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**Tangled up in mood : predicting the disease course of bipolar disorder**  
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CHAPTER 7

**General discussion**

For the studies described in this thesis, we prospectively followed a large cohort of 173 BD patients over a two-year period. The overall purpose of this thesis is to develop and test a more refined model for the complex associations between the bipolar mood course and several (environmental) factors. This aim is based on the assumption that, in order to better understand the complexity of BD and its mood course, one should look beyond cross-sectional and unidirectional approaches. Therefore we investigated: 1) methods to measure and interpret the longitudinal BD mood course 2) potential bidirectional associations between the longitudinal mood course and environmental factors; 3) non-linear associations between mood and divided attention; and 4) symptom networks that might be characteristic of a specific longitudinal course pattern. In the following section the overall findings as well as the clinical implications of these studies will be summarized and discussed. First, the results of a systematic review on the use and interpretation of the The National Institute of Mental Health's Life Chart Method (NIMH-LCM) in longitudinal studies of BD will be summarized. Second the results with respect to both the associations between psychosocial factors (e.g., life events, social support) and subsequent mood symptoms and the association between mood and divided attention will be discussed. Subsequently the more complex bidirectional associations and the findings resulting from the network approach will be addressed. Additionally, clinical implications, strengths and weaknesses and future directions will be discussed.

### 7.1 Investigating the longitudinal bipolar mood course

Although prospective longitudinal study designs are often proposed as one of the most valuable designs for gaining more insight in the complexity of psychiatric disorders and their etiology, the difficulties in valid and reliable assessment and methodological handling of the data are also acknowledged (246, 247). In **Chapter 2** we reviewed methods to handle longitudinal data assessed with the daily NIMH life chart method (LCM). We pointed out the multitude of mood course related measures that can be derived from longitudinal assessment with the LCM, of which the most frequently used are: number of mood episodes, average severity, percentage of time ill and num-

ber of mood switches. Different criteria and methods are used to define these variables. Especially the calculation of number of mood episodes appears to be complex, since the LCM mood ratings are based on the severity of mood associated functional impairment and not on number and severity of symptoms in line with the Diagnostic and Statistical Manual (DSM) IV classification system or as measured with symptom rating scales. In the current study we decided to assess mood both on a symptom level (using the Young Mania Rating Scale (YMRS) and the Quick Inventory of Depressive Symptomatology (QIDS)) and on the level of functional impairment with the LCM. We also showed that these two measures (although not fully overlapping temporarily) are highly associated.

Further we address the issue of detailed versus global measurement of the mood course. Because of the chronicity of BD, mood symptoms can occur at any moment during follow-up. Therefore, it is difficult to determine whether very detailed (daily or even moment to moment) measurements over shorter periods of time are preferable over more global measurements during longer periods of time. Although a combination of both detailed and long follow-up periods two might be most preferable, we found in Chapter 2 that using daily measurements over longer periods of time is burdening to patients and leads to high drop-out rates (73-75). In the current study we therefore decided to measure the mood course more globally, over a relatively long period of 2 year. This prospective repeated measurement design (every 3 months) still allows for the detection of the direction of the associations we were interested in. However, we do acknowledge the potential limitations of this approach, which already have been discussed throughout the different chapters.

In the following sections we will further discuss the results with respect to these mood data and their assumed correlates.

## **7.2 Life events, social support, cognitive impairment and disease course**

It has become increasingly clear that environmental stressors can have a negative impact on the bipolar disease course (31-34). In **Chapter 3 and 4** the specific impact of type of life events (i.e., negative versus positive) and so-

cial support (i.e., enacted versus perceived) on mood polarity was investigated. In the below paragraphs we will first discuss the findings with respect to the unidirectional associations: the association between psychosocial factors and mood in the subsequent months and specific difference in these associations between BD I and II patients. Also the found associations between mood and cognitive performance will be discussed.

### 7.2.1 Life events and subsequent mood symptoms

First, negative life events preceded increases in depressed mood, which is in line with previous studies (31, 32, 98). Further, both negative and positive life events preceded increases in manic mood. Previously, subsequent manic mood has only been associated with positive or goal attainment life events (31) and not with negative events. However, several case studies in the past already suggested that negative events could also trigger mania since they reported the onset of a manic episode after adverse life events such as death of a close relative (248, 249). Moreover, one could hypothesize that negative life events could also induce (hypo-) manic symptoms, for instance through disturbing social rhythms, like sleep, due to worrying or relationships problems (125, 127). In a recent study the current findings have been replicated by demonstrating a similar association between number of negative life events and subsequent (hypo-) manic mood (250). These findings strongly suggest that not only positive life events but also negative life events precede increases in (hypo-) manic symptoms.

