Life events and bipolar disorder
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CHAPTER 6

Summary and Discussion
INTRODUCTION

The general aim of this study was to expand our knowledge on the role of life events as potential risk factor in the onset and course of bipolar disorder (BD), a complex and multifactorial disease with genetic and environmental factors contributing to its clinical expression.

MAIN FINDINGS

CHAPTER 2

In chapter 2 we aimed to clarify the role of life events on first and recurrent admissions in bipolar patients, including the role of the kindling hypothesis in this relation. Our study showed that life event load, operationalized as the number and severity of life events, had an impact on both first and recurrent admissions in bipolar patients. This has also been found in previous studies (Bender & Alloy, 2011; Hunt, Bruce-Jones, & Silverstone, 1992; Kessing, Andersen, & Mortensen, 1998; Kessing, Agerbo, & Mortensen, 2004). Remarkably this effect was not influenced by events related to the illness which suggests that the effect of life events is independent of the disorder itself.

In addition, we demonstrated that the risk for admission increases with each subsequent admission. In other words, the risk of readmission increases as a function of the number of previous admissions. Given our finding that the risk of getting admitted is independent of events related to the disorder, such as admissions, the association between the number of previous admissions and the increased risk of readmission might be interpreted as an indicator for illness severity. Moreover, this finding also suggests a possible kindling effect (e.g. life events play a greater role in the onset of initial episodes than in subsequent later episodes, which can even occur more or less spontaneously; Post, 1992, Post, 2016). However, this finding did not reach statistical significance to support this indication of kindling.

A decay model was applied to the life event data, implying that the presumed effect of life events diminishes over time. The decay model of 25% best explained the impact of stressful life events on the onset of mood disorders, meaning that although the influence of stressful life events accumulates over time, this effect also diminishes with 25% per year. In other words, there is a limited expiration of the effect of stressful life events over time. The underlying mechanisms that cause this decay are unknown; a possible explanation lies in the interaction of life stress with coping strategies and temperament. Coping strategies, depending if they are constructive or maladaptive, can increase or decrease levels of stress and therefore influence the association between stress and the onset of mood episodes. In addition, temperamental traits (innate aspects of personality) influence individual coping styles and in that way modify the impact of stressful life events on mood episode onset (Compas, Connor-Smith, & Jaser, 2004). In the following chapter, we have studied the influence of these psychosocial factors in more detail.

Overall this study demonstrated a significant impact of stressful life events on both first and recurrent admissions in bipolar patients and this effect appeared to be independent of events related to the illness.
CHAPTER 3
In chapter 3 we studied the effect of stressful life events on the onset of a first and recurrent mood episodes in children of parents with BD (bipolar offspring), as well as the impact of temperament, coping and parenting styles on this association. Results of this study indicate that severe life events were associated with an increased risk for first and, although less pronounced, subsequent mood episodes. The study replicated findings of the second assessment at 14 months follow-up of the Dutch Bipolar Offspring Study (Hillegers et al., 2004). Here, we also applied several decay models and similar to chapter 2 the history of life events did not constitute a pure accumulative load as a natural decay effect of 50-75% per year was observed. We also found a large confounding effect for the number of previous mood episodes, suggesting a possible kindling effect for mood disorders among bipolar offspring. Passive coping style increased the risk of first mood episode onset and recurrent episodes, but also had a confounding effect on the association between life events and mood episode onset, suggesting that possibly the way offspring handle stress may be an important target for intervention. Harm avoidance temperament was found to be associated with mood episode recurrence and may possible indicate a general risk factor for mood recurrence.
Overall, this study found several risk factors to be associated with mood episode onset and recurrence in different ways and provides targets for early intervention.

CHAPTER 4
In chapter 4, we describe a study assessing the association between hippocampal volume and life events in a sample of healthy twins. The hippocampus is involved in negative feedback signalling to the hypothalamus during the hypothalamic-pituitary-adrenal (HPA) activated response to environmental stress, a process which results in secretion of glucocorticoids that are vital to short-term survival (Jankord & Herman, 2008). Chronic stress could disrupt the feedback signalling and consequent glucocorticoid toxicity in the hippocampus itself which, as a result may show atrophy and diminished neurogenesis (Sapolsky et al, 1990; Brown et al, 2004; Conrad, 2006; Mirescu & Gould, 2006; Gianaros et al; 2007; McEwen, 2007). Therefore, the association between hippocampal volume and life events was assessed. Moreover, the extent to which genes and environment influenced the association was determined.

