Life events and bipolar disorder

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CHAPTER 1

General introduction

GENERAL INTRODUCTION

In this chapter the diagnostic criteria of bipolar disorder and risk markers associated with the onset and course of the disease are described. Subsequently, the concept of life events will be introduced and it will be explained how these can be measured, followed by a brief introduction into the twin design and genetic model fitting. Finally, the specific chapters of this thesis are introduced.

BIPOLAR DISORDER

DIAGNOSTIC CRITERIA

Bipolar disorder (BD), also known as manic depressive disorder, is characterized by episodes with severe high or low moods combined with changes in activity, sleep, energy, thinking and behaviour. The studies described in this thesis are based on the diagnostic criteria of DSM-IV (American Psychiatric Association, 1994) and not on the more recent DSM-5 (American Psychiatric Association, 2013). Therefore, the description of BD will be limited to the DSM-IV criteria.
There are four types of BD: bipolar I disorder (BD I), bipolar II disorder (BD II), cyclothymic disorder and bipolar disorder not otherwise specified (BD-NOS) (Table 1). In BD I the primary presentation consists of manic episodes which, in most cases, are alternated with depressive episodes. In BD II, the primary presentation consists of depressive episodes, alternated with hypomanic episodes. Cyclothymic disorder is a chronic state of (rapid) cycling between hypomanic and minor depressive episodes which are not reaching the diagnostic criteria for BD I or BD II. BD-NOS is characterized by bipolar features that are not meeting the criteria of any of the above mentioned disorders, e.g. very rapid alternations (days) between manic and depressive symptoms, recurrent hypomanic episodes without interference of depressive symptoms (Goodwin & Jamison, 2007; American Psychiatric Association, 1994).

CLINICAL CHARACTERISTICS OF BIPOLAR DISORDER

The prevalence of BD I and BD II is about 1-2% among adults. The lifetime prevalence of the broader bipolar spectrum ranges between 3-8.3% and is equally prevalent among the sexes (Goodwin & Jamison, 2007; Regeer, Rosso, Ten Have, Volleberg & Nolen, 2002). 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 a late onset with a mean age of 46 (Bellivier et al., 2011; Leboyer, Henry, Paillere-Martinot & Bellivier, 2005). The mean age of onset as found in Europe lies around 25 years (Post et al., 2008). However, BD can remain undiagnosed for many years. There is not only a delay between the first episode and the confirmed diagnosis and treatment, but also between the first symptoms and the first episode (Leverich et al., 2002).
Over 90% of BD patients experience recurrences during their lifetimes. Recurrence rates are about 40-50% over a 2 year period and 68-73% over a 4 to 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). This is also true for the most severe episodes. After a first admission in a psychiatric hospital, 50-75% of patients have a recurrence within 4 to 5 years (Bromet et al., 2005; Leverich et al., 2001).

Table 1. Diagnostic criteria for mood episodes (American Psychiatric Association, 1994)

MANIC EPISODE

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood for at least a week (or any duration if hospitalization is necessary)

B. During this period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree:

1. Inflated self-esteem or grandiosity

2. Decreased need for sleep

3. Pressure to keep talking

4. Flight of ideas and/or racing thoughts

5. Distractibility

6. Increased goal-directed activity or psychomotor agitation

7. Engaging in activities with potentially painful consequences

C. The symptoms do not meet criteria for a Mixed episode

D. The mood disturbance causes marked impairment in occupational functioning or social activities ore relationships with others, or necessitates hospitalization to prevent harm to self or other, or there are psychotic features

E. The symptoms are not due to the direct physiological effects of a substance or a general medical condition

HYPOMANIC EPISODE

Same as the above where episodes are not sever enough to cause marked social or occupational impairment (or necessitate hospitalization) and have no psychotic features but do represent an unequivocal change in functioning that is uncharacteristic of the person and persists for a minimum duration of 4 days