### 7.2.2 Social support and subsequent mood symptoms

The impact of social support on the bipolar disease course has less frequently been studied than the effects of life events (34). Within the existing social support literature (unrelated to BD) it has been repeatedly shown that the distinction between enacted or objective supportive interactions on the one hand and perceived or subjectively felt social support on the other hand, is essential when studying the effects of social support (143). Potential differential effects of these two aspects of support on the bipolar disease course have been investigated in the current study as reported in Chapter 4. The weak

correlation between enacted and perceived support clearly showed this to be distinct, largely independent aspects of social support. Additional evidence for the importance of distinguishing these two aspects of social support in research into BD is the fact that only perceptions of low support were related to subsequent increased depressed symptoms and not the amount of reported enacted support. The clinical implications of these findings will be discussed in a later part of the discussion.

### 7.2.3 Differences between bipolar I and II patients

Finally, there was one other remarkable finding in the current study. In **Chapter 3** we report findings indicating that life events are only associated with subsequent increased mood symptoms in BD I patients and to a lesser extent in BD II patients. These findings seem to apply specifically to the association of mood symptoms with life events, because these differences were not found for the associations of mood symptoms with social support. Interestingly, a recent study by Simhandl and colleagues (251) reported comparable results, that recurrence of depressive episodes was only associated with prior negative life events in BD I patients and not in BD II patients. Moreover, a study by our own group (252) showed that only BD I patients showed an increase in the stress hormone cortisol after negative life events, while this effect was not observed in BD II patients. These findings seem to suggest that BD I patients are specifically reactive to environmental stressors. In **Chapter 3** we described potential underlying mechanism for this specific association. One of the most important potential explanations might lie in the observation that in the current sample BD II patients reported more previous mood episodes and comorbid disorders, which is in line with previous findings that BD II is associated with a more chronic course, with more frequent episodes and more comorbid disorders (25, 26, 116, 130). This specific characteristic of the BD II group might explain the absent association with life events, since the kindling hypothesis states that, when the disorder progresses (more previous episodes have occurred), new episodes will occur more independently from environmental stressors (93). Although this might be a potential explanation for the differential findings, after controlling for comorbidity and previous number of episodes the associations still

differed between BD I and II patients. Moreover, the number of life events did not differ between the BD I and II group, suggesting that the prevalence of life events did not account for the different associations. Since comparable findings have recently been found in a different sample (251), potential differences in stress-reactivity between bipolar I and II patients should be further explored.

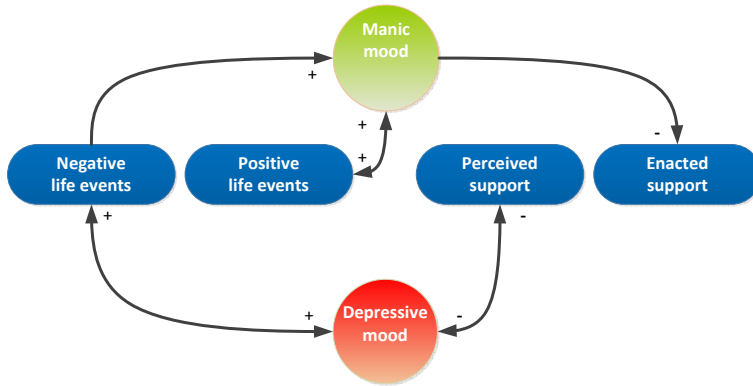
### 7.2.4 Cognition and mood

A second interesting finding of the current thesis concerns the associations between current mood and divided attention performance as described in **Chapter 5**. Cognitive functioning in BD patients is an important topic that generated numerous studies in the last decade, contributing to the notion that cognitive impairments belong to the daily reality of BD patients (177-180). However, effects of the acute mood states on cognitive functioning have less often been studied, particularly when using prospective designs. In this chapter, we specifically investigated non-linear (quadratic) associations between manic mood symptoms and divided attention performance, hypothesizing that (subclinical) hypomanic symptoms might increase attentional performance, while only severe manic symptoms were associated with decreased attentional performance. We found quadratic associations, meaning that subclinical mood symptoms were associated with better divided attention performances, and only when symptoms reached clinical levels these symptoms were negatively associated with cognitive functioning. Further, divided attention performance varied considerably over time within patients.

