 16, n = 102, 53% male; adulthood: mean age 28, n = 85, 55% male. Healthy controls adolescence: mean age 15, n = 80, 63% male; adulthood: mean age 27, n = 49, n = 47% male. (**B**) Within-group analyses: Tukey box-plots of serum BDNF levels and within group analyses in bipolar offspring: a lifetime mood disorder (adolescence, n = 31; adulthood: n = 50), a future mood disorder as diagnosed at follow-up (adolescence: adulthood: not applicable), lifetime non-mood disorder (adolescence: n = 13; adulthood: n = 11) or no disorder (adolescence: n = 25; adulthood: n = 24). P-values are adjusted for age and gender.

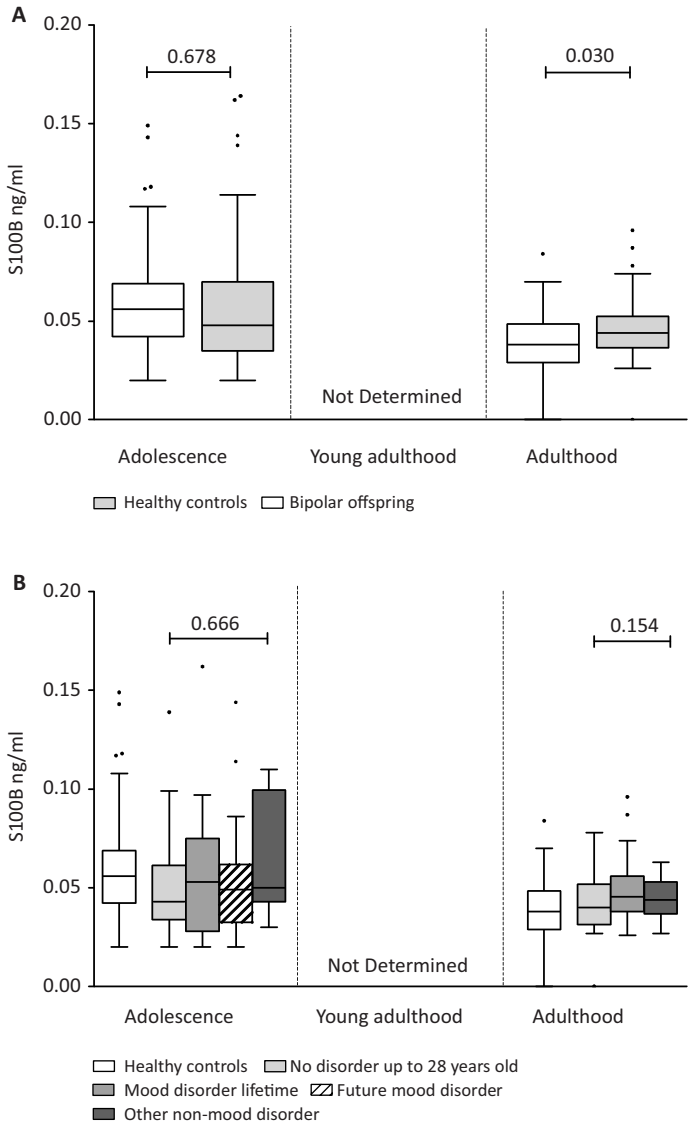

Figure 4 | Serum S100B levels in bipolar offspring versus healthy controls. (**A**) Between-group analyses: Tukey box-plots of serum S100B levels in bipolar offspring and healthy controls. Demographic characteristics per time point: bipolar offspring adolescence: mean age 16, n = 103, 53% male; adulthood: mean age 28, n = 85, 55% male. Healthy controls adolescence: mean age 15, n = 76, 63% male; adulthood: mean age 27, n = 49, 47% male. (**B**) Within-group analyses: Tukey box-plots of serum S100B levels and within group analyses in bipolar offspring: a lifetime mood disorder (adolescence: n = 31;adulthood, n = 50), a future mood disorder as diagnosed at follow-up (adolescence, n = 19; adulthood = not applicable), lifetime non-mood disorder (adolescence, n = 13; adulthood, n = 11) or no disorder (adolescence, n = 25; adulthood, n = 24). P-values are adjusted for age and gender.

DISCUSSION

This study is the first study to explore the dynamic course of an altered neuro-immune state in affected and unaffected bipolar offspring in a longitudinal fashion. However, the findings of this study should be discussed in the light of the following limitations. Although one of the largest longitudinally followed bipolar offspring cohorts, this cohort still has a limited group size and knows varying group sizes, particularly after splitting our sample into future, current and lifetime mood states. Despite the longitudinal design of the study, we were unable to longitudinally analyze the data, as healthy control groups were recruited cross-sectional at various stages of the study and not prospectively. In addition, the unknown effect of long term blood storage on the quality of the PBMC samples did not allow us to perform reliable within-subject/longitudinal data-analysis within bipolar offspring. Another limitation is that the assays used are complex, were performed at different times during the study and show inter-assay variation. Moreover, only a very limited set of immune and neurochemical parameters were measured and other conclusions might have been drawn when e.g. lymphocyte subsets had been analyzed. Also quantification methods (particularly for the monocyte gene expression) are under development and have not fully been worked out yet. In addition, it must be noted that there are many confounding factors for the immune parameters used and, although we were able to correct for age and gender, information was mot available on either body mass index and serum lipid profile of the bipolar offspring and controls, or parameters such as emotional or physical trauma, suicide attempts, head trauma and other chronic neurological disorders for all tim- points measured in all individuals. All these variables have a potential effect on an individual's pro-inflammatory state. Future confirmatory cohort studies are clearly needed and should take these limitations into consideration.

Despite the above limitations, we are of the opinion that this study strongly suggests that monocyte activation – previously associated with bipolar disorder in adult patients – is also present in bipolar offspring. These alterations were present irrespective of lifetime and current psychopathology, thus reflecting a general vulnerability in bipolar offspring for developing a mood disorder rather than being associated with the diagnosis of bipolar disorder. In a previous report (Padmos et al., 2008), we suggested that, based on a study of a much smaller sample of this cohort, monocyte gene activation as found in adolescent bipolar offspring might in potentially be predictive for future development of mood disorders. However, the high prevalence of monocyte gene activation found in this study in offspring with psychopathology from other diagnostic categories or even no lifetime psychopathology, refutes such notion. These findings, together with the alterations found in PTX3, CCL2, BDNF and S100B, suggest a more complex model as a driving force behind the development of bipolar disorder. We assume that risk factors for the development of bipolar disorder involve complex interactions of genetic predisposition acting in concert with multiple environmental factors (e.g. life events and infections) to lead over time to variable activation of the neuro-immune-endocrine system, impacting brain development/ mental health.

The high monocyte gene transcription activation found in this study in adolescence gradually decreased over time via a moderately higher expression level of monocyte genes in young adulthood to a normalized monocyte gene transcription level in adulthood. The high transcription activation of monocytes in adolescent offspring was paralleled by a high protein level of the signature gene PTX3 in serum, and this observation strengthens the view that indeed the inflammatory response system is over-activated in adolescence and early adulthood in bipolar offspring. This over-activation was also reflected in a higher than normal expression of the inactive GR-β gene in the monocytes, suggesting that steroid resistance is part of the over-activation. Recent studies of our group show that high monocyte immune gene transcription is particularly evident in subjects with more chronic bipolar disorder and with symptoms of mania (Haarman et al., 2013). The bipolar offspring in this study were not older than 32 years at the last measurement; hence, it is possible that with longer follow-up the monocyte signature would return, especially in patients with more frequent or more severe recurrences.

Serum levels of CCL2 followed a different pattern than monocyte immune gene transcription. CCL2 serum levels were higher in bipolar offspring compared to healthy controls, but the difference did not reach statistical significance before young adulthood and adulthood. The higher levels of CCL2 in serum, particularly in adulthood when inflammatory gene transcription activation of circulating monocytes had vanished, point to a stronger migrating activity of these monocytes to the tissues in adult bipolar offspring than in healthy controls, showing that monocyte activation also exists at this age, but with a different character than in adolescence.

With regard to BDNF, we found decreased levels of BDNF in bipolar offspring during adolescence. This finding was irrespective of psychopathology outcome or having a current mood episode. Previous studies in adult and pediatric bipolar disorder reported decreased levels of BDNF during acute episodes of mania or depression (Pandey, Rizavi, Dwivedi, & Pavuluri, 2008; Fernandes et al., 2011), but not during periods of euthymia (Fernandes et al., 2011). BDNF has also been shown to decrease as the disorder progresses (Grande, Fries, Kunz, & Kapczinski, 2010; Kauer-Sant'Anna et al., 2009). In this study, we found decreased levels of BDNF in offspring during adolescence and increased levels at adult age; this finding was again irrespective of psychopathology outcome or having a current mood episode. BDNF is involved in neurogenesis, synaptic plasticity, neural growth and cell survival, and therefore we hypothesize that the early decrement of BDNF levels may reflect a delay, or perturbation of brain development due to the immune activation. The meaning of the increase of BDNF levels of adult offspring is unclear, particularly since literature indicates decreases over time.

S100B is produced and secreted by activated astrocytes. In both unipolar depression and bipolar disorder research, increased levels of S100B have been found in acute depressive and manic states (Andreazza et al., 2007; Schroeter et al., 2010). The concentration of S100B reflects neuronal damage or survival (nanomolar concentrations stimulate neurite outgrowth/neuronal survival, micromolar levels induce apoptosis). Elevated levels are

associated with neuropathology in neurodegenerative disease and brain-inflammatory diseases (Rothermundt, Peters, Prehn, & Arolt, 2003). We found that S100B levels were normal in adolescent bipolar offspring, but raised in adulthood, particularly in those with a mood disorder. This is in accord with the earlier findings of increased levels of S100B in active disease (Andreazza et al., 2007; Schroeter et al., 2010).

In conclusion, our study indicates that changing monocyte hyperactivity patterns together with changing patterns of serum BDNF and S100B are typical for the majority of bipolar offspring, irrespective of the actual presence or later development of a mood disorder. If confirmed in future studies, these findings suggest that an activated inflammatory response system and a changing pattern of serum brain factors are essential links in the chain of events leading to the development of bipolar disorder. Thus, these findings may suggest new directions for research to disentangle the mechanisms underlying the development of bipolar disorder.

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SUPPLEMENTAL MATERIAL

Tables S1A-C | Gene expression in circulating monocytes of affected and unaffected bipolar offspring relatively expressed to healthy controls.

1A | Adolescence

Bipolar offspring					
	No disorder	**Lifetime mood disorder**	**Future mood disorder**	**Lifetime non-mood disorder**	
	n = 7	**n = 7**	**n = 4**	**n = 4**	
	Median FC	**Median FC**	**Median FC**	**Median FC**	***p***
Cluster 1					
IL1A	568.8[a]	747.5[a]	547.2	228.6	< 0.001
IL1B	110.4[a]	94.4[a]	94.2[a]	35.6	<0 .001
CCL20	674.7[a]	959.3[a]	646.3[a]	224.3	< 0.001
IL6	1001.5[a]	1133.1[a]	841.6[a]	486.0	< 0.001
PTX3	25.2[a]	22.2[a]	22.5[a]	7.6	< 0.001
IRAK2	120.6[a]	131.4[a]	120.5[a]	69.5	< 0.001
TNF	34.6[a]	46.3[a]	43.9[a]	11.8	< 0.001
BCL2A1	17.8[a]	22.4[a]	24.3[a]	7.6	< 0.001
CXCL2	46.4[a]	52.2 [a]	67.5[a]	14.0	< 0.001
PTGS2	16.6[a]	20.6[a]	21.3[a]	4.7	< 0.001
ADM	17.9 [a]	10.8[a]	8.9	14.3	< 0.001
BTG3	18.6[a]	13.9[a]	14.0[a]	11.7	< 0.001
SERPINB2	102.6[a]	209.0[a]	192.9[a]	21.6	< 0.001
PDE4B	5.7[a]	7.4[a]	7.2[a]	3.7	< 0.001
TNFAIP3	7.7[a]	8.5[a]	7.4	5.0	< 0.001
ATF3	3.2[a]	4.1[a]	3.0	2.4	< 0.001
CDC42	5.6[a]	7.2[a]	5.9[a]	3.4	< 0.001
MAFF	20.3[a]	34.2[a]	26.6[a]	13.4[a]	< 0.001
DUSP2	4.2 [a]	6.6[a]	6.3[a]	1.86	< 0.001
EREG	31.9[a]	61.7[a]	55.3[a]	11.5	< 0.001
Cluster 2					
CCL7	232.4[a]	473.5[a]	869.4[a]	193.6	< 0.001
FCAR	3.3[a]	4.0	4.3[a]	2.2	< 0.001
PTPN7	1.5	2.6[a]	3.9[a]	2.1	< 0.001
THBD	5.9[a]	5.2 [a]	9.4[a]	5.3[a]	< 0.001
RGCC	10.4[a]	19.3[a]	21.9[a]	9.2	< 0.001
STX1A	6.0	5.9	19.9[a]	7.5	< 0.001

1A | *(Continued)*

Bipolar offspring					
	No disorder	**Lifetime mood disorder**	**Future mood disorder**	**Lifetime non-mood disorder**	
	n = 7	**n = 7**	**n = 4**	**n = 4**	
	Median FC	**Median FC**	**Median FC**	**Median FC**	***p***
Cluster 2					
EMP1	2.2	3.9	5.6[a]	1.8[a]	< 0.001
NAB2	2.7	3.2[a]	8.1	1.6	< 0.001
MAPK6	4.8[a]	6.9[a]	7.0[a]	3.4[a]	< 0.001
DHRS3	2.8[a]	2.7[a]	3.2	2.0	< 0.001
MXD1	3.3[a]	3.9[a]	3.9	1.6	< 0.001
IL1R1	4.2[a]	5.1[a]	10.0[a]	1.6	< 0.001
CCL2	5.1[a]	6.9[a]	14.7[a]	4.3	< 0.001
EGR3	4.5[a]	6.1[a]	6.8[a]	5.0[a]	< 0.001
CD9	1.6	3.3	1.2	5.3	0.132
FABP5	2.8[a]	4.8[a]	3.3[a]	2.3[a]	< 0.001
Interferon cluster					
IFI44	1.4	1.4	2.9[a]	1.8	< 0.001
IFI44L	0.6	1.0	2.3	1.5	0.048
IFIT3	6.1[a]	6.9	6.8	5.6	< 0.001
HSPA1A	0.9	1.2	1.0	0.8	0.983
ADAM17	1.0	1.3	1.2	0.7	0.067
IFI27	0.8	0.5	2.5	3.6	0.826
Glucocorticoid cluster					
NR3C1: GR-alpha	1.0	1.2	1.2	0.9	0.107
NR3C1: GR-beta	2.3	1.7	1.5	1.6	0.003

1B | Young Adulthood

Bipolar offspring	**No disorder**	**Lifetime mood disorder**	**Future mood disorder**	**Lifetime non-mood disorder**	
	n = 23	**n = 37**	**n = 13**	**n = 13**	
	Median FC	**Median FC**	**Median FC**	**Median FC**	***p***
Cluster 1					
IL1A	1.48	0.85	1.33	0.70	0.04
IL1B	2.12	1.39	1.25	2.02	0.07
CCL20	3.33	1.45	3.80	2.15	0.33
IL6	2.25	1.80	2.14	2.58	0.18
PTX3	1.48	1.18	1.07	1.76	0.38
IRAK2	3.09[a]	2.02[a]	2.13	2.68	< 0.001
TNF	0.77	0.72	0.77	0.93	0.04
BCL2A1	1.74	1.11	1.62	1.36	0.16
CXCL2	3.50	1.40	1.68	3.31	0.08
PTGS2	1.03	0.91	0.83	1.14	0.01
ADM	2.56[a]	2.31[a]	2.81[a]	2.06[a]	< 0.001
BTG3	2.08[a]	1.90[a]	1.99[a]	1.94	0.001
SERPINB2	1.97	1.09	1.17	1.56	0.14
PDE4B	2.08	1.21	2.11	1.12	0.02
TNFAIP3	1.31	1.20	1.23	1.09	0.002
ATF3	1.21	1.05	1.46	1.43	0.01
CDC42	2.58[a]	2.18[a]	2.03[a]	2.79[a]	< 0.001
MAFF	3.11[a]	2.24[a]	2.13[a]	2.93	< 0.001
DUSP2	1.63	1.25	1.58	1.70	0.43
EREG	4.95	2.50	3.58	2.21	0.07
Cluster 2					
CCL7	39.39	11.23	6.47	25.14	0.05
FCAR	1.68	1.23	1.12	1.36	0.002
PTPN7	2.65[a]	1.72[a]	1.62	2.62[a]	0.001
THBD	2.15	1.34	1.92	1.20	0.001
RGC32	6.16	2.90	3.78	5.80	0.003
STX1A	9.00	3.95	2.49	6.59	0.022
EMP1	4.19[a]	2.61	3.65	3.16	0.001
NAB2	4.26[a]	2.79[a]	2.82[a]	5.47[a]	< 0.001
MAPK6	1.64[a]	1.21	1.42	1.37	0.001
DHRS3	2.07	1.04	1.71	1.46	0.07
MXD1	1.52	1.37	1.57	1.81	0.20

1B | *(Continued)*

Bipolar offspring					
	No disorder	**Lifetime mood disorder**	**Future mood disorder**	**Lifetime non-mood disorder**	
	n = 23	**n = 37**	**n = 13**	**n = 13**	
	Median FC	**Median FC**	**Median FC**	**Median FC**	***p***
Cluster 2					
IL1R1	1.96	1.26	2.08	1.06	0.03
CCL2	3.61	1.01	1.76	1.08	0.04
EGR3	3.11	2.08	1.44	2.22	0.03
CD9	3.47	1.66	1.44	3.96	0.02
FABP5	1.17	0.91	1.16	0.98	0.25
Interferon cluster					
IFI44	0.99	1.06	1.27	1.18	0.32
IFI44L	0.57	0.79	1.12	0.93	0.68
IFIT3	0.59	0.68	0.88	0.89	0.41
HSPA1A	0.39[a]	0.49[a]	0.51[a]	0.64	< 0.001
ADAM17	0.89	0.95	0.80	0.88	0.49
IFI27	0.72	1.08	1.12	0.97	0.86
Glucocorticoid cluster					
NR3C1: GR-alpha	0.95	0.88	0.92	1.0	0.42
NR3C1: GR-beta	1.68[a]	1.35	1.28	2.0[a]	0.001