DEPRESSIVE EPISODE

A. Five (or more) of the following symptoms have been present during the same two-week period and represent a change from previous functioning: at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure

1. Depressed mood

2. Loss of interest or pleasure in activities

3. Significant change in appetite or weight

4. Insomnia or hypersomnia

5. Psychomotor agitation or retardation

6. Fatigue or loss of energy

7. Feelings of worthlessness or inappropriate guilt

8. Diminished ability to think, concentrate or make decisions

9. Recurrent thoughts of death, suicidal ideation or attempt

B. The symptoms do not meet criteria for a Mixed episode

C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

D. The symptoms are not due to the direct physiological effects of a substance or a general medical condition

E. The symptoms are not better accounted for by bereavement, i.e. after the loss of a loved one, the symptoms persist for longer than two months are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation

MIXED EPISODE

A. The criteria are met both for a Manic episode and for a Major depressive episode (except fo dureation) nearly every day during at least a 1-week period

B. The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm toself or others, or there are psychotic features.

C. The symptoms are not due to the direct physiological effects of a substance or a general medical condition

About 65-71% of the BD patients have psychiatric comorbid conditions. Substance use disorders (24-42%) and anxiety disorders (15-42%) are the most common comorbid disorders found in BD (Conus & McGorry, 2002). Next to this the risk for suicide among bipolar patients is about 20-30 times higher than in the general population (Pompili et al., 2013; Schaffer, Sinyor, Reis, Goldstein & Levitt, 2014). BD is also strongly related to comorbid medical conditions such as cardiovascular disease, thyroid dysfunction, diabetes and metabolic syndrome. Medical conditions may be a consequence of lifestyle, adverse effects of medication, but also point to shared etiology (Goodwin & Jamison, 2007)

(GENETIC) RISK MARKERS

The heritability of BD converges on the 60-80% range (McGuffin et al., 2003). Thus although genetic factors play an important etiological role in the disorder, the importance of environmental variables should not be neglected. Family based studies (e.g. twin studies) are crucial in research that aims to disentangle genetic from environmental sources of resemblance, later in this chapter the theory of twin studies is described in more detail. Thus far the etiology of BD is largely unresolved. BD is considered to be a multifactorial disease in which both genes and environment play a (interacting) role. A few factors associated with an increased risk for BD will be addressed.

Structural brain abnormalities

Structural neuroimaging has been used to study brain morphology in BD for over 20 years. BD is frequently associated with subtle brain abnormalities. To date the most consistent findings are increases in white matter hyper intensities and ventricular enlargement (McDonald et al., 2004; Van der Schot, 2009). In addition, there is also a large body of studies that continue to report conflicting findings such as both significantly larger and smaller volumes of the amygdala, hippocampus and thalamus among patients with bipolar disorder (Chang et al., 2005; Altshuler et al., 2000; Frazier et al., 2005; Beyer et al., 2004; Dupont et al., 1995).

The hippocampus is a brain structure that is particularly sensitive to the effects of (chronic) stressful experiences (Fuchs & Flugge, 1998; Lee, Ogle & Sapolsky, 2002; McEwen, 1999; Miller & O'Callaghan 2005; Sapolsky,1999). These stressful experiences are associated with a decreased volume of the hippocampus and with impaired hippocampal-dependent functions in patients with stress-related psychiatric syndromes, including major depressive disorder and post-traumatic stress disorder (Campbell & MacQueen, 2004; Geuze, Vermetten & Bremner, 2005; Kitayama, Vaccarino, Kutner, Weiss & Bremnder, 2005; Smith, 2005). A few studies have investigated the specific association between stressful life events and hippocampal volume in healthy subjects and found hippocampal structural deficits in relation to environmental stress. (Gianaros et al., 2007; Papagni et al., 2011; Rabl et al., 2014; Shepherd, Laurents, Matheson, Carr & Green, 2012).

In **chapter 4** we explore the relationship between life events and hippocampal volume in healthy twins.