## 7.3 Bidirectional models of the associations between bipolar mood and psychosocial variables

As mentioned in the previous section we found strong support for the association between the occurrence of negative and positive life events, lack of perceived support and subsequent mood symptoms. However one of our main aims was to investigate the bidirectional associations between these variables.





**Figure 7.1** | Bidirectional associations between bipolar mood and psychosocial variables.

One of the main findings of the current thesis is the fact that psychosocial factors such as life events and low social support were not only predictors of subsequent mood symptoms, but also seemed to occur as a result of mood symptoms (Figure 7.1).

This reciprocity between the disorder and the patients' environment makes Jean-Pierre Falret's description of bipolar disorder as 'la folie circulaire' even more suitable. It reflects the difficulty of finding 'causes' for relapse of bipolar mood episodes in patients that have been suffering from this disorder for some time.

Previously, two different psychosocial theories have been proposed to explain the complex association between environmental factors and the bipolar disease course: kindling and sensitization. As previously described, the kindling hypothesis (93) describes a mechanism in which the recurrence of episodes is increasingly independent of the occurrence of environmental triggers over time (stress autonomy model). The sensitization mechanism (131) refers to the phenomenon that patients become increasingly sensitive to environmental stressors over time, such that initial episodes might only be triggered by severe stressors, but recurrent episodes can be triggered by small stressors (stress sensitization). Apart from the methodological issues of studying such phenomena, empirical support is still rather weak for both

theories (250, 253, 254). However, based on the current findings possible reciprocal associations may be added to these psychosocial models in order to make them more valid. Taking the reciprocal associations into account, the progressive course of the disorder might then be explained by the mechanism in which the disorder itself leads to a more unfavorable environment, which makes the patient more vulnerable to relapses. However, the current study lacks the follow-up length and rigor to test to what extent the potential progression of the disorder runs parallel with the decline of the psychosocial circumstances. In addition to possible kindling or sensitization mechanisms, it is recommended to test whether there exists an 'accelerating vicious circle', in which mood episodes increasingly generate unfavorable environments, which in turn leads to increased mood symptoms, which ultimately increases the disease course in severity and accelerating the recurrence rate. Additionally, the cumulative load of environmental stressors should also be taken into account. We found evidence that especially the cumulative load of adverse events is related to increased mood symptoms, meaning that especially an addition of several single life events is related to previous and subsequent changes in mood severity. Two recent studies (250, 254) report the same impact of a cumulative load of life events on both depressed and (hypo-) manic recurrence.

Because we only studied cross-sectional associations between mood and cognition, it is difficult to establish the directions of causality within this specific association. The (non-linear) associations between mood states and divided attention (DA), seems most in line with the idea that mood states affect DA performance rather than that decreased DA performance leads to increased mood symptoms. However, patient with more cognitive impairments seem to have an increased risk of recurrence compared to patients with no or little impairments, even when adjusted for previous course severity (255). Hence, the association between increased mood symptoms and decreased DA performance might also be due to the fact that patient with worse cognitive performance display more severe symptoms. In an explorative analysis that was not presented in this dissertation we indeed found that patients with lower DA performance showed higher depression scores on the subsequent time point, even when correcting for mood at the predictor time point. This might

suggest that decreased cognitive functioning is associated with a more severe prospective mood course. Alternatively, one could hypothesize that cognition and mood do not influence one another, but are both an expression of an underlying (biological) mechanism that accounts for both the cognitive impairments and mood symptoms. The current study design is unsuitable for the detection of such mechanisms, nor to draw definite conclusions about causal directions between mood and cognitive performance.

## 7.4 Network approach

In **Chapter 6** we attempted to approach the issue of the development of specific longitudinal course patterns from a different methodological and theoretical angle. Therefore we used the novel network approach to find specific symptom networks for patients with different longitudinal disease courses. With this approach we focused on symptom correlation patterns. The rationale behind linking symptom networks to specific course patterns is the fact that despite all the environmental stressors that seem to have small to moderate impact on the disease course, this course still tends to follow a similar pattern as the pattern displayed in the past (12, 56, 57). Our findings show that symptoms might be differently interconnected among patients with disease patterns that were either minimally impaired, predominantly depressed or cycling over a two-year period. Additionally, we demonstrated that symptoms that play a central role in the network differ across the groups, except for the symptom representing ‘decrease of energy’ which is a highly central symptom across all three course groups. These findings might implicate that a specific course type may be a result of different underlying symptom patterns. Replication of these findings in larger samples, with more frequent measurements is needed to test whether specific mood symptom patterns prospectively predict different course patterns.