The results showed that smaller hippocampal volume was related to higher severe life event load, which is in line with previous studies indicating an association between hippocampal volume loss and higher levels of stress (Gianaros et al, 2007; Papagni et al 2011). Moreover, these findings were extended in the present study as we showed that a severe life event load was associated with smaller hippocampal volume and not total or mild life event loads. Furthermore, environmental factors that were shared between twins fully explained the association between smaller hippocampal volume and a high level of life event load. This suggests that severe life events experienced by both twins, for example the loss of a parent, may have the largest impact on the hippocampus. In addition, hippocampal volume was primarily influenced by genes whereas life event measures were predominantly influenced by shared and unique environmental factors.
Based on these results, it is recommended to assess the influence of life events that affect twins similarly and to distinguish between severe and mild life events when assessing the relation between hippocampal volume and life stress. Addressing the link between stress and hippocampal structure is valuable in expanding our understanding of the mechanisms involved in severe mental illness. Hippocampal abnormalities have been shown in a number of stress-related psychiatric disorders, including BD (Hajek et al, 2012). Unfortunately, we were unable to expand this study with the inclusion of bipolar twins, due to the small sample size. Overall, this study in healthy twins demonstrated that smaller hippocampal volume was strongly associated with a high load of stressful life events, shared between twins. The heritability of hippocampal volume was high, whereas the life event load was predominantly influenced by shared and unique environmental factors.

CHAPTER 5
The study described in chapter 5 explored the role of life events in the association between pro-inflammatory monocytes and BD in twins. We found genetic correlations between BD and life events, but these associations disappeared when life events related to the disorder were disregarded. The disappearance of the genetic association suggests that life events related to the BD also occur for the co-twin (more so for MZ than DZ twins). This is a possible effect of the co-twin often being involved in the severe events of the affected twin (e.g. co-twin being involved in admission in a psychiatric hospital during a severe mood episode). Interestingly, we did not find evidence for our assumption that stressful life events would at least partially explain the association between monocyte inflammatory gene expression and BD. New findings indicate that affective episodes may be classified as pro-inflammatory states where different levels of concentrations of monocytes were found between the different mood episodes, suggesting that mania and depression are associated with a proinflammatory state (Becking et al., 2015). Overall, this study verifies our previous observation that common environmental factors determine monocyte activation in BD patients, yet showing that the experience of stressful life events is not one of these factors. Interestingly, life events were mainly influenced by genetic factors in BD.

METHODOLOGICAL CONSIDERATIONS
The findings of the studies described in this thesis should be viewed in light of a few limitations. For all chapters the relatively small sample size and the life event methodology are the most prominent factors to be considered when interpreting our results. Within each chapter the strengths and limitations of the specific chapters are described in detail. The results described in this thesis should thus only carefully be generalized to the total population of bipolar patients because both designs might be prone to specific selection biases described below.
Offspring Design
The study of children from a parent with BD using a longitudinal study design is an elegant and valid method to study the familial transmission of BD and the early trajectories of BD. Bipolar offspring represent a unique population at increased risk as they do not only inherit a genetic risk, but might also experience impaired family functioning and parenting skills as a result of parental mood episodes. In addition, assortative mating is common in these families resulting in an increased level of familial loading for (bipolar and unipolar depressive) mood disorders and other mental disorders as well as environmental complexities (Goodwin & Jamison, 2007).

In case of the Dutch Bipolar Offspring Study the cohort may not be fully generalizable to bipolar offspring in general. The majority (73%) of the families included in our cohort were recruited via the Dutch Patient Association for Manic Depressives and Relatives (Nederlandse Vereniging voor Manisch-Depressieve en Betrokkenen; VMDB). These families (both patients and their families) may be a selection of better functioning, better informed, motivated and a treatment seeking patient population. However, within our own sample, the families recruited via the VMDB did not differ in illness characteristics (number of hospitalizations, number of manic episodes and age of onset), socio-economic status and divorce rate, from the families recruited via outpatient clinics (Mesman, 2015; Hillegers, 2007).

Twin Design
Our twin sample is not a population-based twin sample, but a selected subgroup of bipolar twins and healthy (control) twins in the Netherlands. For instance, more female bipolar twins (68%) and female control twins (71%) than male twins participated in our study. This is probably a result of selection, as in the general population the prevalence of BD is the same in men and women (Weissman et al, 1996) On the other hand, the whole sample of affected twins can be considered representative as the concordance rates in our sample of 53 affected twins, 55% for MZ twins and 24% for DZ twins, is comparable with other reported concordance rates for BD (McGuffin et al). Also the healthy control twins form a selection, as they were selected for lifetime absence of any psychiatric disorder as well as for absence of a family history of any major psychiatric disorder.

COMPLEXITY OF RISK FACTORS IN THE STUDY TO BIPOLAR DISORDER
BD is a complex multifactorial illness. Empirical and theoretical work on BD has been going back and forth between psychological and biological conceptualizations. With the rise of family- and twin studies the interplay between environmental and genetic factors became a point of focus and has given rise to new and valuable insights into the mechanisms that contribute to psychiatric illness development. While our research contributes to a better understanding of gene-environment interaction (specifically life events) in BD, we should be aware that this is simplified representation of reality.