1C | Adulthood

Bipolar offspring				
	No disorder	**Lifetime mood disorder**	**Lifetime non-mood disorder**	
	n = 27	**n = 53**	**n = 15**	
	Median FC	**Median FC**	**Median FC**	***p***
Cluster 1				
IL1A	0.23	0.55	1.7	0.76
IL1B	0.38	0.75	1.3	0.11
CCL20	0.31	0.62	2.8	0.88
IL6	0.66	0.84	1.85	0.38
PTX3	0.66	0.74	0.87	0.36
IRAK2	0.29	0.56	0.8	0.03
TNF	0.84	0.98	1.25	0.85
BCL2A1	0.87	0.97	1.20	0.33
CXCL2	0.49	0.84	1.1	0.09
PTGS2	0.58	0.68	0.9	0.06
ADM	0.99	1.14	1.04	0.56
BTG3	0.71	0.89	1.0	0.25
SERPINB2	0.74	0.87	1.0	0.90
PDE4B	0.64	0.69	1.05	0.29
TNFAIP3	0.54	0.70	1.4	0.77
ATF3	0.79	0.96	1.19	0.08
CDC42	1.04	1.10	1.1	0.81
MAFF	0.58	0.92	0.9	0.18
DUSP2	0.78	0.93	1.2	0.74
EREG	0.88	1.04	1.4	0.13
Cluster 2				
CCL7	0.41	0.55	1.64	0.87
FCAR	–	–	–	NA
PTPN7	0.62	0.83	1.03	0.28
THBD	1.04	1.24	0.9	0.60
RGCC	0.59	0.66	1.1	0.57
STX1A	0.67	0.75	1.42	0.23
EMP1	0.60	0.66	1.01	0.29
NAB2	0.69	0.85	1.58	0.52
MAPK6	0.97	1.07	0.96	0.82
DHRS3	0.77	0.95	1.0	0.73
MXD1	0.92	1.05	1.0	0.59
IL1R1	1.19	0.78	0.9	0.12

1C | *(Continued)*

Bipolar offspring				
	No disorder	**Lifetime mood disorder**	**Lifetime non-mood disorder**	
	n = 27	**n = 53**	**n = 15**	
	Median FC	**Median FC**	**Median FC**	***p***
Cluster 2				
CCL2	0.55	0.93	1.5	0.85
EGR3	0.43	0.61	0.89	0.22
CD9	0.82	0.78	3.5	0.41
FABP5	1.09	1.19	0.86	0.33
Interferon Cluster				
IFI44	1.25	1.40	1.31	0.02
IFI44L	–	–	–	NA
IFIT3	1.41	1.68	1.77	0.04
HSPA1A	1.18	1.11	1.03	0.47
ADAM17	–	–	–	NA
IFI27	1.45	1.94	2.6	0.18
Glucocorticoid receptors				
NR3C1: GR-alpha	1.11	1.07	1.12	0.13
NR3C1: GR-beta	1.10	1.23	1.08	0.49

Table Legend Supplementary Table 1A-C:
The quantitative value obtained from Q-PCR is a cycle threshold (Ct). The fold change (FC) values between different groups were determined from the normalized Ct values (Ct gene – Ct housekeeping gene (ABL)), via the ΔΔCt method (User Bulletin, Applied Biosystems, Foster City, California). The median fold change of healthy controls (HC) set to 1. Data are expressed relative to this HC-value. Values > 1: bipolar offspring have a higher expression than HC. Values < 1: bipolar offspring have a lower expression than HC. NA means the particular gene expression was not determined. Level of significance was set at 0.001 (Bonferroni correction: p 0.05/44 genes = 0.001).
[a] = post hoc analyses revealed a significant difference in bipolar subgroups in comparison with healthy controls. None of the genes showed significant differences within bipolar offspring subgroups.

Table S2| Biological parameters: comparisons of unaffected offspring with offspring with current and lifetime mood disorders, adjusted for gender and age.

	Bipolar offspring							
	No Disorder		Lifetime Mood disorder		Current Mood disorder			
	n	Beta (CI 95%)	n	Beta (CI 95%)	n	Beta (CI 95%)	Wald X^2	*p*
Gene expression signature[a]								
Adolescence	7	0[b]	4	-0.081 (-0.322-0.161)	3	0.007 (-0.247-0.261)	1.549	0.46
Young adulthood	23	0[b]	31	-0.079 (-0.211-0.053)	6	-0.171 (-0.394-0.052)	2.923	0.25
Adulthood	27	0[b]	39	0.057 (-0.044-0.159)	14	0.092 (-0.039-0.222)	3.002	0.22
PTX3								
Adolescence	27	0[b]	17	0.042 (-0.144-0.227)	18	-0.054 (-0.235-0.128)	0.885	0.64
Young adulthood	15	0[b]	5	-0.065 (-0.440-0.310)	9	-0.007 (-0.322-0.307)	0.185	0.91
Adulthood	24	0[b]	34	0.018 (-0.148-0.184)	6	-0.057 (-0.341-0.227)	0.669	0.72
IL-1B								
Adolescence	29	0[b]	15	-0.036 (-0.184-0.113)	18	0.057 (-0.085-.0198)	1.148	0.56
Young adulthood	23	0[b]	35	-0.065 (-0.191-0.063)	6	0.106 (-0.113-0.324)	3.488	0.18
Adulthood	27	0[b]	34	-0.097 (-0.229-0.036)	13	-0.009 (-0.183-0.166)	2.052	0.36
CCL2								
Adolescence	29	0[b]	15	0.022 (-0.058-0.102)	18	0.006 (-0.070-0.082)	0.325	0.85
Young adulthood	23	0[b]	35	0.012 (-0.075-0.099)	6	0.054 (-0.095-0.203)	1.321	0.52
Adulthood	27	0[b]	34	-0.009 (-0.088-0.070)	13	-0.036 (-0.140-0.068)	0.459	0.80
S100B								
Adolescence	25	0[b]	14	0.000 (0.000- -0.001)	17	0.000 (0.000- -0.001)	1.038	0.60
Adulthood	24	0[b]	36	0.000 (0.000- -0.001)	14	0.000 (-1.375^{e005}- 0.000)	3.482	0.18
BDNF								
Adolescence	25	0[b]	14	0.001 (-0.044-0.046)	17	0.012 (-0.031-0.054)	0.260	0.88
Adulthood	24	0[b]	36	-0.01 (-0.070-0.045)	14	0.001 (-0.072-074)	0.239	0.89

[a] as expressed in relative percentage of positive genes.

[b] Set to 0 because redundant

APPENDIX: GENE SYMBOLS AND APPROVED NAMES

Gene symbols	Approved Names*
Cluster 1	
IL1A	*interleukin 1, alpha*
IL1B	*interleukin 1, beta*
CCL20	*chemokine (C-C motif) ligand 20*
IL6	*interleukin 6*
PTX3	*pentraxin 3, long*
IRAK2	*interleukin-1 receptor-associated kinase 2*
TNF	*tumor necrosis factor*
BCL2A1	*BCL2-related protein A1*
CXCL2	*chemokine (C-X-C motif) ligand 2*
PTGS2	*prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase)*
ADM	*adrenomedullin*
BTG3	*BTG family, member 3*
SERPINB2	*serpin peptidase inhibitor, clade B (ovalbumin), member 2*
PDE4B	*phosphodiesterase 4B, cAMP-specific*
TNFAIP3	tumor necrosis factor, alpha-induced protein 3
ATF3	*activating transcription factor 3*
CDC42	*cell division cycle 42*
MAFF	*v-maf avian musculoaponeurotic fibrosarcoma oncogene homolog F*
DUSP2	*dual specificity phosphatase 2*
EREG	*epiregulin*
Cluster 2	
CCL7	*chemokine (C-C motif) ligand 7*
FCAR	Fc fragment of IgA, receptor for
PTPN7	*protein tyrosine phosphatase, non-receptor type 7*
THBD	*thrombomodulin*
RGCC	*regulator of cell cycle*
STX1A	*syntaxin 1A (brain)*
EMP1	*epithelial membrane protein 1*
NAB2	*NGFI-A binding protein 2 (EGR1 binding protein 2)*
MAPK6	*mitogen-activated protein kinase 6*
DHRS3	*dehydrogenase/reductase (SDR family) member 3*
MXD1	*MAX dimerization protein 1*
IL1R1	*interleukin 1 receptor, type I*
CCL2	*chemokine (C-C motif) ligand 2*
EGR3	*early growth response 3*

Gene symbols	Approved Names*
Cluster 2	
CD9	*CD9 molecule*
FABP5	*fatty acid binding protein 5 (psoriasis-associated)*
Cluster 3	
IFI44	*interferon-induced protein 44*
IFI44L	*interferon-induced protein 44-like*
IFIT3	*interferon-induced protein with tetratricopeptide repeats 3*
HSPA1A	*heat shock 70kDa protein 1A*
ADAM17	*ADAM metallopeptidase domain 17*
IFI27	interferon, alpha-inducible protein 27
Cluster 4	
NR3C1: GR-α	*nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor-alpha)*
NR3C1: GR-β	*nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor-beta)*

*HUGO Gene Nomenclature Committee (www.genenames.org)

Chapter 6

The early signs of bipolar disorder. A study on symptomatology among prospectively followed bipolar offspring

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Under review

ABSTRACT

Objective

Early recognition of bipolar disorder (BD) remains challenging. In this study, we aim to explore the early signs of BD among bipolar offspring prospectively followed from adolescence into adulthood.

Methods

The Dutch Bipolar Offspring Study (n = 140, age range 12-21 years, since 1997) psychiatrically evaluated bipolar offspring at baseline, 1-, 5-, and 12-year follow-up using the K-SADS-PL and the SCID. Subthreshold and threshold symptomatology was assessed with the K-SADS-PL at baseline.

Results

Among offspring with a (mild) unipolar depressive disorder at baseline, subthreshold manic symptoms (elated mood, decreased need of sleep and racing thoughts), suicidal ideation and middle insomnia were specifically associated with a transition to BD. Among offspring without any mood disorders at baseline, the development of a first unipolar mood disorder was associated with subthreshold depressive mood, recurrent thoughts of death, marked feeling of tension, marked self-consciousness and compulsions.

Limitations

Relatively small sample size and low transition rate to BD.

Conclusions

The study extends our knowledge on the prodromal stadia of bipolar and unipolar mood disorders among bipolar offspring. Findings of this study indicate that subthreshold manic symptomatology may be an important key prognostic factor for a switch from unipolar depressive disorder to BD onset. Findings of this study provide potential targets for early recognition and preventive intervention programs.

BACKGROUND

The early trajectories of bipolar disorder (BD) are still poorly understood. Bipolar disorder typically debuts with a (mild) depressive episode during adolescence or early adulthood followed by a first (hypo)manic episode several years later (Duffy et al., 2014; Mesman, Nolen, Reichart, Wals, & Hillegers, 2013). Early identification of BD is challenging, with an approximate diagnostic delay of 10 years from the index episode onwards (Altamura et al., 2010; Drancourt et al., 2013). In retrospect most patients report their first discernable signs and symptoms even years before the onset of the first mood episode including depressed mood, irritability, subthreshold manic symptoms, mood swings, irritability, aggressiveness, sleep disturbances and hyperactivity, as well as non-mood related features including impaired attention and concentration, anxiety, worry and energy changes (for reviews see Hauser & Correll, 2013; Malhi et al., 2014; Skjelstad et al., 2010; Correll et al., 2014a). Reasons for the diagnostic delay of BD are the atypical course of disease, misdiagnosis by clinicians, but also delayed help-seeking. The diagnostic delay and the concomitant treatment delay are associated with serious consequences including suicidality and increased psychosocial burden (Altamura et al., 2010; Drancourt et al., 2013; McCraw, Parker, Graham, Synnott, & Mitchell, 2014). This, together with the progressive nature of BD (e.g. Berk et al., 2010), stresses the importance of a better understanding of the early trajectories. Ultimately, this may lead to earlier detection of those at risk and development of targeted early interventions programs, as successfully illustrated in the field of psychosis in the past decade (Ising et al., 2014; Yung et al., 2005; Yung et al., 2008). In this study, we focus on the early prodromal features of bipolar and unipolar depressive disorders among offspring at high familial risk for developing BD, prospectively followed for 12 years.

As a positive family history for BD is one of the most robust predictors for BD (Craddock & Sklar, 2013; Gottesman, Laursen, Bertelsen, & Mortensen, 2010), prospective studies among the offspring of patients with BD (bipolar offspring) are of interest. In the past decades, numerous studies among the offspring of patients with BD (bipolar offspring) have shown that these children are at increased risk for the development of BD, unipolar depressive disorders, and other non-mood disorders (e.g. DelBello & Geller, 2001; Duffy et al., 2011). In general, prospective bipolar offspring studies have shown that BD typically presents with a (mild) depressive episode in 67-88%, in general years before the onset of the first (hypo) manic episode (Duffy et al., 2014; Mesman et al., 2013; Axelson et al., 2015). In retrospect, this depressive episode can be identified as the first episode of BD, but often is preceded by a variety of affective and behavioral symptomatology. Nurnberger et al. (2011) reported that anxiety disorders and externalizing disorders were important antecedents for major affective disorders (i.e. mood) in bipolar offspring. The 16-year follow-up of the Amish bipolar offspring study followed a more dimensional approach for clinical observations and found that between age 7-12 offspring developing BD were best identified by anxiety symptoms, sad mood, low energy, decreased sleep, fearfulness and role impairment (Egeland et al., 2012). In a 15+ year follow-up, Duffy et al. (2010; 2014) noted that the

early course of BD generally follows a course starting with anxiety and sleeping disorders during childhood, followed by minor mood disorders, major depressive episodes and (hypo) mania years later. They also found that 48% of the bipolar offspring met criteria of BD not otherwise specified (BD-NOS) prior to BD onset, suggesting a role for subthreshold manic symptoms as well. A recent study of the Pittsburgh Bipolar Offspring Study also showed that especially subthreshold manic or hypomanic symptoms were a diagnostic risk factor for subsequent onset of a manic, mixed or hypomanic episode onset (Axelson et al., 2015). To date, most prospective offspring studies have have focused on a clinical categorical outcome of bipolar offspring, whilst especially a more dimensional approach, i.e. identification of subthreshold symptoms, may be essential for early recognition and the development of early intervention programs.

In a previous paper, we reported on the categorical psychopathology outcome of the 12-years follow-up of the Dutch bipolar offspring cohort. At a mean age of 28, 54% of the offspring had developed any kind of mood disorder including 13% bipolar spectrum disorders and overall 72% of the offspring were assigned with any DSM-IV axis I disorder. BD debuted in 90% of the cases with a (mild) depressive episode (Mesman et al., 2013). In the present paper, we aim to go beyond a categorical approach and explore the early threshold as well as subthreshold symptomatology of mood disorders among bipolar offspring as obtained by the K-SADS-PL at a mean age of 16 years (baseline assessment) and compared this across diagnostic outcome groups as observed 12 years later at a mean age of 28 years (final assessment). The primary aim of the study was to explore whether specific symptoms could predict a transition to BD among offspring with a unipolar depressive disorder (UD) at adolescent age. The second aim of the study was to examine whether we could predict the onset of a first mood disorder among offspring without any mood disorder diagnosis at adolescent age.

METHODS

Sample

The Dutch Bipolar Offspring Study is a longitudinal fixed cohort established in 1997. In total, 140 offspring (aged 12-21 years) from 86 families with one bipolar parent (74% bipolar I; 26% bipolar II) were recruited in the years 1997-1999. Families were included if all offspring in the age range 12-21 agreed to participate. Offspring with a severe physical illness or an IQ below 70 were excluded. Participants were recruited through the Dutch Association for Bipolar Patients with bipolar disorder and Relatives (VMDB; 62 families, 102 children) and through outpatient clinics in nine psychiatric hospitals (24 families; 38 children). Bipolar offspring were assessed at baseline, one-, five-, and 12-years of follow-up, T1-T4, respectively (Wals et al., 2001; Reichart et al., 2004; Hillegers et al., 2005; Mesman et al., 2013 respectively). In total, 108 (77%) offspring were followed for the full 12-years. The study was approved by the Medical Ethical Review Committee of the University Medical

Center Utrecht. Written informed consent was obtained from both offspring and their parents after a complete description of the study. A more detailed description of the study design and recruitment procedure has been described elsewhere (Wals et al., 2001).

Procedures

Bipolar offspring were psychiatrically evaluated at all four assessments. All psychiatric interviews were administered by intensively trained interviewers with graduate degrees in psychology or medicine. All interviews were evaluated in consensus meetings with psychiatrists certified in child and adolescent as well as adult psychiatry.

Assessment of lifetime DSM-IV axis I diagnoses

At baseline and one-year follow-up DSM-IV diagnoses were assessed by a direct semi-structured interview with both the child and parent(s) using the Kiddie Schedule of Affective Disorders and Schizophrenia Present and Lifetime Version (K-SADS-PL) (Kaufman et al., 1997). The K-SADS-PL is an interviewer-oriented diagnostic interview designed to assess current (past 2 months) and past DSM-IV symptoms resulting in DSM-IV axis I diagnoses in children and adolescents by interviewing the parent(s) and child separately. In cases of disagreement between child and parent about the presence of a symptom, greater weight was given to parents' reports of observed behavior and children's reports of subjective experiences (Kaufman et al., 1997). Besides the K-SADS-derived diagnoses, we also screened for DSM-IV pervasive developmental disorders. Because of the increasing age of the offspring, the K-SADS-PL was replaced by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (First, Spitzer, Gibbon, & Williams, 1997) at the assessment of the five year follow-up. Lifetime DSM-IV diagnoses are based on all psychiatric interviews that took place during the study. For all diagnoses age of onset was established. Because of the broad determined criteria of bipolar disorder not otherwise specified (BD-NOS) back in 1997 (Goodwin & Jamison, 2007), BD-NOS was not assigned in our studies. A detailed overview of the psychopathology of the 12-year follow-up is published elsewhere (Mesman et al., 2013).

Assessment of symptomatology

Prodromal features were evaluated using individual symptom and sum scores of the K-SADS-PL administered at baseline (T1). The K-SADS-PL interview provides specific probes and scoring criteria to assess each symptom (Kaufman et al., 1997). Symptoms were rated using a 1-3 point scale separately in both the child and the parent: 1) symptom not present; 2) symptom at subthreshold level; and 3) symptom at threshold level. To determine whether a symptom meets the threshold or subthreshold level, severity, frequency and duration of the symptom and level of impairment are to be examined by the assessor. For each symptom a detailed description of the different levels is provided in the K-SADS-PL interview. Parent and child ratings were merged into a summary score per item according to the K-SADS-PL manual (Kaufman et al., 1997). The K-SADS-PL documents a total of 78 symptoms/items.

Data analyses

Clinician-rated threshold and subthreshold symptomatology as obtained by the K-SADS-PL at baseline (T1) was compared across diagnostic outcome groups as observed 12 years later at follow-up (T4).

Symptomatology at baseline (T1)

We used two approaches to examine symptomatology. First, we explored all symptoms at the individual level. Although we are interested in the full spectrum of subthreshold and threshold symptomatology, due to the relatively small group sizes, symptoms were dichotomized. As we were especially interested in subthreshold symptomatology in the prodromal stage, symptoms were recoded in not present (0) versus present meeting subthreshold or threshold criteria (1). A total of 78 symptoms were explored. Second, six K-SADS-PL sum scores were computed based upon the 78 K-SADS-PL items: depression (21 items), mania (4), anxiety (23), externalizing (12 items including ADHD, oppositional defiant- and conduct disorder), substance use (6) and a residual scale (12 items including psychotic symptoms, enuresis/encopresis, eating disorders and tic disorders). For specific symptoms/items per category see the supplemental sTable 1.