Activation of the immune system

There is growing evidence that activation of the immune system plays an important role in the pathogenesis of BD. It was already in the early 1990's that the Macrophage T cell theory of depression was proposed (Smith, 1991), postulating an activated inflammatory response system in mood disorders. Inflammation is a part of the nonspecific immune response that takes place after any type of bodily injury or microbial invasion. Many of these reactions involve cytokines, especially interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-α) and IL-6, produced by dendritic cells, macrophages and other types of cells (Stertz, Magalhaes & Kapczinski 2012).
In previous studies from our group it has been reported that there is a presence of a pro-inflammatory state of circulating monocytes in a considerable proportion of not only patients with BD, but also in the offspring of bipolar parents (Padmos et al., 2008), indicating that the pro-inflammatory state of monocytes precedes the actual mood symptoms. In a subsequent twin study from our group this relation was further explored and it was concluded that common environmental factors are the main contribution to the association of the pro-inflammatory monocytes with bipolar disorder (Padmos et al., 2009).
Both major and minor stressful events can have direct adverse effects on a variety of immunological mechanisms; both animal and human studies have provided convincing evidence that these immune alterations are consequential for health (Padget & Glaser, 2003).
In **chapter 5**, we will explore the relation between BD, pro-inflammatory monocytes and stress.

Stress

Many studies have focused on the impact of stress, varying from daily hassles to traumatic events, on the development of psychiatric illnesses. In BD the focus has been on whether life events predict the timing and severity of symptoms and episodes (Johnson, 2005). Indeed, many studies have demonstrated that environmental stress plays a role in the onset and in the further course BD (Hillegers et al., 2004; Hunt, Bruse-Jones & Silverstone, 1992; Malkoff-Schwartz et al., 1998). However, the precise role of stress in the pathogenesis and course of BD remains poorly understood.
There are various models that aim to clarify the interplay between stress and psychopathology. This section contains a brief description of these models; the stress-generation hypothesis, the diathesis stress models, the kindling hypothesis and the stress buffering hypothesis.

Stress-generation hypothesis

According to the stress generation perspective, individuals are actively creating their life stressors (i.e. dependent events). Meaning that individuals vulnerable to mood disorders, when compared to those without such vulnerability, are likely to experience a higher rate of dependent events, particularly within interpersonal domains (Hammen, 1991, 2006). There is a substantial amount of support for the stress generation effect in depression (Liu & Alloy, 2010), but preliminary results from studies among both bipolar patients and bipolar offspring have failed to find support for this stress generation effect (Grandin, Alloy & Abramson, 2007; Ostiguy, Ellenbogen, Linnen, Walker & Hammen, 2009).

Diathesis stress model
Another model in which the presence of psychopathology is often explained is the stress-diathesis model (Monroe & Simons, 1991). According to this model environmental influences (stressors) trigger the onset of psychiatric disorder, because they interact with non-biological of genetic traits (diatheses).

Kindling hypothesis
An extension of the diathesis stress model is known as the kindling hypothesis, which premises that stressors (e.g. life events) are a more significant trigger in the onset of initial episodes rather than in subsequent episodes, which can at that point occur more or less spontaneously (Post, 1992). The kindling model was originally described as electrical kindling in relation to epilepsy where after many repetitions of kindled seizures 'spontaneity' occurs, i.e. seizures develop in the absence of external stimulation (Pinel, 1981). Several studies have demonstrated that a history of episodes is a significant risk factor for future recurrences in mood disorders (Judd et al., 2008; Keller, Lavori, Lewis, & Klerman, 1983; Perlis et al., 2006). However, studies to the kindling hypothesis in BD are limited and findings are inconsistent. (Bender & Alloy, 2011).

Stress buffering hypothesis
The stress-buffering model is a multifactorial model which includes possible moderators. The model posits a process in which social support is protecting persons from potentially adverse effects of stressful life events (Cohen & Willis, 1985). However, research in BD reporting on multifactorial models is scarce (Mesman, 2015).

