At risk for bipolar disorder
Mesman, Eshter

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Chapter 1

General introduction
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. |

<table>
<thead>
<tr>
<th>Core feature</th>
<th>Associated features</th>
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<tbody>
<tr>
<td>Depressed mood</td>
<td>Change in appetite or weight</td>
</tr>
<tr>
<td>In children and adolescents the mood may be irritable rather than sad</td>
<td>Insomnia or hypersomnia</td>
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<tr>
<td>Loss of interest or pleasure in nearly all activities</td>
<td>Psychomotor retardation or agitation</td>
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<tr>
<td></td>
<td>Fatigue or loss of energy</td>
</tr>
<tr>
<td></td>
<td>Feelings of worthlessness or guilt</td>
</tr>
<tr>
<td></td>
<td>Difficulty thinking, concentrating or making decisions</td>
</tr>
<tr>
<td></td>
<td>Recurrent thoughts of death, suicidal ideation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Manic episode*</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Core feature</th>
<th>Associated features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormally and persistently elevated, expansive or irritable mood.</td>
<td>Inflated self-esteem or grandiosity</td>
</tr>
<tr>
<td></td>
<td>Decreased need for sleep</td>
</tr>
<tr>
<td></td>
<td>Pressure of speech</td>
</tr>
<tr>
<td></td>
<td>Flight of ideas</td>
</tr>
<tr>
<td></td>
<td>Distractibility</td>
</tr>
<tr>
<td></td>
<td>Increased involvement in goal-directed activity or psychomotor agitation</td>
</tr>
<tr>
<td></td>
<td>Involvement in activities with painful consequences</td>
</tr>
</tbody>
</table>
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.

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**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 phenotypes: 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)*

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

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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 Excellence, 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 Axelsson 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 interplay 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](500369-L-bw-Mesman)

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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.,
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.
### General introduction

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

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Parental characteristics</th>
<th>Offspring characteristics</th>
<th>Offspring Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Parent BD index</td>
<td>BD Mother</td>
<td>Study source</td>
</tr>
<tr>
<td>----------------</td>
<td>------------------</td>
<td>------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Waters and Marchekio-Bouer (1980)</td>
<td>16 BAD (NS) 50%</td>
<td>Outpatient clinic</td>
<td>No info</td>
</tr>
<tr>
<td>LaRoche et al. (1981)</td>
<td>10 BAD (NS) 50%</td>
<td>Outpatient clinic</td>
<td>No info</td>
</tr>
<tr>
<td>Decina et al. (1983)</td>
<td>18 61% BD I 61% BD II</td>
<td>Outpatient clinic</td>
<td>No info</td>
</tr>
<tr>
<td>Gershon et al. (1985)</td>
<td>19 100% BD I 29%</td>
<td>Inpatient clinic or NIMH study</td>
<td>Any: ~41.3%</td>
</tr>
<tr>
<td>Kashani et al. (1985)</td>
<td>5 BAD (NS) NS</td>
<td>Inpatient clinic</td>
<td>No info</td>
</tr>
<tr>
<td>Klein et al. (1985)</td>
<td>24 100% BD I 54%</td>
<td>Inpatient clinic</td>
<td>Any: 25%</td>
</tr>
<tr>
<td>Grigoriou-Serbanescu et al. (1989)</td>
<td>47 100% BD I 60%</td>
<td>Inpatient clinic</td>
<td>Any: 28% Mood: 4% SCZ-BD: 2%</td>
</tr>
<tr>
<td>Todd et al. (1996)</td>
<td>9 89% BD I 11% BD II</td>
<td>Subsample NIMH study</td>
<td>Mood: 11%</td>
</tr>
<tr>
<td>Author (year)</td>
<td>$n$</td>
<td>Offspring characteristics</td>
<td>Offspring Assessment</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-----</td>
<td>---------------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Parental characteristics</td>
<td>Offspring characteristics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>n</td>
<td>BD Index</td>
</tr>
<tr>
<td>Chang et al. (2000)</td>
<td>37</td>
<td>BD I or BD II</td>
<td>81%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mother</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Henin et al. (2005)</td>
<td>88</td>
<td>BD I</td>
<td>72%</td>
</tr>
<tr>
<td>Hirshfeld – Becker et al. (2006)</td>
<td>23</td>
<td>BD I</td>
<td>52%</td>
</tr>
<tr>
<td>Jones et al. (2006)</td>
<td>20</td>
<td>BD I</td>
<td>95%</td>
</tr>
<tr>
<td>Singh et al. (2007)</td>
<td>29</td>
<td>BD I</td>
<td>100%</td>
</tr>
<tr>
<td>Petresco et al. (2009)</td>
<td>53</td>
<td>BD I</td>
<td>79%</td>
</tr>
</tbody>
</table>
### Table 3 (Continued)