Diagnostic outcome categories

Of the original 140 bipolar offspring participating at baseline (T1), 32 offspring were lost to follow-up at 12 year follow-up (T4) (retention rate 77%). Offspring lost to follow-up were excluded for analyses, as the diagnostic outcome was unclear. However, two of them had developed BD before dropping out from the study and could therefore be included. Offspring with a BD I or II diagnosis at T1 (n = 4; of which 1 also was lost for follow-up) were excluded from the analyses, resulting in a total sample of 107 subjects.

To dissect for a possible early and late prodrome for BD onset, we chose to differentiate for offspring with already a unipolar depressive disorder (UD, n = 29) versus those without any mood disorder (NoMD, n = 78) at baseline. Next, offspring were assigned to a diagnostic outcome category based upon psychopathology outcome after 12-year follow-up. An illustration of the course of psychopathology and the transition among diagnostic outcome categories over 12-years follow-up is shown in Figure 1. In order to investigate aims of the study we ran two series of comparisons: A and B.

In series A (the primary aim of the study) we examined whether specific symptoms reported at T1 could predict a transition to BD among UD offspring at T1 (n = 29). Based upon psychopathology outcome at the 12-years follow-up offspring were assigned to two possible outcome categories: 1) transition to BD (UD→BD, n = 10) and 2) no transition (UD→UD, n = 19).

In series B we examined whether one could predict the development of mood disorders among NoMD offspring (n = 78) at T1. Offspring were assigned into: 1) transition to any mood disorder (AnyMD) (NoMD→AnyMD, n = 28) and 2) no transition (NoMD=NoMD, n = 50) after 12-years follow-up.

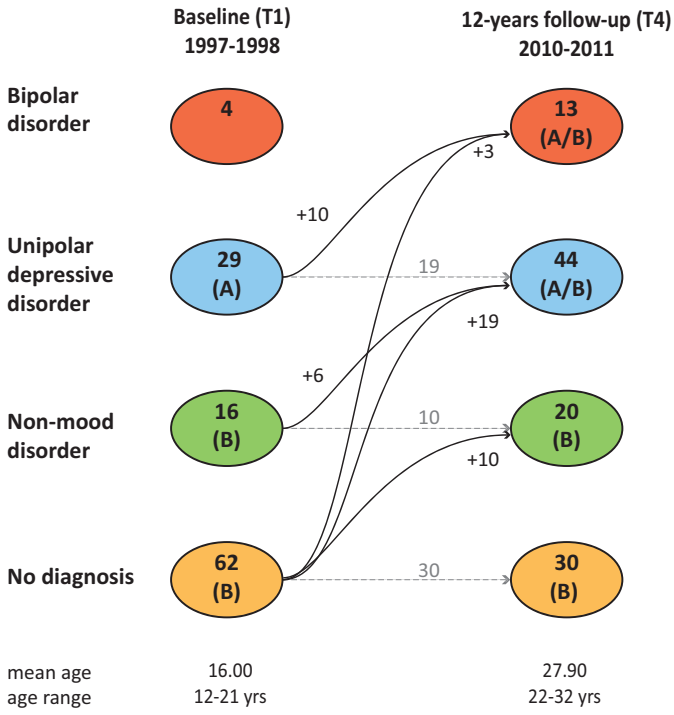

Figure 1 | Flowchart of the transition of psychopathology between T1 and T4 of the Dutch Bipolar Offspring Study.

A and B refer to the performed analyses series. A = prodromal features of (hypo)mania onset, transition from unipolar depressive disorder at T1 to BD at T4; B = prodromal features of mood disorders among offspring without a mood disorder at T1. For a full description of the categories we refer to the section data analyses of the method section.

Statistical analyses

Demographic group characteristics were compared using one-way ANOVA or Fisher exact tests as appropriate. Individual symptom ratings as identified with the K-SADS-PL were evaluated using Fisher exact tests. The predictive value of the K-SADS-PL sum scores was explored using stepwise backward (likelihood ratio) logistic regression analyses were performed. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp, Armonk, NY, USA). For all analyses the two-sided alpha level for statistical significance was set at $p < 0.05$. Because of the exploratory nature of this study, no adjustments for multiple comparisons were performed.

RESULTS

Demographic offspring- and parental characteristics are provided in table 1. No significant differences across the four main outcome groups were observed. A detailed presentation of the prevalence of individual threshold and subthreshold symptoms in adolescent bipolar offspring, including detailed statistical analyses is presented in supplemental table Table S1 online. Mean scores of K-SADS-PL sum scores are presented in Table 1.

Prodromal features of (hypo)mania onset: transition from UD to BD (series A)

A comparison of UD = UD and UD→BD offspring yielded 5 symptoms that significantly differentiated groups (Table S1). Three out of four manic symptoms were significantly more common in the UD→BD group than in the UD = UD group: elated mood 60% vs 11%, p = 0.009, decreased need of sleep 50% vs 5%, p = 0.011 and racing thoughts 40% vs 5%, p = 0.036. Increased goal directed behavior was also more frequently reported in the UD→BD group, yet not significant (40% vs 16%, p = 0.193). Of the depressive symptoms, suicidal ideation (50% vs 11%, p = 0.030) and middle insomnia (40% vs 5%, p = 0.036) appeared to be more frequent in UD→BD offspring. Manic symptoms for all four diagnostic outcome categories are depicted in Figure 2. This figure illustrates both the importance of subthreshold symptomatology, and its relative specificity for transition to BD. Next, looking at K-SADS-PL sum scores, logistic regression analysis revealed, in line with the findings noted above, that only manic symptoms were significantly associated with a transition to BD (OR 4.34, 95% CI: 1.09-17.37, Table 2). The depression scale showed a trend effect (OR: 1.29, 95% CI 0.95-1.76, p = 0.100). None of the other sum scores were significant.

Prodromal features of mood disorders (series B)

Only four symptoms significantly differentiated offspring developing any mood disorder (NoMD→AnyMD) versus those who did not (NoMD=NoMD) (Table S1). The NoMD→AnyMD group reported more frequently: recurrent thoughts of death (32% vs 6%, p = 0.006), marked feeling of tension/unable to relax (43% vs 14%, p = 0.006), marked self-consciousness (36% vs 12%, p = 0.019) and compulsions (25% vs 6%, p = 0.019). Logistic regression analyses were used to evaluate K-SADS-PL sum scores (Table 2). A transition towards MD onset (NoMD→AnyMD) was positively associated with overall depressive symptoms (OR: 1.79, 95% CI 1.20-2.66, p = 0.003). Moreover, the anxiety sum scores showed a trend effect (OR: 1.21, 95% 0.98-1.49, p = 0.075). None of the other sum scores were related to increased odds for the development of mood disorders.

Table 1 | **Demographic characteristics per diagnostic outcome category**

			Diagnostic outcome									
	All offspring		UD, n = 29 (A				NoMD, n =78 (B					
			UD→BD		UD = UD		NoMD→AnyMD		NoMD = NoMD			
	N	%	n	%	n	%	n	%	n	%	Test	*p*
Offspring characteristics												
Offspring	107	100	10		19		28		50			
Male	57	53	5	50	10	53	12	43	30	60	FET	0.540
	Mean	Range	Mean	Range	Mean	Range	Mean	Range	Mean	Range		
Age at baseline	16	12-21	16.2	12-21	16.6	12-21	15.9	12-21	15.8	12-21	*F* = 0.365	0.779
	N	%	n	%	n	%	n	%	n	%		
Parental characteristics												
Bipolar mother	62	58	6	60	8	42	17	61	31	62	FET	0.505
Bipolar I disorder	78	73	8	80	12	63	18	64	40	80	FET	0.320
K-SADS-PL sum scores			Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Depression scale, 21 items			34.1	8.5	30.3	4.5	23.3	2.3	22.1	2.2		
Mania scale, 4 items			6.0	1.8	4.4	0.9	4.1	0.4	4.3	0.9		
Anxiety scale, 23 items			31.8	4.3	30.3	4.0	27.7	3.9	26.0	2.7		
Externalizing scale, 12 items			16.7	4.7	15.5	4.1	13.6	2.3	13.8	3.1		
Substance use scale, 6 items			7.9	1.8	8.0	2.0	7.6	2.2	7.6	1.6		
Residual scale, 12 items			15.2	2.4	13.4	1.8	12.9	1.3	12.6	0.9		

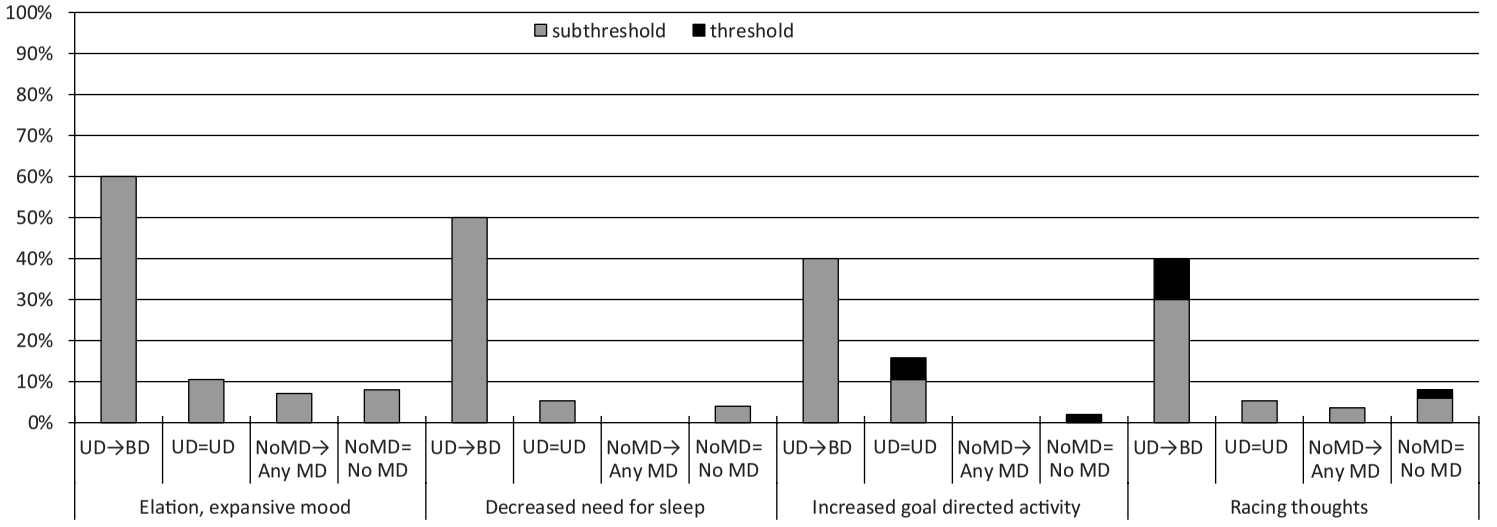

Figure 2 | Manic symptoms in adolescent bipolar offspring (T1)

Table 2 | Logistic regression analyses comparison A and B

					95% CI	
	B	**SE**	***p***	**Odds Ratio**	**Lower**	**Upper**
Comparison A: UD→BD						
Depression scale, 21 items	0.26	0.16	0.100	1.29	0.95	1.76
Mania scale, 4 items	**1.47**	**0.71**	**0.038**	**4.34**	**1.09**	**17.37**
Anxiety scale, 23 items	-0.21	0.25	0.395	0.81	0.50	1.31
Externalizing scale, 12 items	0.04	0.17	0.811	1.04	0.74	1.46
Substance scale, 6 items	-0.35	0.33	0.290	0.71	0.37	1.35
Residual scale, 12 items	0.41	0.28	0.145	1.51	0.87	2.61
Constant	-13.25	6.37	0.038	–	–	–
Comparison B: NoMD→AnyMD						
Depression scale, 21 items	**0.58**	**0.20**	**0.003**	**1.79**	**1.20**	**2.66**
Mania scale, 4 items	-0.88	0.74	0.237	0.42	0.10	1.78
Anxiety scale, 23 items	0.19	0.11	0.075	1.21	0.98	1.49
Externalizing scale, 12 items	-0.13	0.14	0.365	0.88	0.67	1.16
Substance scale, 6 items	0.03	0.15	0.856	1.03	0.76	1.39
Residual scale, 12 items	-0.40	0.28	0.887	0.96	0.55	1.67
Constant	-12.99	5.45	0.017	–	–	–

Series A: reference category UD = UD, R^2 Nagelkerke: 0.58, Model X^2 (2) = 15.684, p = 0.016.
Series B: reference category NoMD = NoMD, R^2 Nagelkerke: 0.28, Model X^2 (1) = 17.234, p = 0.008

DISCUSSION

Regarding the early trajectories, the most prominent finding of this study is the presence of subthreshold manic symptomatology and its relative specificity for transition to BD among adolescent offspring with an initial unipolar depressive disorder. This finding complements previous offspring studies, specifically the Pittsburgh bipolar offspring study (Axelson et al., 2015) and the Canadian offspring study (Duffy, 2010). Moreover, findings are in line with the 5 year follow-up of the course and outcome of bipolar youth (COBY) study in which 45% of the offspring diagnosed with a BD-NOS made the transition into BD-I or II within 58 weeks, especially those with a first or second degree family member (Axelson et al., 2011). Interestingly, none of the offspring of the NoMD→AnyMD category developing BD (n = 3) reported (sub)threshold manic symptoms at baseline (data not shown). Taken together, these findings underscore the importance of detailed evaluation of subthreshold manic symptomatology in bipolar offspring with a history of (mild) mood episodes.

In terms of specific symptomatology associated with future BD, suicidal ideation and middle insomnia were also more frequently reported. Looking at sleep disturbances, the finding of middle insomnia, and decreased need for sleep is in line with a large body of

evidence that sleep disturbances are associated with BD, also prior onset (Duffy, 2010; Duffy et al., 2014; Ritter, Marx, Bauer, Leopold, & Pfennig, 2011; Ritter et al., 2012; Egeland et al., 2012). The association of suicidal ideation and the transition to BD has been studied before in several studies, but results thus far have been inconsistent (Biederman et al., 2009; Kochman et al., 2005; Strober & Carlson, 1982; in Uchida et al., 2015). In sum, besides subthreshold manic symptomatology, sleep disturbances and suicidal ideation possibly have prognostic value to predict a future BD onset, however, findings require replication and further study.

With regard to the prodromal features of development of any mood disorders, we found that subthreshold depressive symptomatology including depressive mood, recurrent thoughts of death, but also more general anxiety symptoms including marked feeling of tension, marked self-consciousness and compulsions were associated with mood disorder onset. These findings are in line with the existing literature (Axelson et al., 2015; Duffy, 2010; Duffy et al., 2014; Nurnberger, Jr. et al., 2011; Skjelstad et al., 2010; Skjelstad, Malt, & Holte, 2011). Although, findings of the prodromal features prior the first mood episode may not converge to the offspring developing BD, findings of this study appear to be in line with previous studies and seem to suggest a sequential onset of BD starting with generic symptomatology including subthreshold anxiety symptoms and mild depressive symptomatology followed by a (mild)depressive episode, subthreshold manic symptomatology and finally a full threshold (hypo)manic episode (Axelson et al., 2015; Correll et al., 2014a; Duffy, 2010; Duffy et al., 2014).

Strengths and limitations

Findings of this study should be interpreted in the light of some limitations. The first limitation is the relatively high (13%) but in absolute numbers still low (n = 13) transition rate to BD which led to inherent power issues in statistical analyses and restricted the possibilities of more sophisticated types of analyses. Second, the majority of offspring developed BD type II. Therefore, one may wonder whether findings generalize for BD type I. Furthermore, as this study only comprises bipolar offspring, results may not generalize to other populations. However, several retrospective and prospective patient studies have also shown the validity of subthreshold manic symptomatology preceding both type I and II in more general patient- and help seeking populations (Boschloo et al., 2014; Correll et al., 2014a; Bechdolf et al., 2014; Faedda et al., 2015). Third, despite the prospective nature of the study, age of onset and diagnoses were assessed retrospectively at baseline and between assessments (at 1-, 5- and 12 years follow-up). Fourth, while we have data on the age of onset of diagnostic categories, we have less exact information about the onset and duration of the specific reported symptoms. Hence, we can only speculate about the sequential order of specific symptoms. To this extent, recently developed interviews such as the Bipolar Prodrome and Symptom Scale-Prospective (BPSS-P) (Correll et al., 2014b) may provide important heuristics for future prospective studies. The key strengths of the present study are its long follow-up, low retention rate and detailed clinical psychiatric evaluations

including subthreshold symptomatologat baseline. Therefore, this study further extends the knowledge on the early prodrome of mood disorders in bipolar offspring

CONCLUSION

Bipolar offspring are at increased risk to develop BD. In a previous study (Mesman et al., 2013), we showed that 13% out of 108 offspring developed a bipolar spectrum disorder. About 90% of the offspring with a BD debuted with a mild unipolar depressive episode. The present work extended our knowledge regarding the early trajectories of BD by a thorough study of subthreshold and threshold symptomatology at adolescent age. This study demonstrated that subthreshold manic symptomatology and possibly additional specific symptomatology such as suicidal ideation and sleep disturbance, appear key prognostic factors for BD onset. Furthermore, subthreshold anxiety and depressive symptomatology appear to be associated with a firer onset. Findings of this study contribute to the construction of a clinical risk profile and provide potential targets for the development of early recognition tools and intervention programs.

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SUPPLEMENTAL MATERIAL

Table S1 | Prevalence (%) of threshold and subthreshold symptoms in adolescent bipolar offspring (T1).