These specific symptom interconnections might also be suitable to gain more insight into the models that were proposed in the previous paragraph. For instance, Cramer et al. (227) report that symptom networks reacted differently in subjects who experienced distinct stressful life events. This means that the network approach potentially could give more insight in the specific effects

that environmental stressors have on mood symptoms. Unfortunately, the current sample was too small and the time between measurements too long to investigate the potential effects of social support and life events on symptom networks. However, by using frequent and daily assessment, ultimately this network approach may have the potential to explain why specific environmental stressors especially seem to ‘activate’ depressive symptoms and others are more prone to ‘activate’ manic symptoms in different patients.

### 7.5 Conclusion and methodological and clinical implications

In the current study we prospectively followed a large cohort of 173 BD patients over a two-year period. The main findings are: 1) The NIMH-LCM is a widely used and valuable method in longitudinal studies on the bipolar disease course, however methods to analyze and interpret the data are not unequivocal and need careful description by the researcher; 2) associations between the bipolar mood and environmental factors (life events and social support) are rather bidirectional than unidirectional; 3) manic and depressed symptoms are differently associated with divided attention performance, with a negative linear association between depression and DA performance and a non-linearly association between manic symptoms and DA performance; 4) symptom networks of bipolar patients significantly differ in overall correlations patterns of symptoms.

Throughout this thesis strengths and limitations of the current sample, the study design and approach have been extensively discussed. In combination with the found results there are some important lessons and conclusions that will be highlighted below.

#### 7.5.1 Research implications

First, over the last decades longitudinal studies have proven their great value for research in BD (e.g. 22, 23, 24). These studies provided ample knowledge about the bipolar disease course and its associated factors. The current study contributed to this knowledge by adding different approaches to analyse and interpret these complex longitudinal associations. These results implicate that it is difficult, and maybe even not very useful, to determine cause

and effect when studying the ongoing interaction between the course of BD and psychosocial factors. Consequently, models in which strict directions of causality are abandoned might lead to a closer approximation of the reality of the disorder and its complex interactions with the environment. Our work suggests that psychosocial influences on the bipolar mood course might not be primarily unidirectional, and therefore statistical models that allow for more bidirectional approach such as network analyses, deserve more attention in longitudinal research on BD. Further, study samples consisting of already diagnosed (and therefore already ill) BD patients may not be ideal to detect causal or unidirectional associations between (psychosocial) factors and the disease course, and within those samples the circularity in the associations should be investigated. Further, samples with 'at risk' subjects (e.g. 256) might be more suitable to detect directions of causality, but even then it remains complex to distinguish cause and effect.

Although we demonstrated that environmental factors play a role in the BD disease course, the design of the study only allowed for a global representation of reciprocal associations between the disorder and the environment. Detailed measures like the Experienced Sampling Method could provide a better understanding of the dynamics of the disorder on a microlevel, in which symptoms are sampled throughout the day using smart electronic devices. The network approach may turn out to be a suitable statistical method to analyse and understand such complex data. Further, it would be valuable to capture symptoms of patients during more severe depressed and manic states, which are underrepresented in the current study as well as in previous studies. This means that most results can only be translated to a relatively stable, well treated BD population. Further, most samples consist of patients that experienced multiple episodes and receive treatment for several years. As a result little knowledge exists about the underlying mechanisms of BD in patients that are untreated/unmedicated while going through the initial phases of the disorder.