LIFE EVENTS

Background

As described above, many studies have focused on the impact of stress on the development of psychiatric illnesses. However, the definition, operationalization and measurement of stress is not a concept that is agreed upon (Cohen, Kessler & Gordon, 1997). Cohen et al. (1997) pointed out that all studies to the impact of stress "share an interest in a process in which environmental demands tax or exceed the capacity of the organism, resulting in psychological and biological changes that may put the person at risk… [for adverse health outcomes]…". Within this definition, life events are important representations of environmental demands.
Life events can vary from regular activities occurring in daily life (daily hassles in domestic, educational or work situations) with minimal impact, to extreme situations beyond one's own control (e.g. wartime, natural disasters). In addition, life events can be both positive (e.g. a graduation) or negative (e.g. discharge from job) and can be both dependent (e.g. buying a house) and independent (e.g. natural disaster) on a person's own behaviour. This leaves us with a huge spectrum of life events that can all possibly cause a stressful experience and potentially trigger mental illness.

Measuring life events

Almost half a century ago Holmes and Rahe (1967) published a checklist of 43 events such as death of a spouse, divorce, fired at work, and sex difficulties: the Schedule

of Recent Experiences (SRE). Its purpose was to inventory "fundamentally important environmental incidents" that were found to frequently precede illness onsets. Stressful events were defined as occurrences that were likely to bring about readjustment-requiring changes in people's usual activities.
Since the publication of the SRE, a tremendous increase has occurred in the construction of such measures and in quantitative research on relations between life events and mental illness (Dohrenwend, 2006).
Checklists in the form of self-administered questionnaires or in the form of structured interviews consisting of closed questions with fixed alternative response categories have been dominant in research on the role of stressful life events in psychopathology. A large body of research on the role of life events in psychopathology that have been conducted in recent years, are making use of checklists. The behavioural genetics study of depression by Kendler et al. (1995), the nationwide epidemiological research on the comorbidity of psychiatric disorders by Kessler, Sonnega, Bromet & Nelson (1995) and the study of gene-by-environment interaction for depression by Caspi et al. (2003) are examples. The fundamental methodological puzzle in inventorying life events as risk factors for psychopathology is how to solve the problem of intracategory variability in traditional checklists. Intracategory variability is the issue that positive responses to event categories (e.g. marriage, divorce, death of a close friends) can represent very different types of actual experiences.
The dominant alternative approach in life event measurement is labour intensive and involves the collection and analysis of detailed information about the events reported. It is this narrative information about the event that makes it possible to reduce intracategory variability. If the details and context of the event are known, then the distinction between major events and minor events within a particular category become less ambiguous than if identified by a positive response to a checklist category only. For example, a positive response to 'death of a close friend' can range from 'death of a long absent, childhood friend to whom the respondent was no longer close' to 'death of a close friend, whom the respondent talked to and relied on from a day-to-day basis' depending on the respondent. This distinction can only be made if there is relevant contextual information available.
Ratings by trained judges can be made of the relevant event characteristics – such as valence, source, and magnitude – that are of interest.

LEDS

The best-known example of a narrative rating method, and the method used in all studies described in this thesis (**chapter 2-5**), is the investigator-based Bedford College Life Events and Difficulties Schedule (LEDS) developed by Brown and colleagues (Brown & Harris, 1978). Bender & Alloy (2011) confirmed that the LEDS should be considered as the gold standard of life stress measurements. Starting with its introduction over 35 years ago (Brown & Harris, 1978), this instrument was designed to deal with the problem of intracategory variability in objective scoring of checklist categories.
The LEDS is a semi-structured interview for assessing life events and long-term difficulties in adults. It collects detailed information about the event itself, the timing of its occurrence (date) and relevant contextual information for each event. Each event

is categorized into one of ten domains, consisting of education, work, reproduction, housing, money/possessions, crime/legal, health, marital/partner, other relationships and miscellaneous/death.
After conducting the interview, the interviewer writes a full report on all events. Based on the contextual information provided in this report, the threat for each event is rated via standardized rating procedures by two independent raters who have not been involved in the interviews. The threat score represents the severity of the event, ranging from mild (1) to severe (4), hereby differentiating between mild life events and more stressful life events. 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, 1989).