	All bipolar offspring			Series A			Series B		
	(sub)threshold[a]	subthreshold	Percent Rank[b]	UD→BD	UD = UD		NoMD→ AnyMD	NoMD = NoMD	
K-SADS-PL symptom items	**%**	**%**		**%**	**%**	***p***	**%**	**%**	***p***
DEPRESSION									
Depressed mood	47	31	3	100	100		39	20	
Irratibility and Anger	28	20	8	80	58		14	14	
Anhedonia, lack of interest, apathy, low motivation, or boredom	24	16	12	80	63		14	4	
Concentration, inattention, or slowed thinking	18	11	18	50	53		4	6	
Indecision	6	6	30	40	11		–	–	
Decreased appetite	15	10	21	40	42		11	2	
Weight Loss	7	5	29	10	26		–	2	
Increased appetite	4	3	32	30	5		–	–	
Weight gain	2	–	34	10	–		4	–	
Recurrent thoughts of death	31	22	6	80	68		32	6	**
Suicidal ideation	10	6	26	50	11	*	11	2	
Suicidal acts – seriousness	4	4	32	20	5		4	–	
Suicidal acts – Medical Lethality	–	–	36	–	–		–	–	
Non-suicidal psysical self-damaging acts	10	9	26	40	21		7	2	
Initial insomnia	30	20	7	60	53		25	18	
Middle insomnia	8	6	28	40	5	*	11	2	
Terminal insomnia	5	2	31	10	11		4	2	
Circadian reversal	1	–	35	–	5		–	–	
Non-restorative sleep	20	14	16	50	53		7	8	
Hypersomnia	10	7	26	30	32		4	–	
Fatigue, lack of energy and tiredness	23	16	13	50	74		4	10	
MANIA									
Elation, Expansive mood	13	13	23	60	11	**	7	8	
Decreased need for sleep	7	7	29	50	5	*	–	4	
Increased goal directed activity	7	6	29	40	16		–	2	
Racing thoughts	9	7	27	40	5	*	4	8	

Table S1 | *(Continued)*

	All bipolar offspring			Series A			Series B		
	(sub)threshold[a]	subthreshold	Percent Rank[b]	UD→BD	UD = UD		NoMD→ AnyMD	NoMD = NoMD	
K-SADS-PL symptom items	%	%		%	%	*p*	%	%	*p*
ANXIETY									
Panic Attacks	7	3	29	20	11		4	4	
Fears Calamitious Event that will cause separation	10	7	26	20	21		7	6	
Fears Harm Befalling Attachment Figure	22	21	14	40	16		25	20	
School reluctance/refusal	14	10	22	30	37		11	4	
Fears sleeping away from home/sleeping alone	16	11	20	20	32		21	6	
Fears being alone at home	13	10	23	20	16		11	12	
Shrinks from contact	36	33	5	20	53		39	32	
Fear of social situations	21	19	15	30	37		21	12	
Social involvement with familiar people	5	4	31	–	5		7	4	
Agoraphobia/Specific phobia	21	18	15	30	21		21	18	
Avoidance	17	14	19	30	21		18	12	
Unrealistic worry about future	25	19	11	70	37		21	14	
Somatic complaints	27	18	9	60	53		25	12	
Marked Self-consciousness	27	20	9	60	37		36	12	*
Marked feeling of tension/unable to relax	36	27	5	70	68		43	14	**
Compulsions	16	12	20	30	21		25	6	*
Obsessions	3	1	33	20	5		–	–	
Traumatic events	74	NA	1	80	79		71	72	
Recurrent thougths or images of event	7	NA	29	20	11		–	6	
Efforts to avoid thoughts or feelings	3	NA	33	–	5		–	4	
Nightmares	4	NA	32	10	5		–	4	
Insomnia	2	NA	34	–	–		4	2	
Irritability or outbursts of anger	1	NA	35	10	–		–	–	
EXTERNALIZING									
Difficulty sustaining attention on tasks or play activities	24	20	12	60	32		18	18	
Easily distracted	21	18	15	60	37		21	8	
Difficulty remaining seated	26	20	10	50	26		29	20	
Impulsivity	23	19	13	40	26		21	20	
Loses temper	23	21	13	50	37		11	20	
Argues a lot with adults	19	15	17	20	21		14	20	

Table S1 | *(Continued)*

	All bipolar offspring			Series A			Series B		
K-SADS-PL symptom items	**(sub)threshold[a] %**	**subthreshold %**	**Percent Rank[b]**	**UD→BD %**	**UD = UD %**	***p***	**NoMD→ AnyMD %**	**NoMD = NoMD %**	***p***
EXTERNALIZING									
Disobeys rules a lot	17	14	19	30	26		14	12	
Lies	10	9	26	20	11		4	12	
Truant	4	2	32	–	11		–	4	
Initiates physical fights	8	7	28	10	11		7	8	
Bullies, threatens, or intimidates others	12	9	24	20	16		14	8	
Nonagressive stealing	6	5	30	20	16		4	–	
SUBSTANCE USE									
Cigarette/tobacco use	28	NA	8	30	32		29	26	
Alcohol abuse	49	NA	2	60	53		32	54	
Alcohol: What's the most you drank in a single day? > 1-2 drinks	40	NA	4	50	37		36	42	
Alcohol: What's the most number of days in a week? > 1-2 days	18	NA	18	10	21		18	18	
Concern from others about drinking	11	NA	25	–	21		18	6	
Substance use	21	17	15	30	32		25	12	
RESIDUAL									
Enuresis night time	28	28	8	50	26		29	24	
Enuresis day time	4	4	32	10	5		4	2	
Encopresis night time	2	–	34	–	5		–	2	
Encopresis day time	2	–	34	–	5		–	2	
Fear of becoming obse	9	7	27	30	11		11	4	
Emaciation	5	4	31	–	16		7	–	
Weight loss methods	3	1	33	20	5		–	–	
Eating binges or attacks	7	4	29	30	16		7	–	
Motor tics	7	4	29	30	5		7	4	
Phonic tics	7	2	29	30	5		7	2	
Hallucinations	5	3	31	10	5		4	4	
Delusions	3	2	33	10	–		–	4	

[a] Prevalence of threshold and subthreshold symptomatology. [b] Percent rank of symptom prevalence in bipolar offspring in general. Tied ranks were allowed. A heat map procedure was applied to indicate higher prevalence, i.e. color intensity corresponds to symptom prevalence. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Chapter 7

The validation of the Seven Up Seven Down (7U7D) among bipolar offspring: screening and prediction of mood disorders. Findings from the Dutch Bipolar Offspring Study

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ABSTRACT

Objective

To validate the Seven Up, Seven Down (7U7D), an abbreviated version of the General Behavior Inventory (GBI) as screener for mood disorders in individuals at risk for bipolar disorder and to test its ability to predict mood disorders in general and bipolar disorder (BD) specifically.

Methods

A total of 108 bipolar offspring from the Dutch Bipolar Offspring Study were assessed at baseline (T1), and at one year (T2), five years (T3) and 12 years (T4) follow-up. Psychopathology was assessed using the K-SADS-PL (T1, T2), the SCID (T3, T4) and the GBI (T1 and T4). Both cross-sectional (T4) and longitudinal analyses (from T1 to T4) were performed using area under the curve (AUC) statistics and logistic regression analyses.

Results

The performance of the 73-item GBI and the 14-item 7U7D was found to be equal. As screener for mood disorders at T4, the 7U7D showed fair diagnostic efficiency for the depression scale (AUC 0.68, $p < 0.1$, OR 1.53, 95% CI 1.15-2.03). Among offspring with a mood disorder, positive scores on the hypomania scale were associated with a BD diagnosis (OR 1.64, 95% CI 1.06-2.54). In terms of prediction of future onset of mood disorders between T1 and T4, the depression scale, but not the hypomania scale, was found to be associated with an increased risk for mood disorder onset (AUC 0.67, $p < 0.5$; OR 1.47, 95% CI 1.09-2.0). The 7U7D did not achieve statistically significant prediction of bipolar diagnoses.

Limitations

A relatively small sample size and low transition rate to BD.

Conclusions

This study shows further evidence for the potential of the 7U7D as brief screening instrument among individuals at risk for BD. In terms of prediction, the 7U7D may also be beneficial in early detection of mood disorders among bipolar offspring.

INTRODUCTION

Early recognition of bipolar disorder (BD) remains challenging for clinicians. BD presents typically with a (mild) depressive episode during early adolescence/adulthood followed by (hypo)mania years later (e.g. Duffy, Alda, Hajek, & Grof, 2009; Mesman, Nolen, Reichart, Wals, & Hillegers, 2013). The diagnostic delay of BD after the first (hypo)manic episode is on average 5-10 years (Drancourt et al., 2013; Suppes et al., 2001). A prolonged duration of unrecognized and thus untreated BD may have serious consequences, including suicide attempts and poorer long-term outcome (e.g. Drancourt et al., 2013). Therefore, sound methods for early detection of BD, and ultimately prediction of its development, would be beneficial.

Screening instruments are needed to assist clinicians to detect BD in the early phase. Presently, several diagnostic and screening instruments exist to examine mania or depression (Youngstrom, Murray, Johnson, & Findling, 2013). Although, screening instruments for BD are well studied in adult populations screening instruments are less studied during the most critical stage for age of onset of BD, i.e. between 15 and 25 years (Waugh, Meyer, Youngstrom, & Scott, 2014).

The General Behavior inventory (GBI) is a validated self-report instrument used to screen for BD in the general population (Depue et al., 1981; Depue, Krauss, Spoont, & Arbisi, 1989). The GBI is a comprehensive self-report 73-item questionnaire that aims to detect both dimensions of BD (Depue et al., 1981; Depue et al., 1989). The GBI intends to capture the tendency for both threshold and subthreshold affective conditions and their fluctuation over time. In the past decades, the GBI has shown its potential as screening instrument for BD in several adult and adolescent populations in the community and clinic (Danielson, Youngstrom, Findling, & Calabrese, 2003; Depue et al., 1981; Depue et al., 1989; Findling et al., 2002; Klein, Depue, & Slater, 1985; Klein, Depue, & Slater, 1986; Pendergast et al., 2014; Youngstrom et al., 2004; Youngstrom, Findling, Danielson, & Calabrese, 2001). However, its considerable length (approximate completion time 20-40 minutes) reduces its clinical applicability (Youngstrom, Frazier, Demeter, Calabrese, & Findling, 2008; Youngstrom et al., 2013).

Recently, Youngstrom et al. (2013) introduced an abbreviated version of the full-length GBI: the *Seven Up, Seven Down GBI* (7U7D). The 7U7D is designed and validated for adolescents and adults in the age range 11-86 years. The 7U7D is a 14-item instrument carved from the full-length GBI. Initial findings suggest that the brief 7U7D has good psychometric properties, showing high internal consistency, criterion- and a fair discriminative validity for diagnostic groups among clinical and non-clinical samples. Taken together, the 7U7D appears a promising screening instrument for BD in adolescents and adulthood, however these preliminary findings need replication and have not been validated for high risk populations.

As BD is more prevalent among individuals with a positive family history for BD, offspring of patients affected with BD (hereafter referred to as bipolar offspring) are a

particular interest for screening. In a previous study from our group, we have shown in a Dutch Bipolar Offspring Study that the GBI can both function as a screening instrument to correctly identify mood disorders in bipolar offspring, but also has potential to detect future BD and other mood disorders across a five year interval (Reichart et al., 2004a; Reichart et al., 2005). Scores of the depression scale were significantly higher in offspring who developed a mood disorder or BD within a five-year interval. (Reichart et al., 2005). The purpose of the present study in the Dutch Bipolar Offspring Study is three fold: 1) validation of the 7U7D as compared to the full length GBI 2) to test the utility of the 7U7D to correctly identify offspring with lifetime mood disorders and more specifically BD in a high risk population; and 3) to test the capacity of the 7U7D to predict mood disorders and specifically BD outcome, using the longitudinal design of the Dutch Bipolar Offspring Study with 12-years of follow-up.

METHODS

Population and procedure

Participants originate from the Dutch Bipolar Offspring Study, a prospective study following bipolar offspring from adolescence into adulthood. Details of the study have been described in detail elsewhere (Wals et al., 2001). Briefly, a total of 140 bipolar offspring (mean age 16.1 years, range 12-21) from 86 families with one parent with BD I or II were recruited between 1997 and 1999 and followed for 12 years. A family was only included if all offspring within the age range 12-21 agreed to participate. Exclusion criteria were a severe physical illness or handicap or an IQ below 70. Participants were recruited through the Dutch Association for Manic Depressives and Relatives (62 families; 102 children) and outpatient clinics in nine psychiatric hospitals (24 families; 38 children). All parents with BD were outpatients at time of recruitment. DSM-IV diagnoses of the parents with BD were confirmed by face-to-face interviews using the International Diagnostic Checklist and were confirmed by the clinical diagnosis of the treating psychiatrist. Offspring were assessed at baseline, one-, five- and 12 years of follow-up (T1, T2, T3 and T4 respectively) (Hillegers, 2007; Mesman et al., 2013; Reichart et al., 2004b; Wals et al., 2001). One hundred and thirty-two offspring were reassessed at T2, 129 at T3 and 108 at T4, a retention rate of 77%. At T4, 54% of the offspring were diagnosed with a lifetime mood disorder, including 13% bipolar spectrum disorders. There were no statistically significant demographic or clinical differences between the 108 offspring who completed all 12 years of follow-up and the 32 offspring who dropped out (see Mesman et al. (2013) for details). The Medical Ethics Committee of the University Medical Center Utrecht approved the study. Written informed consent was obtained for both the offspring and their parents.

Instruments

Psychopathology

All psychiatric interviews were administered by intensively trained interviewers with graduate degrees in psychology or by a child and adolescent psychiatrist. All interviews were evaluated with psychiatrists certified in child and adolescent psychiatry as well as adult psychiatry to reach consensus on final diagnoses. At T1 and T2, DSM-IV diagnoses were obtained by a face-to-face interview with both the child and the parent using the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL) (Kaufman et al., 1997). After offspring reached the age of 18, the K-SADS-PL was replaced by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) (First, Spitzer, Gibbon, & Williams, 1996). Because the SCID does not cover attention deficit hyperactivity disorder, oppositional defiant disorder, conduct disorder, and tic disorders, sections derived from the K-SADS-PL including the symptoms of these disorders were administered alongside the SCID. Each psychiatric assessment evaluated current and past symptoms during the interim period. Lifetime DSM-IV diagnoses at T4 were based on the psychiatric interviews that took place during all four assessments.

The General Behavior Inventory

The 73-item GBI self-report was administered at each assessment. The GBI entails 73 items and comprises a depression- (46 items) and hypomania-/biphasic scale (21 and 7 items respectively) (Depue et al., 1981; Depue et al., 1989). Each of the 73 items asks the subject to which extent he/she has experienced the symptom or feeling to which the item alludes. The response set is based on a four-point Likert scale; 1 (hardly ever), 2 (sometimes), 3 (often) and 4 (very often). According to Youngstrom et al. (2013), the 14-item 7U7D was extracted from the original full length GBI. The 7U7D follows the same response set as the full length GBI. The seven down (7D) scale and the seven up (7U) reflect the depression and hypomania- and biphasic scale respectively.

Data analysis

In the first set of tests we investigated cross-sectionally the value of the GBI and subsequently the 7U7D as a screener for mood disorders in general and BD specifically in bipolar offspring. Due to the relative low number of transitions to BD it was decided to focus on the latest assessment to capture most transitions (T4). Based upon this assessment offspring were assigned to a diagnostic outcome category, namely: any lifetime mood disorder (AnyMD) versus no lifetime mood disorder diagnosis (NoMD). The mood disorders category was then divided into BD spectrum (BD) and unipolar depression (UD).

In the second set of analyses, we aimed to assess the applicability of the 7U7D to predict development of mood disorders in the future, i.e. during 12 year follow-up (between T1 and T4). As illustrated in Figure 1 a total of 28 offspring developed a first mood disorder between T1 and T4 (NoMD→AnyMD). Twenty-five offspring developed a first unipolar depression and three offspring developed BD between T1 and T4. Overall, during follow-

up 13 cases made a transition to BD between T1 and T4 (NoBD→AnyBD). As the majority of these BD subjects already had a mood disorder diagnosis at T1, this outcome category was compared to offspring with unipolar depression at T1, who did not develop BD during follow-up (UD = UD).

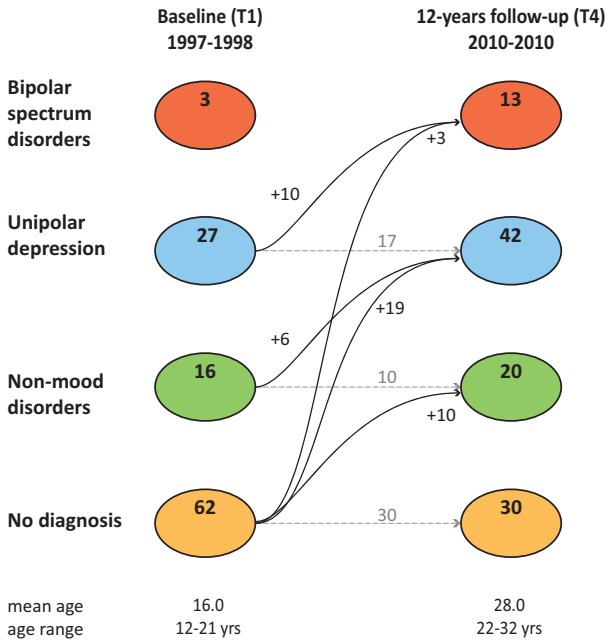

Figure 1 | Development of psychopathology among bipolar offspring over 12 year follow-up

Statistical analyses

Demographic group characteristics were compared using descriptive statistics including one-way ANOVA, χ^2- or Fisher exact tests as appropriate. Using Receiver Operating Characteristic (ROC) analyses, Area Under the Curve (AUC) statistics were calculated to discriminate diagnostic outcome categories and compare the diagnostic efficiency of the GBI and 7U7D. ROC analyses aim to capture the sensitivity and specificity of a test, the AUC quantifies the accuracy of a test. An AUC may be interpreted as the probability that someone with e.g. BD would have a higher score on a test than a randomly selected individual without BD. Some rules of thumb for the interpretation of the diagnostic efficiency of AUCs: ≥ 0.90 "excellent", ≥ 0.80 "good", ≥ 0.70 "fair", ≤ 0.70 "poor" (Swets, Dawes, & Monahan, 2000; Youngstrom, 2014). Logistic regression analyses were used to calculate odd's ratios per unit increase of the scores on the *depression* and *hypomanic/biphasic scale* of the GBI and *seven down* and *seven up* scale of the 7U7D respectively. Moreover, logistic regression analyses allowed us

to check whether there was an incremental value for a combination of the *depression* and *hypomanic/biphasic scale* or its abbreviated counterparts. We considered an alpha of ≤ 0.05 statistically significant. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp, Armonk, NY, USA).

RESULTS

The validation of the GBI and 7U7D as a screener for mood disorders in bipolar offspring

Table 1 presents the characteristics, Area Under the Curve (AUCs) statistics and logistic regression analyses on the GBI and 7U7D. No significant differences in gender or age were found across diagnostic outcome categories. The diagnostic efficiency of the GBI and 7U7D in terms of discriminating diagnostic groups were examined using Area Under the Curve (AUCs) statistics. As shown in Table 1, the performance of the GBI and the 7U7D did not differ significantly. As we are especially interested in the performance of a brief screening instrument, further analyses were performed for the 7U7D only.

As screener for lifetime mood disorders in a familial high risk population the diagnostic efficiency of the seven down (7D) scale shows a fair to good performance. Moreover, a fair performance of the seven up (7U) scale was found for identification of BD subjects as compared to offspring not developing BD. However, no significant AUCs were found between participants with BD or unipolar depression.

Additional logistic regression analyses were performed to test whether there was an incremental value for a combination of the scales. The odds ratio for a clinician based mood disorder diagnosis was significant among offspring with a mood disorder 1.53 (95% CI 1.15-2.03) per unit of the 7D scale. No significant odds ratio for the 7U scale was found. Among those offspring with a lifetime mood disorder, a unit increase of the 7U scale increased the odds of lifetime BD diagnosis with 1.64 (95% CI 1.06-2.54), the odds for the 7D scale were not significantly elevated.