We know that the study of environmental risk factors poses various challenges. Many different environmental factors have been suggested to influence onset of
psychiatric disorders, e.g. urbanity, diet, but also traumatic events or pre-natal and perinatal conditions somatic etc. (Rutter et al. 2001; Brown & Harris, 1978; Bergink et al., 2013).

An additional complicating factor is that in most cases environmental variables are not purely environmental, but act under the influence of both genetic and environmental factors. In our studies, we aimed to measure stress by using life events as an environmental factor, but simultaneously showed that they are (at least moderately) influenced by genetic factors (chapter 4 – 5). This is not a recent finding as it was shown by Kendler and Baker (2007) in a review of 55 studies that measured the genetic influence on a wide variety of environmental influences, such as general and specific life events, parenting as reported by child or parent, family environment, social support, peer interactions, and marital quality. They showed that these environmental measures are indeed at least partly, varying from small to moderate, influenced by genetic factors. A more recent study replicated this finding (Vinkenhuizen et al., 2010), but explicitly stated that these influences were small and the reviewed findings were often inconsistent. Therefore, heritability of environmental factors could introduce a bias to models that treat these factors as purely environmental in origin and may therefore impede our understanding of individual differences in complex traits.

In addition to showing that life events are influenced by genetic factors, psychosocial factors also influence the effect of life events on the onset and course of BD (chapter 3). Passive coping style was involved in the effect of life events, but also contributed to the onset and recurrence of bipolar episodes. This is a good reflection of the complexity in the study to risk factors. Even though a direct effect of psychosocial factors is not always established they can play a crucial role in influencing direct risk markers as life events. Previous studies also suggest that both coping responses to stress may be influenced by temperamental traits that can influence the association between stress and mood episodes (Compas, Conner-Smith & Jaser, 2010). To add to the complexity, psychosocial factors like coping and temperament are also influenced by genetic factors themselves (Plomin & Crabbe, 2000).

Regarding the study to genetic factors, it is apparent that in the great majority of cases, genetic effects will involve multiple susceptibility genes where each of which only has a small effect (as also discussed in chapter 5). While it is still unclear whether all or even most of these genes will ever be identified, there will still remain an anonymous background genetic effects to be taken into account (Rutter, Pickles, Murray & Eaves 2001).

The complexity of these interactions has created the need for a more comprehensive methodology. Epigenetics, the study of changes in gene function that are mitotically and/or meiotically heritable and that do not entail a change in DNA sequence (Wu & Morris, 2001), is the next step in understanding the interactions of these factors. Epigenetic change is a relatively new frontier of temporally dynamic, reversible, molecular change that can be measured genome wide, revealing mechanisms of genomic control as well as consequences of environmental exposures. Epigenetic influences on gene regulation help mediate response and adaptation to the environment, accounting for part of the liability to psychiatric diseases (Schuebel, Gitik, Katharina & Goldman, 2016). Epigenetics also plays an important role when studying offspring
of parents with psychiatric illnesses. Although studies are limited, there is some evidence that different types of environmental stimuli can alter the epigenome of the whole brain or related neural circuits, contributing to long-lasting behavioural phenotypes that may be transmitted from parent to offspring via transgenerational mechanisms (Schuebel, et al., 2016; Post, 2016). Recent evidence points to a potentially transgenerational transmissible effect of stress on an epigenetic level, as holocaust exposure had an effect of FKBP5 methylation that was observed in exposed parents as well as in their offspring (Yehuda et al., 2016).

While epigenetic studies of mental illness remain at early stages, understanding how environmental factors recruit the epigenetic machinery within specific brain regions to cause lasting changes in disease susceptibility and pathophysiology is revealing new insight into the aetiology and treatment of these conditions are an important next step.

**CLINICAL IMPLICATIONS**

This study provides insights that may become relevant in day-to-day clinical practice for the treatment and guidance and psychoeducation of patients and their social support system. Findings of chapter 2 and 3 indicate that life events and psychological aspects play a role in the susceptibility for the onset and course of mood episodes and admissions. Therefore, they may be taken into account in the development of (early) intervention strategies. For individuals at risk for BD, structure in life and avoiding highly stressful situations may attribute to the prevention of illness onset and/or recurrence. For instance, training focusing on adopting active coping strategies to harness individuals against the effects of severe stressful events might be of additional value.

To date, studies to psychotherapeutic treatment with a focus on coping mechanisms and problem solving skills are limited.