Genes & Environment

Concurrent with the rise of the use of life events in research to environmental influence on development of psychopathology is the question whether measures of environment are influenced by genetic factors themselves (Plomin, 1986). Genetic influence on measures of environment is not as paradoxical as it seems because genetically influenced characteristics, such as cognitive abilities and personality, might affect how individuals construct their environment and how they feel about and behave towards other (Plomin, Lichtenstein, Pedersen, McClearn & Nesselroade, 1990).
Kendler and Baker (2007) reviewed 55 studies that measured the genetic influence on a wide variety of environmental factors, such as general and specific life events, parenting style, family environment, social support, peer interactions, and marital quality. Ten twin studies were identified that examined the heritability of general stressful life events (Wierzbicki, 1989; Plomin et al., 1990; Kendler, Neale, Kessler, Heath & Eaves, 1993; Billig, Hershberger, Lacono & McGue, 1996; Foley, Neale & Kendler, 1996; Thapar & McGuffin 1996; Saudino, Pedersen, Lichtenstein, McClearn & Plomin, 1997; Bolinskey, Neale, Jacobson, Prescott & Kendler, 2004; Wang, Trivedi, Treiber & Snieder, 2005). Six of these studies reported on the total SLE's (Wierzbicki 1989; Plomin et al., 1990; Kendler et al., 1993; Thapar & McGuffin 1996; Bolinskey et al., 2004; Wang et al., 2005). In five of these studies the heritabilities (i.e., the proportion of individual differences for a train in a particular population that results from inter-individual genetic differences) ranged from 24% to 47%. They concluded that every aspect of the environment that was examined, was significantly influenced by genetic factors, however the role of genetic influences was modest at most. A more recent study replicated this finding (Vinkhuyzen, van der, de Geus, Boomsma, & Posthuma, 2010), but explicitly stated that these influences were small and that the reviewed findings were often inconsistent.
The described findings suggest that what we think of as measures of the 'environment' are better described as 'external factors'. Therefore, interplay between genes and environment in the study of life events is an important facet to keep in mind when trying to disentangle how environmental factors shape individual differences in behaviour.

SAMPLES

The studies described in this thesis are from the Dutch Bipolar Offspring study (DBOS; **Chapter 3**) and the Dutch Bipolar Twin Study (DBTS; **Chapter 2, 4 and 5**). Both studies have been described in detail in previous PhD theses (DBOS; Wals, 2004; Reichart, 2005; Hillegers, 2007; Mesman, 2015. DBTS; van der Schot, 2009; Vonk, 2016; Bootsman, 2016). Below I briefly describe the samples. Demographic characteristics of both samples are presented in Table 2.

The Dutch Bipolar Offspring Study

The Dutch Bipolar Offspring Study is a prospective fixed cohort study established in 1997 with up to now a follow-up of 12 years. The main objective to initiate the Dutch Bipolar Offspring Study, 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).
Families with at least one parent with bipolar I or II disorder having children in the age range 12-21 years old were recruited via patient associations, outpatient clinics and psychiatric hospitals.
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). The fourth and most recent assessment (T4) was performed 12-years after baseline (Mesman, 2015) (Figure 1). All study assessments were approved by the Medical Ethics Committee of the University Medical Center Utrecht.