Prediction of mood disorders

In this section we explore the predictive value of the GBI and 7U7D for adolescent bipolar offspring to predict BD and mood disorders during follow-up. Descriptive characteristics and AUC analyses are presented in Table 2. Figure 1 illustrates the transition of DSM-IV psychopathology over 12-year follow-up. Again no significant differences across diagnostic outcome categories were found for age or gender. AUC's showed a poor to fair diagnostic efficiency for prediction of mood disorders over a 12-year interval. Once more, the performance of the GBI and 7U7D was similar and AUC analyses did not differ significantly; hence, further exploration of the data was examined using the 7U7D.

Table 1 | The GBI as screener in a high risk population

	Demographic characteristics				7U7D				GBI					
		Age at T4		Gender	Seven down (7D)		Seven Up (7U)		Depression (D)		Hypomanic/biphasic (HB)			
Descriptives by Dx	**n**	**Mean**	**SD**	**% girls**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**		
All bipolar offspring	102	28.0	3.0	46	1.8	2.8	1.1	1.9	12.2	14.5	5.5	8.0		
Any mood disorder (AnyMD)	55	28.0	3.0	52	2.6	3.4	1.3	2.0	16.7	16.9	7.4	9.5		
Bipolar spectrum disorder (BD)	13	27.8	3.2	43	4.6	4.8	2.7	2.8	27.3	21.3	13.8	13.9		
Unipolar depression (UD)	42	28.5	2.5	55	2.0	2.6	0.9	1.4	13.4	14.0	5.4	6.7		
Non-mood disorder or no disorders (NoMD)	47	27.4	3.4	40	0.7	1.4	0.8	1.8	6.5	8.1	3.0	4.8		
Offspring without BD (NoBD)	89	27.9	3.0	47	1.3	2.2	0.9	1.6	9.8	11.8	4.2	5.9		
													Comparison of 7U7D and GBI	
													7D vs D	**7U vs HB**
Area Under the Curve (AUC) statistics					**AUC**	**SE**	**AUC**	**SE**	**AUC**	**SE**	**AUC**	**SE**	**z**	**z**
AnyMD vs. NoMD					0,68**	0.05	0.59	0.06	0.69**	0.05	0.66**	0.05	0.02	0.90
BD vs. NoBD					0.73**	0.08	0.69*	0.09	0.77**	0.07	0.73**	0.08	0.38	0.33
BD vs. UD					0.66	0.09	0.67	0.10	0.71*	0.09	0.68*	0.09	0.39	0.07
Logistic regression					**OR**	**(95% CI)**	**OR**	**(95% CI)**						
AnyMD vs. NoMD					1,53*	(1.15-2.03)	0.90	(0.67-1.20)						
BD vs. NoBD					1.26**	(1.01-1.59)	1.35	(0.69-1.89)						
BD vs. UD					1.09	(0.86-1.40)	1.64*	(1.06-2.54)						

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table 2 | Prediction of future mood disorders

	Demographic characteristics				7U7D				GBI					
Transition from T1 to T4		**Age at T1**		**Girls**	**Seven down (7D)**		**Seven Up (7U)**		**Depression (D)**		**Hypomanic/biphasic (HB)**			
Descriptives by Dx	**n**	**Mean**	**SD**	**%**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**		
All bipolar offspring	106	16.0	2.7	47	2.6	4.0	2.1	2.8	16.7	19.9	9.5	10.7		
NoBD→BD	13	15.8	3.3	46	5.9	4.9	4.1	4.1	35.0	21.4	17.2	12.2		
UD = UD	19	16.6	2.2	47	3.7	3.7	3.0	3.0	25.3	21.1	14.1	12.0		
NoMD→AnyMD	28	15.9	2.8	57	3.6	5.4	1.8	2.8	18.8	23.8	10.1	12.1		
NoMD = NoMD	49	15.8	2.9	40	0.9	1.5	1.3	1.8	7.3	8.8	5.2	6.3		
													Comparison of 7U7D and GBI	
													7D vs D	**7U vs HB**
Area Under the Curve (AUC) statistics					**AUC**	**SE**	**AUC**	**SE**	**AUC**	**SE**	**AUC**	**SE**	**z**	**z**
NoMD→Any MD vs. NoMD = NoMD					0.67*	0.07	0.52	0.07	0.66*	0.07	0.63	0.07	-0.03	-1.15
NoBD>BD vs UD = UD					0.65	0.10	0.57	0.11	0.64	0.10	0.59	0.10	-0.03	0.16
Logistic regression					**Odds Ratio**	**(95% CI)**	**Odds Ratio**	**(95% CI)**						
NoMD→Any MD vs. NoMD = NoMD					1.47*	(1.09-2.0)	0.87	(0.65-1.16)						
NoBD→BD vs UD = UD					1.12	(0.94-1.35)	1.06	(0.85-1.32)						

* p < 0.05, ** p < 0.01, *** p < 0.001

Results from the logistic regression are shown in Table 2. Among offspring (mean age 16) without a mood disorder at baseline (T1), the odds for a transition to mood disorders at follow-up (T4) significantly increased per unit increase at the 7D scale (OR: 1.47, 95% 1.09-2.0). As expected from the AUCs the 7U scale did not significantly contribute to the 7D scale. It was not possible to predict the transition to BD between baseline (T1) and 12-year follow-up (T4) with the 7U7D.

DISCUSSION

In this study we aimed to investigate the validity of the 7U7D as compared to the GBI and its utility to screen for mood disorders and predict future onset of mood disorders in bipolar offspring. Results of this study indicated that the performance of the 73-item GBI and the 14-item 7U7D was found to be equal. As screener for mood disorders among bipolar offspring, the 7U7D showed potential as screener. In terms of prediction of future onset of mood disorders during the 12-year follow-up, the depression scale, but not the hypomania scale, was found to be associated with an increased risk for transitions to mood disorders. Prediction of BD specifically was not possible with the 7U7D.

In line with the study by Youngstrom et al. (Youngstrom et al., 2013) we found that the performance of the full length GBI and 7U7D was found to be equally good. Results of this study provide therefore further validation for the 7U7D as brief screening instrument for use in clinical practice. The first study on the 7U7D focused on a broad clinical and non-clinical population; this study extends the population the 7U7D may be used for, as this study is the first to test the 7U7D among a high risk population for BD.

As screener for mood disorders in bipolar offspring at the mean age of 28 years, we found that the depression scale of the 7U7D was significantly associated with mood disorders among bipolar offspring. This finding is in line with a previous study by our group on the Dutch Bipolar Offspring Study at the mean age of 16 (Reichart et al., 2004a). Among offspring with a mood disorder, especially higher scores on the hypomania scale were indicative for a BD diagnosis. This finding again replicates findings from previous studies and supports the notion that the hypomania scale is beneficial in the identification of BD (Pendergast et al., 2014). The hypomania scale was only associated with BD onset among those offspring with a mood disorder. Suggesting a sequential approach may be useful: use the depression scale to identify those with a mood disorder, and then next use the hypomania scale to detect and search for possible BD.

In terms of prediction, the diagnostic efficiency of the 7U7D was found to be poor to fair over a 12-year interval. However, a positive score on the depression scale was associated with increased odds for a future onset of mood disorders. This finding complements the finding of the 5 year follow-up of the Dutch Bipolar Offspring Study (Reichart et al., 2005). This time, the follow-up interval was 12-years and includes higher numbers of mood disorders in general and BD specifically. As with the 5-year follow-up, the hypomania scale

was not informative in terms of prediction of mood disorders. To the best of our knowledge no other studies on prediction of BD among bipolar offspring and the 7U7D or the GBI exist.

Several bipolar offspring studies, have now demonstrated that subsyndromal symptoms of mania are an important feature of the BD prodrome (Axelson et al., 2015; Duffy, 2010; Duffy et al., 2014) [Mesman et al., chapter 6]. The fact we do not find an association between the 7U7D hypomania scale and a future transition to BD may have several explanations. At first, the interval of 12-years may be too wide. Moreover, with the relatively low absolute number of BD transitions, the study may be underpowered. However, it is also known that individuals with BD, and probably also offspring during the prodromal phase, normally do not consider symptoms of elevated mood or increased activity as problematic, but perceive them as adaptive and therefore do not report these symptoms spontaneously (i.e. Smith & Ghaemi, 2006). Furthermore, several studies on the GBI have shown that among children and adolescents that parental reports outperform those of adolescents in diagnostic efficiency (Youngstrom et al., 2004), especially in case of hypomania symptoms (Youngstrom et al., 2005). Future studies could benefit from incorporating also the parental GBI. However, until further notice, we recommend that based on the clinical reports as noted above (Axelson et al., 2015; Duffy, 2010; Duffy et al., 2014; Mesman, chapter 6), that even very low scores on the 7U dimension should clinically be alarming and request full clinical assessment and follow-up.

Findings of the present study should be interpreted with caution as sample sizes are limited and only a low absolute number of bipolar offspring developed BD. Therefore larger offspring studies are needed. Also, since we used an enriched population of adolescent bipolar offspring, these findings must be regarded as helpful in identifying those adolescents at high risk to develop mood disorders and BD in particular. Unfortunately, we could not compare the performance of the 7U7D with other BD screening instruments for adolescents and young adults like the Bipolar Spectrum Diagnostic Scale (BSDS) (Ghaemi et al., 2005), Mood Disorder Questionnaire (MDQ) (Hirschfeld et al., 2000) and Hypomania Checklist (HCL-32) (Angst & Cassano, 2005; Waugh et al., 2014). But, the prospective design with long-term follow-up, in combination with the validation of all diagnoses by face to face clinical interview (SCID-I) is a strength of this study.

In conclusion, this study provided further validation for the 7U7D. The 7U7D shows potential as brief screening instrument among individuals at risk for BD. In case of mood disorders, high scores on the hypomania scale may indicate a BD diagnosis. In terms of prediction, the 7U7D may be beneficial in early detection of mood disorders among bipolar offspring, however further research is required.

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Chapter 8

Summary and General Discussion

Bipolar disorder (BD) is characterized by episodes of depression and (hypo)mania alternated with periods of normal (euthymic) mood. The early trajectories and the pathogenesis of BD are still poorly understood. Early recognition of BD is challenging with an approximate diagnostic delay of 5-10 years from the first (hypo)manic episode until the diagnosis is made. Reasons for diagnostic delay are the typical course of disease, misdiagnosis by clinicians, but also delayed help-seeking (McCraw, Parker, Graham, Synnott, & Mitchell, 2014). The diagnostic delay and the concomitant treatment delay are associated with serious consequences including suicidality and increased psychosocial burden (Conus, Macneil, & McGorry, 2013). The most robust risk factor for developing BD is a positive family history for BD (Craddock & Jones, 1999; Craddock & Sklar, 2013). This thesis describes a series of studies among a prospectively followed cohort of offspring from parents with BD: the Dutch Bipolar Offspring Study. Bipolar offspring were followed from adolescence into adulthood, the most critical phase for the onset of BD and other mood disorders. The primary aim of the Dutch Bipolar Offspring Study was to explore the early trajectories and potential risk mechanisms of BD with the ultimate goal to detect the early stage of BD and to prevent or at least delay onset and/or diminish the severity of the illness (Reichart, 2005). Below we present a summary of the main findings of the studies performed in the context of this thesis followed by methodological considerations. Next, we discuss the clinical implications of our work and provide a perspective on options for early intervention. Finally, recommendations for future research will be addressed.

MAIN FINDINGS

A cross-national comparison of bipolar offspring

In chapter 2 we performed a cross-national comparison study between Dutch and US bipolar offspring. Differences between US and European patients with BD are commonly reported, including higher prevalence, younger age of onset, more severe illnesses, and increased parental history of bipolar disorder (Bellivier et al., 2011; Post et al., 2008; Post et al., 2014a; Post et al., 2014b). Also, among offspring studies there is a large variation in psychopathology rates and age of onset of mood disorders across studies and countries (Duffy et al., 2011; DelBello & Geller, 2001, see also chapter 1). In chapter 2 we aimed to explore and clarify cross-national differences in terms of categorical (DSM-IV classification) and dimensional psychopathology in bipolar offspring taking into account demographic and parental characteristics. For this study we used data of the baseline assessment of Dutch Bipolar Offspring Study and the Pittsburgh Bipolar offspring Study from the US and selected all bipolar offspring within the age range between 10 and 18 for further study. Findings of this study indicate that US and Dutch bipolar offspring share a similar susceptibility for mood disorders, including similar prevalence of bipolar-I disorder (BD-I) and bipolar-II disorder (BD-II). Moreover, no differences in the age of onset of mood disorders were observed. However, based on the K-SADS-PL, US offspring showed higher

rates of categorical psychopathology in general and in mood affected offspring higher levels of comorbid psychopathology. These differences were partially explained by differences in sample characteristics, including: age of the offspring at study entry, maternal BD, parental age of BD onset and substance use disorders in the bipolar parent as well as the co-parent. Indicating that differences across offspring studies may indeed be partially explained by differences across studies (Duffy et al., 2011). However, unexpectedly, the cross-national differences in clinician based categorical psychopathology were not confirmed in parental based dimensional psychopathology as ascertained by the CBCL. The discrepancy of this finding leave us puzzling in how to interpret the differences observed between these instruments. Are US and Dutch bipolar offspring really different from each other? Or are we looking at methodological- (i.e. type of instrument) or cultural issues across informants or clinicians (i.e. to what extent do cross-national differences in prevailing attitudes and beliefs regarding psychiatric diagnoses in youth by parents, offspring and clinicians affect our findings). The biggest caveat of this study was the lack of inter-rater reliability across study sites. Inter-reliability could have possibly helped us in the understanding of the observed differences. Currently, efforts are made to obtain an inter-rater reliability for the US site by the Dutch interviewers.

Results of this study suggested that US and Dutch offspring share a similar susceptibility for mood disorders. However, some cross-national differences were observed and these were partially accounted for by differences in sample characteristics. Unexpectedly, differences in clinician based categorical psychopathology, were not confirmed in parental based dimensional psychopathology, leaving room for speculation about methodological, cultural and informant issues in relation to cross-national variation.

The Dutch Bipolar Offspring Study: 12-year follow-up

Chapter 3 served as a basis for chapter 4 to 7. In chapter 3, the clinical outcome of bipolar offspring after 12 years of follow-up is presented. Bipolar offspring (n = 140) was followed from a mean age of 16 years up to the mean age of 28 years and psychiatrically evaluated at baseline (T1), after one (T2), five (T3) and twelve years (T4) of follow-up. The retention rate at T4 was 77% resulting in a total of 108 offspring. At a mean age of 28, 13% developed a bipolar spectrum disorder (BD-I 3%), 54% a mood disorder, and 72% of the offspring was diagnosed with a lifetime DSM-IV axis I disorder. Seven years after the five-year follow-up a further increase of 3%, 14% and 13% respectively was observed (Hillegers et al., 2005). BD tended to debut with a (mild) depressive episode (88%). The conversion to a manic or hypomanic episode developed on average 5.1 years (range 0-14 years) after the first depressive episode. None of the offspring had a pre-pubertal onset of mania or hypomania. Moreover, mood

disorders in bipolar offspring were often recurrent (33%) and prone to be complex (68% with comorbid disorders). In concordance with other offspring studies (Table 3-4, Chapter 1), BD-I was relatively rare among bipolar offspring. Nevertheless, the risk of developing psychopathology in general was high, mainly accounted for by severe and recurrent mood disorders. Future follow-up of the study is essential to determine whether transitions to BD I are to be expected.

Seven years after the 5-year follow-up of the Dutch Bipolar Offspring Study a further increase of psychopathology was observed. At a mean age of 28, 13% developed bipolar spectrum disorder, 54% a mood disorder, and 72% of the offspring was diagnosed with a lifetime DSM-IV axis I disorder. BD tended to debut with a mild depressive episode. Moreover, mood disorders in bipolar offspring tend to be recurrent and likely to be complex.

Risk mechanisms among bipolar offspring

Life events and psychological aspects

In chapter 4 we studied the effect of severe life events on mood episode onset and recurrences in bipolar offspring, as well as the influence of temperament, coping and parenting styles on this association. Results of this study indicate that severe life events were associated with an increased risk for first and, although less pronounced, subsequent mood episodes. The study replicated findings of the 14 months follow-up (T2) of the Dutch Bipolar Offspring Study (Hillegers et al., 2004). Interestingly, the history of life events does not constitute a pure accumulative load, but a natural decay effect of 50-75% per year was observed, suggesting that stabilization of environment is important. We also found a large confounding effect for the number of previous mood episodes, suggesting a possible kindling effect for mood disorders among bipolar offspring. Passive coping style increased the risk of mood episode onset and recurrent episodes, but also had a confounding effect on the association between life events and mood episode onset, suggesting that possibly the way offspring handle stress may be an important target for intervention. Harm avoidance temperament was found to be associated with mood episode recurrence, and may possibly indicate a general risk factor for mood recurrence. Overall, this study found several risk factors to be associated with mood episode onset and recurrence in different ways and provide targets for early intervention.

Monocyte activation, BDNF and S100B

As described in this thesis there is an increasing interest in the link between BD and abnormal immune function, in particular inflammation. Over 12 years of follow-up our group has investigated several immunological aspects among bipolar offspring. The first

study, was the study about autoimmune thyroiditis (AITD) among bipolar offspring (Hillegers et al., 2007). AITD was found to be more prevalent among female bipolar offspring, but not related to psychopathology. In a latter study, Padmos et al. (2008) found a pro-inflammatory monocyte signature of 19 genes to be present in BD patients compared to healthy controls. This pro-inflammatory signature, was also present in bipolar offspring. More interestingly, 3 out of 3 offspring subjects developing a mood disorder during follow-up showed a positive monocyte signature. These findings hinted towards a possible diagnostic or vulnerability marker for mood disorders in bipolar offspring. Chapter 5 aimed to replicate and elaborate on this latter study and evaluated possible biological risk factors that were previously reported in patients with BD in bipolar offspring, including gene-expression in monocytes, serum level pro-inflammatory cytokines PTX-3, CCL2 and IL-1β, neurotrophin BDNF and a product of activated astrocytes S100B. During adolescence (T1, T2), bipolar offspring showed increased inflammatory gene expression in monocytes, high serum PTX3 levels, but normal CCL2 levels. BDNF levels were decreased, while S100B levels were normal. During young adulthood (T3), monocyte activation remained elevated, although to a lesser degree. Serum PTX3 levels remained high, and signs of monocyte migration became apparent through increased CCL2 levels. BDNF and S100B levels were not measured at the adolescent phase. In adulthood (T4), circulating monocytes had lost their activation state, but CCL2 levels remained increased. Both BDNF and S100B were now increased. Abnormalities found in this study were independent of psychopathology (mood disorder, non-mood disorders or no disorder) at all stages. This study suggested an aberrant neuro-immune state in bipolar offspring, which was present irrespective of lifetime or future mood disorders and which followed a dynamic course from adolescence into adulthood. We therefore concluded that the aberrant neuro-immune state reflects a general state of vulnerability for mood disorders, and possibly for other auto-inflammatory conditions (e.g. diabetes type II), rather than being of direct predictive value.