### 7.5.2 Clinical implications

The current reciprocal association between psychosocial factors and mood course might also be of clinical value. Currently, psychotherapeutic inter-

ventions do not necessarily focus on this reciprocity. Within Interpersonal Social Rhythm Therapy (IPSRT) social relationships are perceived as 'Zeitgebers' and the focus is on the effect of interpersonal relations on daily rhythms and mood (136). The opposite association, the effects of mood on (the perception of) the quality of interpersonal relationships, is not specifically addressed in this therapy, but given our findings this might be a beneficial approach to the patients. Within Family Focused Therapy (FFT) there is attention for these reciprocal interactions. However, significant others of the patients are not commonly involved in the general treatment, let alone questioned about the impact of the disorder on their lives and well-being. Currently, our own group is studying the impact of the disorder on intimate relationships and on well-being of significant others. In several explorative interviews with patients and their partners on this topic, the strong burden for significant others and the severe impact on the relationships were repeatedly expressed by the couples. Besides, the opportunity to express these problems was highly appreciated by both patients and partners, emphasizing the importance of involving the significant others of the patient.

Additionally, with help of tools like the life-chart methodology patients are able to gain more insight in the effects that psychosocial circumstances can have on the disorder course and vice versa. This means that a patient should be aware that he or she is 'an active contributor instead of passive player in his or her environment' (48). Further, as we showed, both negative and positive events are associated with mood symptoms, but every individual patient should investigate what specific events are related to the recurrence of mood episodes. In addition, some patients tend to avoid specific psychosocial circumstances, such as parties, festivals, intimate relationships, since they perceive these as triggers for new (manic) mood episodes. It is important to find out, together with the patient, whether these are genuine triggers for mood episodes, or rather consequences of hypomanic mood states during which a patient increasingly engages in these specific situations. This may be important, since avoiding all mania associated circumstances can have serious consequences for the quality of life of a patient, and may even lead to depression. So although on a group level causes and consequences are difficult to disentangle, in clinical practice it will be valuable trying to detect

these causal directions to some extent with the individual patient.

Further careful monitoring of the mood state might also give insight in how mood symptoms are interconnected. In the form of ‘early signal’ plans, patients nowadays already gain more insight in how new mood episodes start with subtle symptoms. In line with the network approach it might also help to identify core symptoms that strongly influence the emergence of other symptoms in the network. These central mood symptoms might than be identified as specific targets of (psychotherapeutic) interventions. According to the network approach, a decrease in severity of a central symptom, will consequently lead to changes in the peripheral symptoms. Ideally, targeting the central symptoms might establish the ‘dismantling’ of the whole symptom network, eventually leading to a symptom free state. Moreover, generic ‘warning signals’ have been derived from network models in many different fields of research, such as the phenomenon of ‘Critical slowing down’ which may help the individual patient to predict when a devastating mood change is imminent (i.e., tipping point) (245). Future studies should investigate to what extent the network approach is a valid and useful method in clinical practice.

One of the other findings that might have important clinical implications is the fact that especially negative *perceptions* of social support seem to be associated with depressed mood, rather than low amounts of enacted support. Previous studies on the effects of negative cognitions in BD also demonstrated adverse effects on mood symptoms (257). Changing these negative perceptions or cognitions falls within the domain of cognitive behavioral therapy (CBT) and related psychotherapeutic interventions such as schema therapy. Within these therapies perceptions of social support might be adjusted with help of cognitive and behavioral strategies, potentially leading to reduced depressed symptomatology.

Additionally, possibly not only perceptions about social support are important to target, but also perceptions about the self and one’s own functional abilities might be relevant. One of our current findings shows that subclinical hypomanic mood seems to improve cognitive functioning potentially leading to a ‘hyperthymic mood state’. Clinically it is relevant to realize that this ‘hyperthymic mood state’ may be an asset in daily functioning for the

patient. The use of medication may suppress this active and positive phase and hence might be one of the reasons for medication non-adherence (215, 216). Treatment adherence might lead to a stable mood and therefore the absence of this supranormal level of functioning. Consequently, patients might perceive this stable situation as a decreased level of functioning compared to their previous experience with supranormal levels of functioning. Losing this level of functioning might result in feelings of failure and disappointment, and potential instable mood. So, discussing perceptions of what level of functioning is 'normal' could also be a complex but important area of psychotherapeutic interventions.

Finally, models for BD are predominantly based on biological theories, simply because increasing evidence points towards a strong biological underpinning of this disorder. However, I want to emphasize that the psychological and psychosocial impact of this disorder and the potential benefits of psychotherapeutic interventions should not be overlooked. Although it is worrying that for a very long time (and even nowadays) psychotherapeutic treatment strategies for BD have received relatively little attention, this also means, that this is a relatively unexplored and exiting field of clinical psychology in which much progress can be gained in the near future.