The Dutch Bipolar Twin Study

The Dutch Bipolar Twin Study is a longitudinal twin study on BD of the University Medical Center Utrecht (UMCU), The Netherlands. The main objective of this study was to examine factors related to an increased risk for bipolar disorder; i.e. obstetric complications, dermatoglypic alteration, life events, autoimmune thyroiditis with levels of thyroperoxidase antibodies, school performance and structural brain abnormalities. Twin pairs were enrolled between 2001 and 2006 for the first measurement (van der Schot, 2009; Vonk, 2016) and the second assessment was performed between 2009 and 2011 (Bootsman, 2016)(Figure 1).
Twin pairs, aged 18 to 60 years, with at least one twin suffering from either BD I or BD II were recruited via patient associations, outpatient clinics, psychiatric hospitals and Dutch media. Healthy control twins were drawn from an ongoing twin study on schizophrenia of the UMC Utrecht (Van Oel et al., 2001) and from the Netherlands Twin Register (NTR) at the VU University in Amsterdam. A total of 53 affected twin pairs took part in the study, as well as 51 control twin pairs.
Zygosity was determined by DNA fingerprinting using high polymorphic microsatellite markers to 9 to 11 in the laboratory of the Division Biomedical Genetics, University Medical Center Utrecht.

All psychiatric diagnoses were confirmed with the Structured Clinical Interview for DSM-IV (First, Spitzer, Gibbon & Williams, 1996) and the Structured Interview for DSM-IV Personality (Pfohl, Blum & Zimerman, 1997). Current mood state was assessed using the Young Mania Rating Scale (YMRS – Young, Biggs, Ziegler & Meyer, 1978) and the Inventory for Depressive Symptomatology (IDS – Rush, Gllion, Basco, Jarret & Trivedi, 1996). At the time of inclusion, all patients were euthymic with an YMRS score of 4 or less and an IDS score of 12 or less. All patients were treated naturalistically.
The medical ethics review board of the UMCU approved the study and all participants gave written informed consent after full explanation of the study aims and procedures.

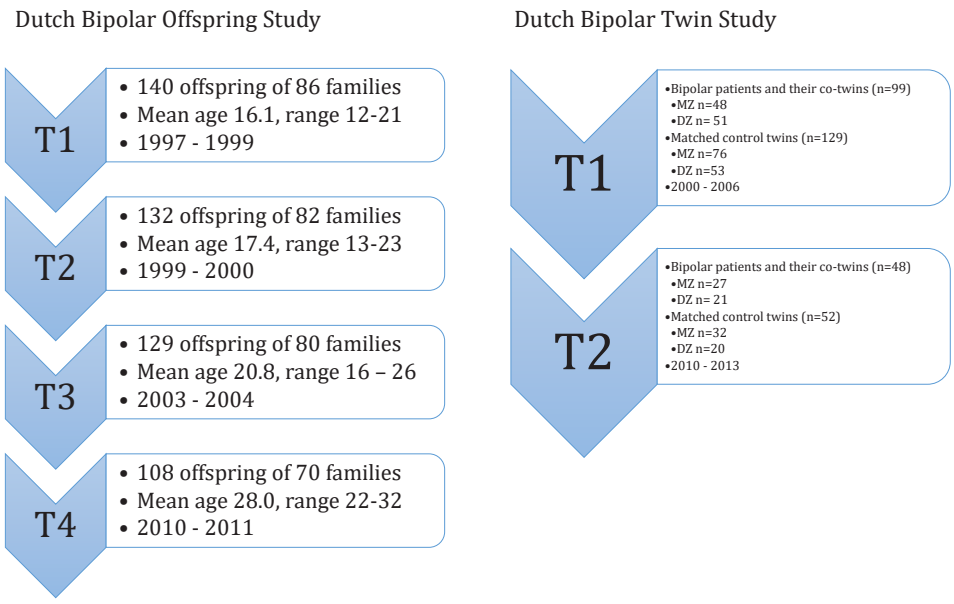

Figure 1. Study flows of the Dutch Bipolar Offspring Study and the Dutch Bipolar Twin Study