In recent years also in BD patient studies there is increasing evidence for stage-related changes. Kauer-Sant Anna et al. (2009) demonstrated that IL-6 and TNF-α were both present in early and late stage disorder, whereas IL-10 only was elevated in the early stage. BDNF was normal in the early stages and decreased in its later stages. In another study by our group, Haarman et al. (2013) found an association between illness duration and a pro-inflammatory monocyte gene expression suggesting illness progression. These studies provide further support for a staging hypothesis for BD. Results in this thesis also suggest that prior to BD onset neuro-immune alterations are already present and follow a dynamic course and should be incorporated in staging approaches.

Chapter 4 and 5 evaluated potential risk markers among bipolar offspring. Determinants were found to contribute differently to the at risk status of bipolar offspring. The study of life events and psychological factors showed that these factors were found to be independently associated with the onset of mood episodes, but also showed a confounding effect of passive coping on the life event-mood episode onset association. The study on biological mechanisms in bipolar offspring, showed an aberrant neuro-immune state among bipolar offspring irrespective of psychopathology status, suggesting a rather general state of vulnerability. These findings provide important targets for future research and early intervention strategies.

Early clinical phenomenology of mood disorders among bipolar offspring

In chapter 3 we presented the lifetime prevalence rates of mood disorders in bipolar offspring after 12-year follow-up and found that in about 90% of the offspring developing BD debuted with a (mild) depressive episode. In chapter 6 the primary aim of the study was to explore whether specific symptoms could predict a transition to BD among offspring with a unipolar depressive disorder (UD) at adolescent age. Threshold and subthreshold symptomatology as administered at adolescent age (T1) with the K-SADS-PL were evaluated at individual symptom and scale level across diagnostic outcome groups at T4. As differentiation in prodromal stages may be important we made a distinction between offspring with and without a unipolar mood disorder diagnosis at T1 and analyzed these groups separately. Among offspring with a unipolar mood disorder, subthreshold manic symptoms (elated mood, decreased need of sleep and racing thoughts), suicidal ideation and middle insomnia were associated with a transition to BD in the future. Among offspring without a mood disorder at T1, it was shown that development of a first mood disorder was predicted by subthreshold depressive symptomatology, recurrent thoughts of death, marked feeling of tension, marked self-consciousness and compulsions. Findings of this and other studies suggest a gradual onset of BD starting with generic symptomatology including subthreshold anxiety symptoms and mild depressive symptomatology followed by a (mild) depressive episode, subthreshold manic symptomatology and finally a full threshold (hypo)manic episode (Axelson et al., 2015; Correll et al., 2014; Duffy, 2010; Duffy et al., 2014a). Overall, the most prominent and new finding of this study is the presence of subthreshold manic symptomatology and its relative specificity for transition to BD among offspring studies. This finding underscores the importance of subthreshold symptomatology among those at risk. Also, other prospective studies have found subthreshold manic symptomatology to be related to an increased risk for BD especially in the context of other risk factors such as familial loading, a history of depression/depressive symptoms (for a review see Faedda et al., 2015).

Seven up Seven Down: screening and prediction of mood disorders

As BD is associated with a long diagnostic delay, screening instruments may be helpful for clinicians to detect BD at an earlier stage. Although, screening instruments for BD are well studied in adult populations screening instruments are less studied during the most critical stage for age of onset of BD, i.e. between 15 and 25 years (Waugh, Meyer, Youngstrom, & Scott, 2014). In chapter 7 we tested the utility of the General Behavior Inventory (GBI, 73 items) and its abbreviated counterpart the Seven up Seven Down (7U7D, 15 items) as screener for mood disorders and future mood disorders among bipolar offspring. The GBI and the 7U7D showed similar diagnostic efficiency across tests and thus the 7U7D may be considered equally good as the GBI. At T4, the depression scale showed a fair diagnostic efficiency to correctly identify offspring with a lifetime mood disorder diagnosis. Moreover, among those offspring with a mood disorder, higher scores on the hypomania scale were associated with a clinician based BD diagnosis. In terms of prediction, we investigated scores of the 7U7D at adolescent age (T1) among those without a mood disorder. Higher scores on the depression scale were associated with a new mood disorder onset over 12 years of follow-up. It was not possible to predict a switch from unipolar depression to future BD between T1 and T4. This study showed the potential of the 7U7D as brief screening instrument among individuals at risk for BD. The 7U7D may aid clinicians in terms of early detection of BD, but also may help us to identify those at risk for a first mood episode onset.

Taken together, Chapter 3, 6 and 7 provide important information on the clinical phenomenology of the early trajectories of BD and other mood disorders among bipolar offspring. The development of a first mood episode was preceded by subthreshold depressive and general anxiety symptomatology. Regarding BD, the illness tends to debut with a mild depressive episode. A switch from unipolar depression to BD was associated with subthreshold manic symptomatology, suicidal ideation and sleep disturbances. Screening instruments such as the 7U7D may be helpful. Moreover, the 7U7D may aid clinicians in terms of early detection of those with a mood disorder and possibly BD. In conclusion, these studies provide potential targets for early recognition, detection and possible early intervention among bipolar offspring.

METHODOLOGICAL CONSIDERATIONS

Strengths and limitations of the Dutch Bipolar Offspring Study

Within each chapter the strengths and limitations of the specific chapters are discussed. Here we highlight the most prominent strengths and limitations that characterize the study. The Dutch Bipolar Offspring Study is one of the longest followed and largest bipolar offspring

studies worldwide. In the past three decades, a total of 29 studies on bipolar offspring have been performed. Ten out of these 29 studies used a prospective design (for an overview see Table 3, 4 in Chapter 1) of which four carried out a follow-up over a decade (Duffy et al., 2014a; Egeland et al., 2012; Mesman, Nolen, Reichart, Wals, & Hillegers, 2013; Meyer et al., 2004) highlighting the unique status of the Dutch Bipolar Offspring Study within the field of familial high risk studies.

As mentioned in the introduction, among cohort studies both *fixed* and *dynamic* prospective study designs are used. The Dutch Bipolar Offspring Study is a *fixed* cohort study. *Fixed* cohort studies include fixed memberships and as soon follow-up starts, enrollment of new offspring stops. As a result all subjects are studied for a similar period of time. One major disadvantage of this type of design is the decline in sample size, due to loss to follow-up. Nonetheless, after 12 years of follow-up the Dutch Bipolar Offspring Study maintained a high retention rate of almost 80%. With this follow-up rate the sample size of the study belongs to the top 8 out of 29 bipolar offspring studies (for references see Table 3, 4, Chapter 1). *Dynamic* cohort studies on the other hand allow a subject to enroll or leave the study at any moment throughout the course of the study. Dynamic study designs, thus have a fluctuating sample size with a variable time of follow-up. The biggest advantage of a dynamic design over fixed designs are larger sample sizes reducing potential power issues. However, as a result, interpretation of dynamic studies is more complex. The Canadian Bipolar Offspring Study illustrates this issue clearly with a follow-up of 16 years and mean follow-up time of the complete cohort of 6.3 years (Duffy et al., 2014b).

Although the Dutch Bipolar Offspring study belongs to one of the largest offspring studies, the sample size of this study – and bipolar offspring studies in general (see Chapter 1, Table 3 and 4) – is still relatively small and therefore studies of this thesis are likely underpowered. Especially, for example when focusing on the transition to bipolar disorders as 'only' 13% (n = 17) developed a bipolar spectrum disorder during the study. In order to detect differences with a medium effect size (Cohen's *d*), statistical power of 80% and significance level of .05, an ideal sample size for a simple T-test should contain 64 offspring per group (Sopper, 2014). Thus, for comparisons of offspring developing BD specifically, the sample size of future cohorts should preferably be about 4 times larger. Currently, some large prospective bipolar offspring studies are underway, such as the prospective Pittsburgh Bipolar Offspring Study with 357 subjects (Axelson et al., 2015). As prospective studies are costly, an alternative for classical offspring designs is an ultra-high risk design. A positive family history is a risk factor for BD, but does not predict BD onset per se, an ultra high risk design or a so called "close in" strategy aims to include several anchors such as social impairment, clinical features and familial risk for example in order to identify those at the highest risk (McGorry, Yung, & Phillips, 2003). In case of bipolar offspring, ultra high risk designs should then focus on bipolar offspring with a history of mild mood episodes or mild mood disorders plus subthreshold manic symptomatology (Chapter 3, 5 and 6). By doing so, ultra high risk designs are able to capture higher transition rates, reduce the follow-up period and lower the false positive rate in case of early intervention. This strategy

was successfully explored and implemented in the field of psychosis and has led to early detection and intervention programs in the past decade (Ising et al., 2014; Yung et al., 2005; Yung et al., 2008). However, a disadvantage of this approach is that only the latest stages of the transition to bipolar disorder are covered and thus the early developmental trajectories remain unclear.

Another challenge to encounter in prospective studies is a methodological issue related to the transition from childhood into adulthood. Most instruments used during childhood or adolescence are not or at least less suitable for (young) adults and vice versa. In the Dutch Bipolar Offspring Study this has led to several challenges. For psychiatric assessment the K-SADS-PL was replaced with the more age-appropriate SCID-I from the five years follow-up (mean age of 21 years) onwards. This change of instruments limited us in prospective analysis of the symptomatology over the full 12-years follow-up (e.g. Chapter 6).

Also, since during adolescence personality traits are developing, the age at which the examination of temperament and coping styles took place, might have affected the outcome. In addition, information on standard values of several biological parameters during adolescence and young adulthood are scarce, especially regarding complex issues such as neuroimmunological findings. Therefore it is challenging to put such findings into a developmental perspective.

Another major limitation of the Dutch Bipolar Offspring Study is the lack of a prospective control cohort. Due to budgetary limitations no prospective control cohort was established at the start of the study. For comparison of prevalence rates (*Chapter 2 and 3*) we now referred to national epidemiological and community studies (de Graaf, Ten Have, & van Dorsselaer, 2010; Ormel et al., 2014; Verhulst, van der Ende, Ferdinand, & Kasius, 1997). However, different methodology in our offspring study and the national epidemiological study in terms of instruments (for an example see: Regeer et al., 2004), applied definitions of prevalence and incidence rates, and varying age ranges have limited the comparison.

For the studies on determinants and early clinical phenomenology (Chapter 4, 6 and 7), we could compare subgroups of bipolar offspring (e.g. affected versus unaffected) within the bipolar offspring sample. However, definitions of affected versus unaffected (i.e. no mood disorder or no disorder) offspring may be somewhat arbitrary because at least some of these 'unaffected' offspring actually had subthreshold symptomatology and/or may convert to BD or mood disorders at an older age.

In order to obtain a control group for our biological studies (Chapter 2), we recruited several cross-sectional control subsamples (Chapter 5), including high school students (2001-2002), laboratory and medical staff and healthy control samples available from other studies (2001-2005) and students (2010-2011). For this reason, no longitudinal within-group analyses were possible for the controls which makes the prospective interpretation of our data limited. Moreover, the assessments of controls were less extensive than those of bipolar offspring, thus several possible confounding factors could not be controlled for. Taken together, our 'solutions' for not having a prospective control group are not ideal

and future prospective studies could benefit from including parallel a longitudinal control cohort.

Despite these limitations, we do consider the Dutch Bipolar Offspring Study a unique study with several key strengths and studies in this thesis provide important heuristics to guide hypotheses and serve as base for future studies. However findings should be interpreted in the light of above noted limitations.

Bipolar offspring: a specific study design

The study of children from a parent with BD using a longitudinal study design is an elegant and valid method to study the familial transmission of BD and the early trajectories of BD. Nonetheless, the generalizability and specificity of bipolar offspring research needs to be considered. Bipolar offspring represent a unique population and findings of this thesis may only converge to offspring of patients with BD and not per se to all individuals with familial loading for BD. Bipolar offspring do not only inherit a genetic risk, but also grow up in a complex environment related to parental bipolar illness. Offspring might be exposed to a less predictable family environment, can get parentificated and might experience emotional neglect during parental mood episodes. In addition, assortative mating is common in these families resulting in an increased level of familial loading and environmental complexities (Goodwin FK & Jamison KR, 2007).

In case of the Dutch Bipolar Offspring Study, the cohort may also not be fully generalizable for bipolar offspring in general. The majority (73%) of families included in our cohort were recruited via the Dutch Patient Association for Manic Depressives and Relatives (Nederlandse Vereniging voor Manisch-Depressieven en Betrokkenen (VMDB)). These families may be a selection of better functioning (both the patient as their families), better informed and a treatment seeking patient population. However, within our own sample, the families recruited via the VMDB did not differ in illness characteristics (number of hospitalizations, number of manic episodes and age of onset), socio-economic status and divorce rate, from those families recruited via outpatient clinics (Hillegers, 2007).

Is it ethical to study bipolar offspring?

Despite the approval by a Medical Ethical Review Board, high risk studies bring up ethical issues. Participation in high risk research may lead to increased awareness of such a familial risk and may be associated with distress caused by the ‘at risk status’ and possible stigmatization. On the other hand, parents participating in our high studies often give the feedback that participation in the high risk study opens up the conversation about the mental illness of the parent. This has also been reported in previous studies as well (Festen et al., 2014; Nauta et al., 2012). Very often, offspring do not know about the parental illness. Not knowing the specifics about the illness and the attributable behavioral changes of the parents, make their environment unpredictable. Rather than telling about the illness, parents often try to comfort children, without an explanation for change in behavior, leaving the offspring confused and distressed behind which may actually cause bigger

harm (Sturges, 1977; Mordoch & Hall, 2002; Algorta et al., 2013; in Algorta, Van Meter, & Youngstrom, 2015). Participation in a study like the Dutch Bipolar Offspring Study may lead to a first positive experience with psychiatry and might lower the threshold for help-seeking in both parents and offspring. In a brief survey among the offspring participating in our study at a mean age of 21, offspring reported that 86% of the offspring would recommend other children between the age of 12 and 20 years old to participate in similar studies. This, together with the high retention rate at the final assessment, suggests that although participation may be somewhat uncomfortable, bipolar offspring valued the importance of the study and were sincerely committed to the project.

Bipolar offspring: specificity of the familial transmission?

Findings of this thesis focus on bipolar offspring. The default message communicated in the field of bipolar offspring is that children of patients with BD are at increased risk for BD and mood disorders. However, less is known about the specificity of the familial transmission in comparison to offspring of patients with other severe mental illnesses such as major depressive disorder (MDD) and schizophrenia. The issue of specificity of familial transmission is relevant as this may have consequences for the etiological perspective on the severe mental illnesses, classification of illnesses and early intervention methods (Rasic, Hajek, Alda, & Uher, 2014). In a meta-analysis of 33 studies it was shown that schizophrenia, bipolar and MDD offspring had a 3-fold risk to develop the same disorder as their parent. However, schizophrenia offspring were also at increased risk to develop mood disorders and bipolar offspring had an increased risk to develop both MDD and schizophrenia (the latter not confirmed in this study, see Chapter 3). MDD offspring were found to be at increased risk to develop BD, but not schizophrenia. Increased risk for anxiety disorders was- common in bipolar and MDD offspring, but not schizophrenia offspring. Thus findings of this meta-analysis suggest that familial transmission is only partially diagnosis specific (Rasic, Hajek, Alda, & Uher, 2014). However, comparison of studies was limited as for MDD offspring only a few studies included adult offspring, and for schizophrenia offspring, studies with young offspring were scarce. Moreover, findings of the study may be biased due to methodological issues, for example misdiagnosis of BD among MDD patients may alter findings of the transmission of BD among MDD offspring (e.g. Angst et al., 2011). Therefore, systematic comparisons of these families are necessary in order to make firm conclusions about the familial transmission, such as the study on MDD and bipolar offspring on young adolescents by Vandeleur et al. (2012). Also, our group has started a new prospective cohort including both schizophrenia and bipolar offspring, using similar methods starting from age 8 onwards.

CLINICAL IMPLICATIONS

Recognition of the early trajectories of BD is the first step to slow down illness progression. Findings of this thesis show that bipolar offspring are at increased risk to develop BD and mood disorders in general. In the majority of the cases BD did debut with a (mild) depressive episode (Chapter 3). Findings of chapter 6 revealed that the antecedents of mood episodes are likely to start with a gradual onset. Subthreshold depressive and anxiety symptomatology may indicate future onset of a depressive episode, whereas after a first (mild) depressive episode additional subthreshold manic symptomatology may indicate a future transition to BD. These findings underscore the importance of awareness and knowledge on subtle, subthreshold depressive and manic symptomatology by clinicians treating this population. If parents or others have concerns about the wellbeing of these children at high familial risk or bipolar offspring present with (mild) symptomatology, referral for psychiatric evaluation is recommended. Screening tools such as the *Seven Up Seven Down* may help clinicians in both the early detection of already present BD and also has potential in the screening process of those at increased risk to develop a first mood episode (Chapter 7). Monitoring of the environment for severe stressful life events, harm avoidant temperament and passive coping styles may be of additional value in the diagnostic assessment and choice of the target intervention (Chapter 4). To date, no specific early intervention- or prevention programs for bipolar offspring are recommended for clinical practice. The first essential step in early intervention is to determine the target of intervention and perform a fine risk/benefit ratio of these interventions per particular stage. Intervention options may vary from low frequent monitoring to intensive interventions. Below, the current state of research in the literature on interventions in bipolar offspring/individuals at risk for BD is discussed.

Psychotherapeutic interventions

In case of mild symptomatology psychotherapeutic interventions are preferred over pharmacological treatment for adolescents at risk for BD (Pfennig et al., 2014). Findings of chapter 4 indicate that life events and psychological aspects (passive coping style/harm avoidant temperament) play a role in the susceptibility for the onset and course of mood episodes in bipolar offspring and thus should be part of early intervention. Results of this study infer that focusing on stress reduction among individuals at risk is a must. Depending on the context, psycho-education, cognitive behavioral therapy, EMDR (in case of severe trauma), and/or coping skill training or a mix of above may be chosen.

To date, only a few studies have investigated specific psychotherapeutic interventions for youth at risk for BD. In the first study, Nadkarni & Fristad (2010) focused on young children (mean age 9.9) with depressive spectrum disorders with and without transient manic symptoms (n = 37 and n = 13 respectively). They provided eight weekly 90 minute group sessions of multi-family psycho-educational psychotherapy for parents and offspring including psychoeducation, social support, and skills development based on cognitive behavioral therapy and family system interventions. After one year follow-up, the risk

for conversion to bipolar spectrum disorder was the highest among the offspring with depressive spectrum disorders and transient manic symptoms (48%) versus those without (12.5%). However, those who were in the treatment condition had a significant lower risk to convert after 12 months follow-up than those on the wait-list condition, 16% versus 60% respectively.

In a randomized trial Miklowitz et al. (2013) studied the effectiveness of a 4 month family focused therapy among 40 youth (mean age 12.3) with a first degree relative with BD I or II and a diagnosis of BD-NOS, major depressive disorder or cyclothymia and current active mood symptoms. Families followed 12 sessions of family focused therapy, including psycho-education and training in social and problem solving skills or an educational control of 1-2 family sessions. Individuals of the treatment condition reported a sooner recovery of mood sympoms, a more favorable trajectory and more weeks in remission over 1 year of follow-up.