In a randomized trial, Miklowitz et al. (2013) studied the effectiveness of a 4 month family focussed therapy among 40 youth at risk for mood disorders. Families followed sessions of family focused therapy, including psycho-education and training in social and problem solving skills or educational control sessions. Individuals of the treatment condition reported a sooner recovery of mood symptoms, a more favourable trajectory and more weeks in remission over 1 year of follow up.

In a more recent study by MacPherson et al. (2016), they evaluated mediators (family functioning, parent/child coping) on primary treatment outcome (child’s mood and functioning) in a randomized trial of Child- and Family-Focused Cognitive Behavioral Therapy (CFF-CBT) versus Treatment As Usual (TAU) for pediatric BD. Several parent- and family factors significantly improved, specifically parenting skills and coping showed promise as mediators of child mood symptoms and global functioning. Although mediating effects for youth coping were not significant, this study highlights the importance of psychosocial factors in the early treatment of BD.

Taken together, the discussed studies show promising results for therapeutic interventions focussing on coping and problem solving skills, but more studies with larger samples and longer follow-up are required.
DIRECTIONS FOR FUTURE RESEARCH

We conducted an explorative study where we considered a few possible risk factors to be of influence in illness onset and course. Although the word ‘risk factor’ implies causality, this term includes both causal and predictive factors. Twin studies and offspring studies provide the design to further disentangle these factors. However, given the limitation in our studies of a small sample size, prospective longitudinal studies with adequate sample sizes are needed. Therefore, large national as well as international collaborations, such as ENIGMA, offer a great opportunity and a huge step forward in psychiatric research as they create enormous amounts of valuable data collected with harmonized measurement protocols. The ENIGMA Network consists of over 20 working groups worldwide that are collaborating on imaging genomics to understand brain structure, function, and disease based on brain imaging and genetic data (http://enigmainsi.usc.edu). In 2012, ENIGMA formed working groups on schizophrenia (van Erp et al., 2015), BD (Hibar and the CHARGE and ENIGMA2 Consortia, submitted for publication: Hibar et al, 2015a,b in press), major depression (Schmaal et al., 2015), and ADHD (Hoogman et al., 2015). Additional groups meta-analysing data on eight additional disorders have been formed since (Thompson et al., 2016). The initial goal of ENIGMA’s disease working groups has been to meta-analyse effects of these disorders on the subcortical brain measures in the GWAS study. However, ENIGMA does not have the ideal design for all types of research. For the study to the impact of life events, or treatment outcomes for example, longitudinal designs instead of the cross-sectional comparisons in ENIGMA are preferred. International collaborations between longitudinal studies, like the BIOS and DBOS (Mesman, 2016) should be encouraged and supported as together they can create the power to solve (statistical) issues that the we are currently facing. In addition, prospective longitudinal studies should aim to limit the time between measurements to reduce time-bias in measurements and resolve the limitations that now prevent us from answering questions regarding causality.

A recent development which offers opportunities for not only research, but also prevention and treatment is the use of mobile E-health applications (Nicolas, Larsen, Proudfoot & Christensen, 2015; Faurholt-Jepsen et al., 2015). The use of smartphones in data collections allows respondents to monitor their mood state, levels of experienced stress and life events in real-time. Smartphones are not only a valuable tool in research, but can also be used to deliver interventions and psychoeducation, supplement treatment and enhance therapeutic reach in BD. Especially in adolescents, who are often hard to motivate to engage in face-to-face preventive therapy, offering an online tool or smartphone application could increase their engagement in (preventive) interventions (Faurholt-Jepsen et al., 2015). Although the evidence-based development of smartphone applications with the specific use for research or treatment is still in its infancy, it is a feasible and promising tool for an at risk population.

A valuable addition to life event measures, would be to combine the clinical interview data with biological measures that are known as biomarkers for the stress response (e.g. cortisol levels, ACTH levels, blood pressure). This would provide better insights in the direct physiologic effects of life stress especially if this could be com-
bined with brain measures as we established that hippocampal volume is influenced by severe life stress as well in chapter 4.
Inclusion of euthymic patients is often preferred in research in BD to minimize the bias in measurement. As we discussed in chapter 5, this could be providing a limited view on the disorder especially with measurements prone to change based on mood state, like inflammation. Therefore, measurements during both euthymic and mood episodes should be considered, as it might provide new insights on factors affecting the long-term course of the illness.

CONCLUDING REMARKS
In this thesis we described results of studies in two longitudinal research populations; the Dutch Bipolar Offspring Study and the Dutch Bipolar Twin Study. The general aim of these studies was to expand our knowledge on the role of life events as potential risk factor in the onset and course of BD.
The main finding is that severe life events influence the onset and recurrence of both mood episodes and admissions. In addition, psychosocial factors (passive coping style, harm avoidant temperament) proved to have a confounding effect on the influence of life events. These findings broaden our understanding on the role of life stress in BD and provide potential targets for (early) intervention.