Table 2. Demographic characteristics of the Dutch Bipolar Twin Study (baseline) and the Dutch Bipolar Offspring study (T1 & T4)

	Bipolar twin pairs (n=53)		**Control twin pairs (n=51)**	
	MZ (n=24)	**MZ (n=24)**	**MZ (n=32)**	**DZ (n=19)**
Female, N (%)	34 (71)	34 (71)	40 (63)	25 (66)
Mean age, yrs (SD)	37.8 (10.6)	37.8 (10.6)	40.3 (11.5)	42.0 (7.4)
	Bipolar patients (n=66)	Non-bipolar cotwins (n=40)	Control twins (n=102)	
Female, N (%)	45 (68)	27 (68)	65 (64)	
Mean age, yrs (SD)	40.8 (10.1)	42.4 (9.9)	40.9 (10.1)	
Mean age of onset, yrs (SD) [range]	28.3 (9.7) [14 – 59]			

	Bipolar offspring T1 (n=140)	Bipolar offspring T4 (n=108)
Female, N (%)	68 (49)	50 (46)
Mean age, yrs (SD)	16.1	28.0 (2.82)
Any disorder life time, N (%)	61 (44)	78 (72)
Any mood disorder life time, N (%)	38 (27)	58 (54)
Bipolar disorder (BD I, BD II), N (%)	4 (3)	12 (11)
Age of onset first mood episode BD, yrs (SD)	14.6 (4.65)	

GENES & ENVIRONMENT

Family-based studies such as high-risk populations (offspring design) and twin studies are of indescribable value in the quest to disentangle genetic from environmental influences. The longitudinal offspring design as described in this thesis is an elegant way to explore the early trajectories of BD in a high risk population.
With this design, it is possible to detect BD in an early stage and to prevent/delay the onset and/or diminish the severity of the illness. Twin studies are crucial in research that aims to disentangle genetic from environmental sources of resemblance and are described in detail below.

Twin model

The twin design is a classic design that dates back to almost a century ago when Merriman conducted the first real twin study in 1924, to assess the genetic influence on IQ (Merriman, 1924).
Identical twins, also called monozygotic (MZ) twins derive from one fertilized egg (zygote) and are therefore genetically identical. Unlike identical twins dizygotic (DZ)

twins develop from separately fertilized eggs. They are on average 50% genetically related, equally to other siblings. If genetic factors have a significant contribution in a certain trait, MZ twins must be more similar than DZ twins. Both type of twins share many aspects of their environment (e.g., parenting style, education, socioenomic status) as they are being born and raised at the same place and time. However, both also experience unique environmental influences (e.g., unique life events, i.e. diseases, employment and peers not shared with their co-twins).
The classical twin study begins with assessing the variance of a trait in a large group of MZ and DZ twins and then estimating how much of this is due to: genetic effects (heritability), shared environment (e.g., events that happen to both twins and affect them equally,) and unique (or unshared) environment (e.g. events that are unique to one twin). These three parts are typically called A (additive genetics), C (common environment) and E (unique environment).
The basic logic of the twin design relies on the assumption that differences between MZ twins raised in the same family are due to unique environment, since they share 100% of their genes and all of the common environment. The correlation of the MZ twins provides an estimate of the proportion of the variance that can be attributed to genetic and common environmental factors. DZ twins share on average 50% of their genes and all of the common environment leading to an estimate of the correlation of DZ twins. The twin pair correlations (rMZ and rDZ), representing the resemblance of the twin pairs, offer an estimate of the relative influence to which genes or shared/unique environment determine phenotypic variation of that trait.
To study the genetic contribution of variance in a certain phenotype, the trait needs to be heritable. Heritability of a phenotype, denoted in the literature as (h^2) or alternatively as (a^2), for additive part of heritability (narrow heritability), is assumed if the MZ correlation is twice as high as the DZ correlation. The influence of common environmental factors is indicated when the correlation in DZ twins is larger than half the MZ correlation. Finally, the part of the variance where MZ twins do not resemble each other is attributable to unique environmental factors.