Another pilot study tested interpersonal and social rhythm therapy (IPSRT) among 13 adolescents with a positive family history (1st or 2nd degree) with either externalizing, internalizing disorders or no DSM-IV psychopathology (Goldstein et al., 2014). IPRST focuses on stabilization of daily routines and sleep/wake cycles and interpersonal relationships. After 12 sessions – delivered over 6 months – improvement of sleep and circadian patterns were observed, suggesting that stabilizing daily rhythms and interpersonal relationships may be beneficial for bipolar offspring.

The studies discussed are promising, however, sample sizes were small and follow-up studies no longer than 12-months. Therefore, not only larger controlled studies are required, but also longer follow-up is desired. Moreover, studies comparing specific high risk intervention programs with regular psychotherapeutic interventions are also required (Pfennig et al., 2014).

Pharmacological interventions

In our opinion, pharmacotherapy for adolescents or young adults should only be considered in case of moderate to severe depression or already overt BD. The prescription of antidepressants in bipolar offspring with depressive or anxiety symptoms/disorders is not without risk as it may trigger adverse effects in about half of the individuals (Baumer et al., 2006; Pfennig et al., 2014; Strawn et al., 2014; Findling, Lingler, Rowles, McNamara, & Calabrese, 2008). Reported adverse effects are increased irritability, aggression, impulsivity, hyperactivity (Strawn et al., 2014), new onset suicidal ideation or induction of hypomanic or manic episodes (Baumer et al., 2006; Findling et al., 2008).

Some studies have also looked at the effects of mood stabilizers in high risk populations with subthreshold symptoms, i.e. not yet fulfilling the criteria of BD or other mood disorder. Thus far, neither lithium (Geller et al., 1998) nor valproate acid/divalproex (Findling et al., 2007) have been found more effective than placebo in the prevention of a full mood disorder or BD.

Normalization of the activated inflammatory system?

In chapter 5 we found support for an aberrant neuro-immune state in bipolar offspring, which followed a dynamic course from adolescence into adulthood, irrespective of lifetime or future psychopathology. These findings need further validation in larger studies. However, if replicated, studies with anti-inflammatory interventions to neutralize the activated inflammatory system in bipolar offspring might be undertaken with the ultimate goal to prevent onset of BD or another mood disorder. The dynamic course of this neuro-immune state as observed in our study suggests that timing of such an anti-inflammatory intervention is essential.

There are now several studies that investigated the efficacy of anti-inflammatory agents as add-on treatment in patients with BD. In a recent systematic review of the available literature on this topic a total of sixteen studies on the add-on treatment with anti-inflammatory agents – such as n-acetyl cysteine, aspirin, omega-3 fatty acids and celecoxib – during acute episodes of depression and/or mania in adult BD patients were discussed (Ayorech, Tracy, Baumeister, & Giaroli, 2015). Add-on treatment with n-acetyl cysteine was found to reduce oxidative stress and inflammatory markers and had a positive effect in bipolar depression. Results of add-on treatment of celecoxib and aspirin were found unsatisfactory. However, some studies in psychosis did report a beneficial effect of celecoxib especially in the early stage of illness onset (Muller et al., 2002; Muller et al., 2010; Nitta et al., 2013; in Ayorech et al., 2015). Studies on omega-3 fatty acids as add-on treatment in BD showed variable results. One neuro-imaging study observed a short-term effect in membrane fluidity and neuronal activity in BD patients, although this effect did not reflect a change in depression scores (Frangou, Lewis, Wollard, & Simmons, 2007). A study among individuals at ultra high risk for psychosis, omega-3 fatty acids were found to reduce the risk for progression to psychosis after 12-months (5% transition in the intervention group versus 28% in the placebo group) (Amminger et al., 2010). If replicated, these studies underscore the importance of timing in treatment of psychiatric disorders and the need for further exploration of a staging approach.

DIRECTIONS FOR FUTURE RESEARCH

Studies in this thesis showed that bipolar offspring are at increased risk to develop BD and mood disorders in general. BD typically debuted with a mild depressive episode followed by a first (hypo) manic episode on average 5 years later (range 0-13 years). At the final assessment, a total 18 offspring were diagnosed with a first onset of a depressive episode less than 10 years ago. Future assessment of the Dutch Bipolar Offspring Study is essential to see whether more transitions from unipolar depressive disorders to BD, or from BD-II to BD I will occur. Moreover, as illustrated in Table 3 and 4 of chapter 1 bipolar offspring studies where participants are followed above the age of 25 are scarce, and thus little is known about the risk to develop mania at older age among bipolar offspring.

As indicated in the section methodological considerations, for new offspring studies further refinement is recommended. Most obviously, recommendations for new offspring studies are larger sample sizes, healthy control cohorts and more frequent follow-ups, preferably every two years. Future offspring studies should start recruiting at younger age to capture important developmental milestones. Another issue, would be to study specificity of the familial transmission by studying the differences among offspring of patients with different subtypes of mood disorders (recurrent depression, BD-II, BD-I) and also to look at the overlap with offspring of patients with psychotic disorders, as the recently launched Dutch Bipolar and Schizophrenia Offspring Study by our research group.

Regarding the study of risk factors as discussed in chapter 4 and 5 (life events and immunological aspects respectively) also other domains such as cognition, structural and functional brain development, biomarkers and circadian rhythms should be considered to further unravel the underlying pathways of BD.

This thesis also shows that identification of those at risk for BD at an early stage is complex. The next step in the study of determinants is to start building more sophisticated risk models including both the early clinical stages, but also a dynamic perspective as illustrated in the study on immunological aspects. Combining early clinical signs and more sophisticated risk models may increase the predictive value, but also allow us to focus on stage appropriate interventions (Berk et al., 2014; Kapczinski et al., 2014).

And finally, as described in the previous section, now the early trajectories of BD are further unraveled a focus on early intervention is desired to enhance normative development among high risk populations.

CONCLUDING REMARKS

In this thesis, we followed bipolar offspring throughout the most critical phase for the onset of mood disorders during the 12-year follow-up of the Dutch Bipolar Offspring Study. Our aim was to improve our knowledge on the early trajectories of BD and mood disorders in general and related risk mechanisms in bipolar offspring. Bipolar offspring are at increased risk for developing BD and mood disorders in general. BD typically debuts with a (mild) depressive episode. A first mood episode generally starts with mild depressive symptoms and anxiety symptoms, while associated subthreshold manic symptoms preceded (hypo) mania onset. The *seven up seven down*, a screenings instrument for mood disorders, may aid clinicians in terms of early detection of those with a mood disorder and possibly BD. Potential risk mechanisms studied in this thesis were found to contribute in different ways to the at risk status of bipolar offspring. Whereas some risk factors were associated with mood episode onset (life events, passive coping style), others were found to be associated with mood episode recurrence (passive coping style, harm avoidant temperament). The study of biological mechanisms showed a rather general state of vulnerability independent of psychopathology, but also a dynamic course during adolescence. With these findings,

this thesis provides targets to improve early recognition of BD and other mood disorders among bipolar offspring and also potential targets for intervention strategies to prevent or delay onset of these disorders. Today, 18 years after the Dutch Bipolar Offspring Study was initiated, the early trajectories of BD are further unraveled and it seems the right time to move on to a focus on early intervention.

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Samenvatting

"Toen ik een aantal jaar geleden overspannen werd, kwam ik er achter dat mijn vader Daan ruim 30 jaar geleden op exact dezelfde leeftijd ook overspannen was geworden. Hij werd vervolgens manisch, raakte zijn baan kwijt, richtte in korte tijd verschillende bedrijven op en kocht ons gezin de bijstand in. Mijn moeder vocht voor ons gezin, maar verloor het uiteindelijk van de ziekte van mijn vader. Hij werd met de diagnose manisch depressief opgenomen in een psychiatrische inrichting, werd dakloos en leefde tussen de Groningse zwervers verder onder de naam Engel. Mijn ouders scheidden en na anderhalf jaar zonder contact met mijn vader veranderde ik mijn achternaam in die van mijn moeder." – Roderik Schaepman, documentaire 'Ver van Daan' –

Het hierboven beschreven citaat is afkomstig uit de documentaire 'Ver van Daan', een documentaire die de zoektocht laat zien van een zoon naar de ziekte van zijn vader en de daardoor verstoorde familiebanden. Roderik's vader heeft de diagnose manisch-depressief, ook wel bekend als bipolaire stoornis. De documentaire illustreert feilloos de ernst van de bipolaire stoornis, hoe deze stoornis het leven van iemand volledig op zijn kop kan zetten, en de impact ervan op de omgeving. In de documentaire houdt Roderik zich ook bezig met de vraag of hijzelf, en ook zijn eigen kinderen, kwetsbaar zijn voor het ontwikkelen van een bipolaire stoornis; de stoornis is immers erfelijk.

Nog altijd is er weinig bekend hoe en waardoor een bipolaire stoornis ontstaat. De bipolaire stoornis komt vaker voor binnen families, dus genen spelen hierbij een rol. Maar zoals bij de meeste psychiatrische aandoeningen, gaat het om een gen-omgeving interactie. Welke factoren hier precies een rol in spelen is vooralsnog een voortdurende zoektocht.

In Nederland komt de bipolaire stoornis bij zo'n 2% van de bevolking voor. De stoornis wordt vaak pas laat ontdekt, veelal jaren nadat de eerste klachten zijn ontstaan. Ook in het verhaal van Daan, duurt het anderhalf jaar voor het duidelijk wordt wat er precies aan de hand is, en ook in dit verhaal is het niet ondenkbaar dat er mogelijk ook al op jongere leeftijd klachten waren. De eerste stemmingsepisode bij een bipolaire stoornis doet zich vaak al voor tussen het 15^{e} en 25^{e} levensjaar, een periode waarin ontwikkeling en zelfontplooiing centraal staan. Voor de prognose en de impact op het leven van patiënt en omgeving is het van belang dat we de ziekte in een vroeg stadium kunnen signaleren en adequaat kunnen behandelen. Om dit te kunnen bereiken is beter inzicht in de vroege ontwikkeling van de stoornis en in risicofactoren nodig. Op deze manier zal het in de toekomst wellicht mogelijk zijn om behandeling vroegtijdig te starten en de gevolgen van de ziekte te beperken, dan wel het ontstaan van de ziekte uit te stellen.

Het onderzoek beschreven in dit proefschrift richt zich op kinderen van een ouder met een bipolaire stoornis. Omdat de bipolaire stoornis vaker voor komt binnen families, zijn kinderen van een ouder met een bipolaire stoornis een interessante doelgroep voor onderzoek naar het vroege beloop van de bipolaire stoornis en naar eventuele risicofactoren. De studies beschreven in dit proefschrift zijn gebaseerd op de zogenaamde Nederlandse

KBO studie, een studie waarbij kinderen van een ouder met een bipolaire stoornis vanaf de adolescentie tot aan de vroege volwassenheid zijn gevolgd, een kritieke periode voor de ontwikkeling van psychopathologie. De studies beschreven in dit proefschrift hebben als doel onze kennis te vergroten over de vroege ontwikkeling van stoornissen en eventuele risicofactoren bij deze kwetsbare groep.

DE NEDERLANDSE KBO STUDIE

De Nederlandse KBO studie is een uniek prospectief cohort, een zogenaamde langlopende studie. Wereldwijd behoort de studie tot één van de langst gevolgde en tevens grootste studies naar kinderen van een ouder met een bipolaire stoornis. Tussen 1997en 2011 volgden we een groep van 140 kinderen uit 86 families. De deelnemers werden gevolgd van gemiddeld 16-jarige (variërend van 12 tot 21 jaar) tot gemiddeld 28-jarige leeftijd. De deelnemers werden in de afgelopen jaren vier maal gezien voor onderzoek: bij aanvang van de studie, na 1 jaar, na 5 jaar en na 12 jaar. Bevindingen van de eerste drie metingen werden beschreven in drie eerder verschenen proefschriften. In dit proefschrift presenteren we de resultaten van voornamelijk de vierde meting, de zogenaamde 12-jaars meting.

Nederland versus Amerika

Hoofdstuk 2 beschrijft een studie waarin een Amerikaanse en de Nederlandse studie naar kinderen van een ouder met een bipolaire stoornis werden vergeleken. Diverse studies bij volwassenen met een bipolaire stoornis uit Amerika en Europa laten zien dat Amerikaanse patiënten vaker een ernstiger beeld vertonen dan patiënten uit Europa. Ook rapporteren zij vaker een vroegere beginleeftijd van de ziekte en is er veelal sprake van een ernstiger beloop van de ziekte. Niet alleen bij patiënten studies, maar ook onder de studies naar kinderen van een ouder met een bipolaire stoornis worden verschillen gevonden tussen de Verenigde Staten en Europa betreffende prevalentie en type psychopathologie en de beginleeftijd van stemmingsstoornissen. Het doel van de studie in **hoofdstuk 2** was om te onderzoeken of deze verschillen daadwerkelijk bestaan en als ze bestaan te onderzoeken of ze misschien worden veroorzaakt door verschillen in de populaties, zoals verschillen in de ernst van de ziekte van de ouders of leeftijdsverschillen tussen de diverse studies.

Er werd gebruik gemaakt van de eerste meting van de Nederlandse KBO studie en de eerste meting van de Pittsburgh BIOS studie. Van beide studies werden alle kinderen tussen de 10 en 18 jaar oud meegenomen in het onderzoek. Psychopathologie werd gemeten aan de hand van een klinisch interview met een psycholoog of psychiater, ouder en kind en een klachtenvragenlijst ingevuld door de ouders.

Eén van de bevindingen was dat Nederlandse en Amerikaanse kinderen van een ouder met een bipolaire stoornis een ongeveer gelijk risico hebben op het ontwikkelen van een stemmingsstoornis; de prevalentie van een bipolaire stoornis type I of II is eveneens vergelijkbaar. Ook de beginleeftijd van stemmingsstoornissen is niet anders wanneer

gecorrigeerd wordt voor verschillen tussen de twee studiepopulaties. Wel vonden we dat Amerikaanse kinderen van een ouder met een bipolaire stoornis vaker een diagnose krijgen en dat stemmingsstoornissen vaak complexer zijn, zo gaan stemmingsstoornissen vaker gepaard met comorbide stoornissen zoals angststoornissen, ADHD en gedragsstoornissen. Aanvullende analyses lieten zien dat deze verschillen voor een deel samenhangen met verschillen tussen beide studiecohorten op demografisch niveau en in karakteristieken van de ouders. Opvallend was echter dat bovengenoemde verschillen in psychopathologie minder sterk naar voren kwamen uit een klachtenvragenlijst ingevuld door de ouders. Dit doet de vraag rijzen of Amerikaanse en Nederlandse kinderen van een ouder met een bipolaire stoornis eigenlijk wel echt verschillen van elkaar op bovengenoemde aspecten. Dit suggereert dat er mogelijk andere factoren een rol spelen, zoals bijvoorbeeld een cultureel bepaalde discrepantie in het oordeel van de onderzoekers, of andere niet gemeten methodologische aspecten. Momenteel worden Amerikaanse interviews door Nederlandse onderzoekers beoordeeld aan de hand van audiomateriaal om dit nader te onderzoeken.

Amerikaanse en Nederlandse kinderen van een ouder met een bipolaire stoornis hebben een ongeveer gelijk risico op het ontwikkelen van stemmingsstoornissen. Wel worden verschillen gevonden in de prevalentie van algemene psychopathologie en comorbiditeit bij stemmingsstoornissen, deze verschillen worden deels verklaard door populatiekenmerken. Een opmerkelijke bevinding van deze studie is echter dat op een klachtenvragenlijst ingevuld door ouders geen significante verschillen gevonden worden. Dit suggereert een mogelijk cultureel bepaalde discrepantie in het oordeel van clinici en de ouders, dan wel een rol voor methodologische aspecten.

Nederlandse KBO studie: 12-jaar gevolgd

In **Hoofdstuk 3** worden de eerste resultaten, een beschrijving van de psychopathologie, van de 12-jaars meting van de Nederlandse KBO studie gepresenteerd. Zeven jaar na de 5-jaarsmeting werkten nog altijd 108 van de oorspronkelijke 140 kinderen mee aan ons onderzoek, dit is 77% van de oorspronkelijke studiepopulatie.

Op een leeftijd van gemiddeld 28 jaar, heeft 13% een bipolaire spectrum stoornis, 54% een stemmingsstoornis, en 72% enige vorm van psychopathologie ontwikkeld. Ter vergelijking, in een Nederlandse bevolkingsstudie (NEMESIS-II) worden in dezelfde leeftijdscategorie de volgende percentages gerapporteerd: bipolaire spectrum stoornis 2%, stemmingsstoornissen 19%, en 46% enige vorm van psychopathologie. In vergelijking met de 5-jaars meting zijn de percentages respectievelijk 3%, 14% en 13% gestegen.

Net als bij de 5-jaars meting, kwam naar voren dat een bipolaire stoornis in bijna alle gevallen begint met een (milde) depressieve stoornis (88%), gevolgd door een eerste (hypo)manie gemiddeld 5 jaar later. Ook uit andere studies naar kinderen van een ouder

met bipolaire stoornis, blijkt dat 'slechts' een kleine groep van deze hoog-risico groep een bipolaire I stoornis ontwikkeld, te weten 3%. Het risico op het ontwikkelen van een stemmingsstoornis in het algemeen is 54%. Dit percentage omvat zowel milde als ernstige depressieve stoornissen, als ook de bipolaire stoornis. In het geval er eenmaal sprake is van een stemmingsstoornis, dan is de kans op een nieuwe stemmingsepisode, een zogenaamd recidief, hoog: 33%. Naast stemmingsstoornissen worden vaak ook andere stoornissen gerapporteerd, zoals angst- of ontwikkelingsstoornissen.

Toekomstige metingen van de Nederlandse KBO-studie moeten uitwijzen of meer transities naar (hypo)manie binnen deze populatie te verwachten zijn.
Hoewel het risico op het ontwikkelen van een stoornis dus hoog is, is het belangrijk om te benadrukken dat het in deze studie gaat om 'lifetime' observaties en dat stoornissen ook van voorbijgaande aard kunnen zijn; bovengenoemde percentages zeggen dus niet persé iets over het huidige functioneren van de deelnemers.

Zeven jaar na de 5-jaars meting van de Nederlandse KBO studie is de prevalentie van algemene psychopathologie verder toegenomen. Op een leeftijd van gemiddeld 28 jaar, heeft 13% een bipolaire spectrum stoornis, 54% een stemmingsstoornis, en 72% enige vorm van psychopathologie ontwikkeld. 'Slechts' 3% ontwikkelde een bipolaire I stoornis. Een bipolaire spectrum stoornis werd in vrijwel alle gevallen voorafgegaan door een milde depressieve episode. Stemmingsstoornissen zijn veelal recidiverend (31%) en gaan vaak gepaard met comorbide stoornissen (67%).

Risicofactoren

In dit proefschrift worden verder twee studies beschreven waarin we onderzoek doen naar mogelijke risicofactoren. Hierbij ligt de nadruk op stressvolle levensgebeurtenissen en de rol van een afwijkend functioneren van het afweer systeem, voornamelijk het bestaan van de verhoogde neiging tot ontstekingsreacties in het brein. Over beide onderwerpen wordt veel geschreven bij stemmingsstoornissen, er is echter nog maar weinig bekend over deze factoren bij hoog-risico groepen zoals kinderen van een ouder met een bipolaire stoornis.