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Parental characteristics</th>
<th>Offspring characteristics</th>
<th>Offspring Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>BD index</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Parent</td>
<td>BD</td>
</tr>
<tr>
<td>Birmaher et al. (2010)</td>
<td>83</td>
<td>61% BD I</td>
<td>39% BD II</td>
</tr>
<tr>
<td>Nurnberger et al. (2011)</td>
<td>91</td>
<td>86% BD I</td>
<td>NS</td>
</tr>
<tr>
<td>Zappitelli et al. (2011)</td>
<td>26</td>
<td>100% BD I</td>
<td>83%</td>
</tr>
<tr>
<td>Garcia-Amador et al. (2013)</td>
<td>36</td>
<td>70% BD I</td>
<td>55%</td>
</tr>
<tr>
<td>VandeLeur et al. (2012)</td>
<td>76</td>
<td>BD I, BD II 60% or SCZBD</td>
<td>In- and outpatient clinics</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Published work</th>
<th>Cohort characteristics</th>
<th>Parental characteristics</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Years of follow-up; Follow-up interval; (# interviews)</td>
<td>Drop-out rate</td>
<td>Type of cohort</td>
</tr>
<tr>
<td>Nurnberger et al. (1988)</td>
<td>2 Baseline, 1-, 2-years (3)</td>
<td>F</td>
<td>BAD (NS)</td>
</tr>
<tr>
<td>Zahn-Waxler et al. (1988; 1984)</td>
<td>4 Baseline, 3-, 4 years (3)</td>
<td>0%</td>
<td>F</td>
</tr>
<tr>
<td>Hammen et al. (1987; 1990)</td>
<td>Up to 3 Every 6 months</td>
<td>15%</td>
<td>D</td>
</tr>
<tr>
<td>Weintraub and Carlson (1987); Carlson and Weintraub (1993; 1987)</td>
<td>3 Baseline, 3 years (2)</td>
<td>15%</td>
<td>D</td>
</tr>
<tr>
<td>Meyer et al. (2004; 1992); Radke-Yarrow et al. (1992)</td>
<td>23 Baseline, every 12% 3-5 years (5)</td>
<td>D/F</td>
<td>22</td>
</tr>
<tr>
<td>Hillegers et al. (2005)</td>
<td>5 Baseline, 1-, 5-years (3)</td>
<td>6%</td>
<td>F</td>
</tr>
<tr>
<td>Reichart et al. (2004b); Wals et al. (2001)</td>
<td>16 Annually (16)</td>
<td>0%</td>
<td>D/F</td>
</tr>
<tr>
<td>Egeland et al. (2012; 2003); Shaw et al. (2005)</td>
<td>Up to No info</td>
<td>18%</td>
<td>D</td>
</tr>
<tr>
<td>Nijar et al.(2004; 2014); Ellenbogen et al. (2004)</td>
<td>Up to 10 No info</td>
<td>18%</td>
<td>D</td>
</tr>
<tr>
<td>Duffy et al. (1998; 2002; 2007; 2009b; 2010; 2014; 2011)</td>
<td>Up to 16</td>
<td>18%</td>
<td>D</td>
</tr>
<tr>
<td>Axelton et al. 2015 Birmaher et al. (2009)</td>
<td>Mean follow-up 7 years</td>
<td>Mean follow-up 7 years</td>
<td>2.5 years</td>
</tr>
</tbody>
</table>

**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; **DYS T** = 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.
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

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

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 antecedents 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.
Chapter 1

REFERENCE LIST