Genetic model fitting

Structural equation modelling (SEM) or model fitting approaches involve constructing a model that best describes the observed data. SEM is a statistical technique which tries to fit observed data to models of genetic and environmental effects. It is suitable to test whether genetic of environmental factors contribute significantly in explaining the (co)variance within or between traits (Van der Schot, 2009). SEM involves path analyses, that as defined by Ullmann (1996): 'allows examination of a set of relationships between one or more independent variables, either continuous or discrete, and one or more dependent variables'. A measured variable is a variable that cannot be observed directly and must be inferred from measured variables (also known as factors). By using path analyses, specific hypotheses about relationships between the variables are quantified by parameter estimates or path coefficients. The overall phenotypic variance is explained by using three factors: A, C and E which are latent (unobserved) variables. The factor loadings a, c, e are the parameter estimates that represent the variances due to those factors: a^2, c^2, and e^2. Parameters can be removed from the full ACE-model. For example, an ACE model is compared to an AE model. In this case the influence of common environment is excluded. The CE model excluded additive genetic influence and the E model excludes all familial

resemblance. The aim is to find the most parsimonious model that most accurately describes the observed data. This can be tested via likelihood ratio tests (LRT). This LRT statistic follows a chi-square distribution. A chi-square larger than 3.84 (1df) indicates a significant difference at alpha=0.05 and implies that the discarded effect (e.g. effect of C on a trait) cannot be left out of the model without seriously deteriorating the goodness of fit.
The liability threshold model for a disorder (e.g. BD) holds that for binary traits (presence or absence of the disorder) influenced by multiple factors of small effect, an underlying liability exists, with a threshold that divides the population into two categories for the trait. Liability is a hypothetical continuous variable that determines whether an individual will develop the disorder (Rijsdijk & Sham, 2002). In a continuum of risk it is assumed that the disorder is normally distributed within the population occurring only when a certain threshold of liability is exceeded. A person with a high value on the liability scale crossing a certain threshold would be scored 'patient' on our dichotomous variable and in all other cases considered to be healthy (discordant co-twin of patient or healthy comparison twin pairs). Since twin pairs are selected for bipolar disorder, this would result in an overestimation for the prevalence of bipolar disorder. Therefore, we fixed prevalence to 1% and heritability of bipolar disorder to 85% (Ten Have, Vollebergh, Bijl & Nolen, 2002; Regeer et al., 2004; Smoller & Finn, 2003; van der Schot 2009).
In summary, the twin design augmented by the sophisticated structural equation modelling techniques, is able to examine the extent of genetic overlap between two traits, such as a disease and a putative endophenotype (Boomsma, Busjahn & Peltonen, 2002; Hall et al., 2007). Understanding the extent of genetic overlap may be crucial, because significant genetic associations validate the proposed phenotypic measure as an endophenotype for the disorder (Lenox, Gould & Manji, 2002; Hall et al., 2007).

AIMS AND OUTLINE OF THIS THESIS

The general aim of this study is to expand our knowledge on the role of life events as potential risk factor playing a part in the onset and course of bipolar disorder.

In **chapter 2** and **3** I explore the influence of life events on onset and course of bipolar disorder.
Chapter 2 aims to clarify the role of life events on first and recurring admissions in bipolar patients including testing the role of the kindling hypothesis in this relation.
Chapter 3 aims to elucidate the interplay of life events, psychological aspects and social support on mood episode onset and recurrences among bipolar offspring

In **chapter 4** I take a side step to a healthy twin study in which we explore the influence of life events on hippocampal volume.

In **chapter 5** I aim to clarify the role of life events in the association between pro-inflammatory monocytes and bipolar disorder.

The final chapter provides a summary of all above noted chapters followed by a general discussion, clinical implications and suggestions for future research.