De rol van levensgebeurtenissen en persoonlijkheidsaspecten bij het ontstaan van stemmingsstoornissen

Hoofdstuk 4 richt zich op de rol van levensgebeurtenissen bij het ontstaan van stemmingsstoornissen bij kinderen van een ouder met een bipolaire stoornis. De deelnemers werden op alle vier de metingen uitgebreid ondervraagd aan de hand van een 90 minuten durend levensgebeurtenissen-interview. Net als bij de eerste meting van de Nederlandse KBO-studie (Hillegers et al. 2005) vonden we ook op de 12-jaars meting aanwijzingen voor een relatie tussen stressvolle levensgebeurtenissen en het ontstaan van een eerste stemmingsepisode.

Ook werd opnieuw duidelijk dat het effect van levensgebeurtenissen niet puur een opeenstapeling van stress betreft, maar dat er tevens een temporeel, uitdovend effect voor levensgebeurtenissen wordt gemeten, met een verval van 50 tot 75% per jaar.

Zoals beschreven in **hoofdstuk 3** is het risico op een recidiverende stemmingsstoornis hoog, te weten 33%. Een invloedrijke theorie bij onderzoek naar stemmingsstoornissen is de 'kindling hypothese'. Deze theorie veronderstelt dat levensgebeurtenissen/stress vooral een rol spelen bij de eerste stemmingsepisode(s), en dat latere episodes (recidieven) daar meer en meer los van komen te staan. Om deze reden werd in dit hoofdstuk ook onderzocht of levensgebeurtenissen ook een rol spelen in het beloop van de stoornis gekenmerkt door recidieven. Het blijkt dat levensgebeurtenissen ook bij een recidief een rol spelen. Echter, het aantal stemmingsepisodes in de voorgeschiedenis is ook een sterke voorspeller voor het optreden van een recidief. Hoewel het interactie-effect *aantal episodes x levensgebeurtenissen* net niet significant werd bevonden, werd de associatie tussen levensgebeurtenissen en stemmingsstoornissen minder sterk bij het toevoegen van het aantal stemmingsepisodes in de voorgeschiedenis. Dit suggereert dat er mogelijk sprake is van een 'kindling' effect.

Ook persoonlijkheidsaspecten lijken een rol te spelen bij de kwetsbaarheid van stemmings-stoornissen, er is echter weinig bekend in hoeverre deze de relatie tussen levensgebeurtenissen en stemmingsstoornissen beïnvloeden. In een vervolgstap werd daarom gekeken naar een aantal persoonlijkheidsaspecten zoals de manier waarop omgegaan wordt met problemen (coping), temperament en hoe kinderen de opvoedingsstijlen van hun ouders ervaren. Er blijkt een associatie te bestaan tussen passieve coping (een ontwijkende, afwachtende houding bij probleemsituaties) en stemmingsepisodes. Opmerkelijk is dat het toevoegen van passieve coping aan het statistische model van invloed is op de sterkte van de associatie tussen levensgebeurtenissen en stemmingsstoornissen, een zogenaamd 'confounding' effect. Bij een eerste stemmingsepisode, lijkt de relatie tussen levensgebeurtenissen en stemmingsgevoeligheid te versterken, bij recidiverende stemmingsstoornissen doet passieve coping het effect van levensgebeurtenissen vervagen tot een niet-significant niveau. Dit laatste geldt ook voor een conflict vermijdend temperament en recidiverende stemmingsstoornissen. De resultaten suggereren dat niet enkel stressvolle levensgebeurtenissen, maar ook psychologische-/persoonlijkheidsaspecten een belangrijke rol spelen bij de kwetsbaarheid voor (recidiverende) stemmingsstoornissen. Deze nieuwe inzichten bieden aanknopingspunten voor vroeg-interventie in deze kwetsbare groep.

De rol van het afweer systeem in interactie met het brein- bij de bipolaire stoornis en KBO: monocytenactivatie, BDNF en S100B

Een forse ontsteking in het lichaam kan leiden tot depressie, denkt u maar eens aan een heftige griep die gepaard kan gaan met ook psychisch onwel bevinden. Depressie komt vaker voor bij mensen met een auto-immuunziekte, en andersom komen bij patiënten met een bipolaire en/of depressieve stoornis vaak auto-immuun ziekten voor. Binnen onze onderzoeksgroep werd in de afgelopen 15 jaar veel onderzoek gedaan naar diverse

aspecten van het afweer systeem bij patiënten met een bipolaire stoornis. Zo werd eerder beschreven dat niet alleen patiënten met een bipolaire stoornis, maar ook bij kinderen van een ouder met een bipolaire stoornis, een hogere neiging hebben voor schildklierauto-immuun ziekten. Dit suggereert dat gedeelde factoren een rol spelen bij het ontstaan van auto-immuunziekten en stemming stoornissen. In vervolgstudies werd onderzoek gedaan naar de monocyt, een belangrijke cel in het niet-specifieke immuunsysteem. In deze studies is een genexpressie signatuur van een twintig tal genen gevonden die de staat en de neiging van de monocyt tot ontsteking weergeven. Er werd een verhoogde ontstekingsstaat van monocyten gevonden bij patiënten met een bipolaire stoornis ten opzichte van een controle groep. Deze ontsteking signatuur was niet alleen aanwezig in een groot deel van de patiënten met een bipolaire stoornis, maar ook bij kinderen van een ouder met een bipolaire stoornis zoals gemeten in een beperkte groep tijdens de 1-jaar follow-up. Opmerkelijk was dat deze zogenaamde 'monocyten ontsteking signatuur' bij kinderen van patiënten voornamelijk aanwezig was bij diegene die op de 5-jaarsmeting een stemmingsstoornis ontwikkelden, wat zou kunnen betekenen dat deze test aan monocyten prognostische waarde zou hebben.

De studie beschreven in **hoofdstuk 5** bouwt voort op de resultaten van bovenstaande studies aan monocyten. We keken niet alleen naar de ontsteking signatuur in monocyten, maar ook naar de ontstekingsstoffen (zogenaamde cytokinen) PTX-3, CCL2 en IL-1β in het serum van bloed. Ook is er gekeken naar BDNF en S100B, stoffen voornamelijk afkomstig uit de hersenen, die ons meer vertellen over de groei en het functioneren van neurale circuits. BDNF is betrokken bij vrijwel alle stadia van ontwikkeling van neurale circuits. S100B is een stof die wordt afgegeven door astrocyten en die zowel een beschermende als beschadigende werking op zenuwcellen kan hebben, waarbij voornamelijk verhoogde waardes geassocieerd worden met neuropathologie.

Vergeleken met controles, vonden we gedurende de adolescentie (in de beginmeting en de 1-jaars meting) bij kinderen van een ouder met een bipolaire stoornis verhoogde monocytenactivatie zoals gemeten op het niveau van de monocytensignatuur, als op het cytokinenniveau (gemeten met PTX-3). BDNF was verlaagd, S100B en CCL2 lieten geen afwijkingen zien. In de 5-jaarsmeting, op gemiddeld 21-jarige leeftijd, was de monocytenactivatie nog steeds verhoogd, maar minder en met een ander ontstekingsprofiel dan bij de metingen gedurende de adolescentie. PTX-3 bleef verhoogd op deze meting en ook werden er nu verhoogde waardes van serum CCL2 waargenomen, een stof betrokken bij het migratieproces van monocyten. BDNF en S100B konden niet gemeten worden voor de 5-jaarsmeting. In de 12-jaarsmeting op gemiddeld 28-jarige leeftijd, was de monocytenactivatie niet meer afwijkend, behoudens CCL2. Daarentegen waren BDNF en S100B wel verhoogd.

Bovenstaande afwijkingen in het afweer systeem en neurale circuits kwamen voor in de totale groep van kinderen van een ouder met een bipolaire stoornis, en vertoonden geen directe relatie tot de ontwikkeling van psychopathologie. Ze lijken dus vooral te wijzen op een algemene kwetsbaarheid voor immuun ziekten, maar een directe relatie met het ontstaan van stemmingsstoornissen zal in verder onderzoek zichtbaar moeten worden.

In de studies zoals beschreven in hoofdstuk 4 en 5 werd onderzoek gedaan naar risicofactoren. Uit deze studies blijkt dat de verschillende determinanten op verschillende manieren bijdragen aan de hoog-risico status van kinderen van een ouder met een bipolaire stoornis. Zo werden aanwijzingen gevonden voor een relatie tussen stressvolle levensgebeurtenissen, passieve coping stijl, en het ontstaan van de eerste stemmingsepisode. Bij recidiverende stemmingsstoornissen lijken stressvolle levensgebeurtenissen echter in mindere mate een rol te spelen, maar lijken voornamelijk het aantal voorgaande episodes, passieve coping stijl en een conflict vermijdend temperament een belangrijke voorspeller. De studie naar immuun aspecten (monocytenactivatie, BDNF en S100B) laat een generiek kwetsbaarheidsprofiel zien, dat wil zeggen onafhankelijk van aanwezigheid van psychopathologie.

De vroege ontwikkeling van stemmingsstoornissen bij kinderen van een ouder met een bipolaire stoornis

De studies beschreven in **hoofdstuk 6 en 7** richtten zich op vroege herkenning van stemmings-stoornissen bij deze kwetsbare groep. In **hoofdstuk 3** werd gevonden dat een bipolaire stoornis vrijwel altijd begint met een (milde) depressieve stoornis, gevolgd door een eerste hypomane of manische episode gemiddeld vijf jaar later.

Het doel van de studie beschreven in **hoofdstuk 6** was om de voorstadia van de bipolaire stoornis en stemmingsstoornissen bij kinderen van een ouder met een bipolaire stoornis verder te verfijnen op symptoomniveau. We maakten voor deze studie gebruik van de symptoomscores van de K-SADS-PL tijdens de eerste- en de einddiagnose van de 12-jaars meting.

Van de kinderen met een lifetime depressie tijdens de eerste meting, rapporteerden degenen die later een bipolaire stoornis ontwikkelen, bij die eerste meting vaker subklinische symptomen van manie, suïcidale gedachten en doorslaapproblemen. Een eerste stemmingsstoornis, werd voorafgegaan door milde depressieve symptomen, terugkerende gedachten aan de dood, en meer algemene angstsymptomen zoals je gespannen voelen, verhoogd zelfbewustzijn en compulsies. De resultaten van **hoofdstuk 3, 6** en enkele andere recente studies samengenomen laten de vroege ontwikkeling van een bipolaire stoornis steeds duidelijker zien. De bipolaire stoornis start vrijwel altijd met een (milde)depressieve episode, vaak voorafgegaan door meer generieke angst en depressieve symptomatologie. De personen die dan vervolgens een bipolaire stoornis ontwikkelen vertonen al vroeg milde manische symptomen overgaand in een (hypo)manie. Meer onderzoek is nodig naar het tijdsbestek waarin deze symptomatologie plaats vindt, desalniettemin onderstrepen deze bevindingen het belang van gedetailleerde psychologische diagnostiek bij een kwetsbare populatie als kinderen van een ouder met een bipolaire stoornis.

De studie beschreven in **hoofdstuk 7** richtte zich eveneens op symptomen, nu aan de hand van een zelf-rapportage vragenlijst ingevuld door het kind. Voor deze studie werd gebruik gemaakt van een vragenlijst die zowel depressieve symptomen als symptomen van (hypo) manie meet: de 'General Behavior Inventory' (GBI) een vragenlijst met 73 items en een recent ontwikkelde verkorte variant van deze vragenlijst de 'Seven-up, Seven-down' (7U7D) met slechts 14 items.

Het doel van de studie was te onderzoeken of deze vragenlijsten bruikbaar zijn als screener voor stemmingsstoornissen in een kwetsbare groep zoals kinderen van een ouder met een bipolaire stoornis, hiervoor werd gebruik gemaakt van de data van de 12-jaars meting. Een tweede doel van de studie was om te testen of de recent verschenen verkorte vragenlijst even effectief was als de volledige GBI. Uit de studie komt naar voren dat de GBI en de 7U7D ongeveer gelijke resultaten opleveren: de 7U7D lijkt dus evengoed bruikbaar als de GBI met 73 items. Scores gemeten op de depressieschaal van de 7U7D kunnen in een redelijke mate voorspellen dat er sprake is (geweest) van een stemmingsstoornis. Bij de aanwezigheid van een depressieve stoornis, wijzen positieve scores op de hypomanie schaal op een mogelijke diagnose bipolaire stoornis. De 7U7D kan dus behulpzaam zijn als screener.

Vervolgens werd onderzocht of de GBI of de 7U7D ook voorspellende waarde heeft over de tijd. Er werd gekeken naar de scores op de vragenlijst ten tijde van de eerste meting en de diagnostische uitkomstmaat van de 12-jaarsmeting. Hoewel van beperkte diagnostische waarde, vonden we net als in een eerdere studie op de 5-jaarsmeting (Reichart *et al.* 2005), dat positieve scores op de depressieschaal tijdens de eerste meting geassocieerd zijn met een verhoogde kans op het ontwikkelen van een toekomstige stemmingsepisode. Hogere scores op de depressieschaal zijn dus mogelijk indicatief voor de ontwikkeling van een stemmingsstoornis in de toekomst.

Concluderend kan de 7U7D kan dus een zinvolle aanvulling zijn in de vroeg detectie van stemmingsstoornissen en mogelijk ook de bipolaire stoornis.

Samengenomen leiden de bevindingen van hoofdstuk 3, 6 en 7 tot belangrijke inzichten voor de clinicus ten aanzien van het vroege beloop en de ontwikkeling van de bipolaire stoornis en unipolaire depressie bij kinderen van een ouder met een bipolaire stoornis. Uit de studies beschreven in dit proefschrift komt naar voren dat een eerste stemmingsstoornis vaak voorafgegaan wordt door milde depressieve en angstklachten. Een bipolaire stoornis wordt vrijwel altijd voorafgegaan door een (milde) depressieve stoornis gevolgd door een hypomanie enkele jaren later. In de periode voorafgaand aan de transitie naar de bipolaire stoornis, worden vaak milde symptomen van manie, suïcidale gedachten en slaapstoornissen gerapporteerd. Ook blijkt dat een screeningsinstrument zoals de 7U7D behulpzaam kan zijn in de (vroeg) detectie van de bipolaire stoornis en andere stemmingsstoornissen bij kinderen van een ouder met een bipolaire stoornis.

DISCUSSIE

In **hoofdstuk 8** worden alle studies beschreven in dit proefschrift samengevat. Tevens worden de enkele methodologische aspecten van de Nederlandse KBO studie uitgelicht, waaronder de grootte van de studiepopulatie, uitdagingen bij longitudinaal onderzoek en het ontbreken van een controle cohort. Ook wordt de generaliseerbaarheid van de Nederlandse KBO studie, ethische kwesties bij hoog-risico onderzoek, en de specificiteit van de familiaire belasting besproken en wordt er stilgestaan bij de klinische implicaties van de resultaten van dit onderzoek. Er wordt een overzicht gegeven van de huidige stand van zaken ten aanzien van vroeg interventie op het gebied van psychologische en biologische interventies. Tenslotte sluit dit hoofdstuk af met aanbevelingen voor toekomstig onderzoek.

Concluderend hebben de studies beschreven in dit proefschrift geleid tot nieuwe inzichten en kennisverbreding ten aanzien van de ontwikkeling van stemmingsstoornissen bij kinderen van een ouder met een bipolaire stoornis. Achttien jaar na de start van de Nederlandse KBO studie, krijgen we langzaam maar zeker meer zicht op de vroege ontwikkeling van de bipolaire stoornis en stemmingsstoornissen in het algemeen bij kinderen van een ouder met een bipolaire stoornis. Hoewel meer onderzoek naar de vroege ontwikkeling nodig is, lijkt de tijd nu ook aangebroken voor een verschuiving naar onderzoek op het gebied van vroeg interventie.

List of publications

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Kemner, S.M., **Mesman, E.**, Nolen, W.A., Eijckemans M.J.C. & Hillegers, M.H.J. (2015). The role of life events and psychological factors in the onset of first and recurrent mood episodes in bipolar offspring: results from the Dutch Bipolar Offspring Study. *Psychological Medicine, x(x), 1-11.* DOI: 10.1017/S0033291715000495.

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MANUSCRIPTS IN PROGRESS

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CONFERENCE PRESENTATIONS AND PUBLISHED ABSTRACTS

Mesman, E. Bipolaire stoornis bij jeugdigen en jongvalwassenen. Oral presentation at the Autumn Conference Bipolar Disorders, Utrecht, The Netherlands, September 2014

Mesman, E., Nolen, W.A., Reichart, C.G., Wals, W. & Hillegers, M.H.J. 'Kinderen van ouders met een bipolaire stoornis: 12 jaar gevolgd'. Oral presentation at the Spring Conference of the Dutch Society of Psychiatry, Maastricht, The Netherlands, 2013.

Mesman, E. & Hillegers, M.H.J. (2013). Kinderen van een ouder met een bipolaire stoornis: 12-jaar follow-up. Published abstract in: Tijdschrift voor Psychiatrie, 55, (5), 385-386.

Mesman, E., Hillegers, M.H.J., Nolen, W.A. & Drexhage, H.A. Aberrant set points of the immune system in a Dutch Bipolar Offspring cohort: 12-year follow-up. Oral presentation at the Biennial Conference of the International Society for Bipolar Disorder, Istanbul, Turkey, 2012.

Mesman, E., Böhmer, M.N., Hillegers, M.H.J. & Nolen, W.A. Cognitive impairment in bipolar disorder: an endophenotype or a result of disease? A study in bipolar offspring. Poster presentation at the Biennial Conference of the International Society for Bipolar Disorders, Istanbul, Turkey, 2012.

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Curriculum Vitae

Esther Mesman was born in Lisse in the Netherlands on August 6th 1985. She studied Psychology at Utrecht University from September 2003 until February 2009. Between her Bachelor's and Master's degree, she volunteered at a non-governmental organization for orphans and street children in Arusha, Tanzania for about a year. In February 2009 she completed her Master's degree in Clinical Neuropsychology. She wrote her Master thesis at the schizophrenia program of the University of Toronto/Centre for Addiction and Mental Health and the University Medical Center Utrecht (UMCU). After obtaining her Master's degree she continued working at the UMCU and started working as a research assistant at a large epidemiological study focusing on the association of cannabis use and psychotic symptoms. In august 2009, she started her PhD-candidacy at the UMCU in collaboration with the University Medical Center Groningen and Erasmus Medical Center Rotterdam. Her PhD-candidacy was supervised by Manon H.J. Hillegers, PhD, MD, Hemmo Drexhage, MD, PhD and Willem A. Nolen, MD, PhD. In January 2014 she started her two year clinical training in psychology at the department psychiatry, of the Academic Medical Center in Amsterdam with a focus on early psychosis (2014) and mood disorders (2015). She will complete her clinical training in December 2015.