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Title: Tangled up in mood : predicting the disease course of bipolar disorder

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Summary

Background

Bipolar disorder (BD) is a common mood disorder, which is characterized by periods of major depression alternated with periods of hypomania (bipolar type II) or mania (bipolar type I). The life time prevalence of BD is estimated around 1% for bipolar I disorder and between 1%-2% for bipolar II disorder. Both the high recurrence rates of mood episodes and the relatively early age of onset (on average around age 25) of the disease are responsible for the high burden of the disorder.

Longitudinal studies have shown that there is strong variability among bipolar patients in the manifestation of their disease course. Further, environmental factors such as stressful life events and lack of social support are associated with a more unfavourable disease course. However, to what extent the disorder itself creates its own downwards spiral is rather unknown, since most previous research mainly focused on unidirectional associations the psychosocial environment and the disorder. With the growing interest and need for effective psychosocial interventions for bipolar patients a better understanding of the complex interactions between the illness and associated psychosocial factors is of great importance.

Further it appears that, regardless of which factors may have triggered new mood episodes, the longitudinal course displays rather consistent symptom course patterns over time. So a patient with a predominantly pattern of depressed episodes, will likely display this specific pattern in the future. To date, there is no clear explanation for this rather consistent course pattern over time.

The overall purpose of this thesis is to develop a more refined model for

the complex associations between several (environmental) factors and the bipolar mood course. This aim is based on the assumption that, in order to obtain a better understanding of the complexity of BD and its mood course, one should look beyond cross-sectional and unidirectional approaches. We investigated this in the context of the 'Bipolar Stress Study'. This cohort contains 173 BD I and II patients that were followed over a 2-year period. Mood, positive and negative life events and levels of social support were measured repeatedly over time. In the following section the findings of this study will be summarized and discussed.

Results

As a first step in studying the longitudinal disease course of BD we reviewed the use and interpretation of the prospective National Institute of Mental Health's Life Chart Method (NIMH LCM-p) in **chapter 2**. The LCM-p is a frequently used tool to assess the disease course both in clinical and in research settings by daily scoring of the depressive and manic symptomatology. Processing and analysing the LCM-p for research purposes, is challenging because of the multitude of complex aggregate measures that can be derived from the data. We showed that there are several frequently calculated LCM-p course variables (mood episodes, average severity, proportion of time ill and mood switches), which are not univocally defined across studies. Especially for the calculation of number of episodes and mood switch no consistent definition and operationalization seem to exist. However, based on the specific research question at hand we provided some guidelines for the most appropriate variables and definitions. Additionally, we showed that daily monitoring of the mood course might be burdening to patients, and might lead to high drop-out rates.

In **chapter 3 and 4** we investigated potential bidirectional associations between environmental factors and the disease course. In **chapter 3** we first studied these potential bidirectional association between negative and positive life events and mood severity over time. We showed that negative life events preceded increases in both depressed and manic mood. Positive life events only preceded increases in mania and not in depression. Surprisingly,

these associations were only present in the bipolar I patients, and not in the bipolar II patients. For the opposite temporal direction (life events as a result of mood symptoms), we found that mania symptoms preceded the occurrence of positive life events and depressive symptoms preceded the occurrence of negative life events. This means that associations between bipolar mood and life events are reciprocal, with life events preceding increases in mood symptoms, but mood symptoms also leading to more life events, implicating a vicious cycle.

Similar reciprocal associations were investigated in **chapter 4**. In this chapter we focussed on the association between social support and bipolar mood. We distinguished between the actual amount or enacted support and perceptions of support, since in previous studies (in non-bipolar samples) especially the amount of perceived social support was related to well-being, and not the actual amount of received support. The results showed that lower perceived support was associated with subsequent higher levels of depression. As in chapter 3, we also found evidence for the opposite association, with previous depressive symptoms being associated with less perceived support in the following three months. Further, manic symptoms during three months were associated with less enacted support in the subsequent 3 months. These findings suggest that perceived, but not enacted, support is consistently related to depressive symptoms in a bidirectional way, while mania is specifically associated with a subsequent loss of enacted support.

In **chapter 5** the effect of current mood state on divided attention (DA) performance was investigated. Previously, studies only found a negative linear association of cognitive performance with depressed symptoms and not with manic symptoms. Hypothesizing that the relationship with manic symptoms did not have to be linear, we specifically examined possible beneficial effects of the (hypo-)manic state using a non-linear approach. It appeared that DA performance varied considerably over time within patients. Further, we did not find a linear relationship, but found a significant quadratic relationship between manic symptoms and DA performance. This means that very mild manic symptoms may have a positive effect on divided attention performance, while more severe symptoms may be impairing. No association between depressive symptoms and DA performance was found.

As previously mentioned, course patterns are rather consistent over time in individual patients. In **chapter 6** we therefore investigated whether associations between specific symptoms can account for these different course patterns. To this end, we explored the potential a novel network approach by exploring specific symptom networks for patients with different longitudinal disease courses. We compared symptom networks of patients with a minimally impaired, a predominantly depressed and a cycling course. We demonstrated that symptom networks of bipolar patients with different longitudinal course types are significantly different. And different symptoms play a central role in the three course groups. Further manic and depressed symptoms did not form separate clusters, but were closely interconnected. These findings might implicate that a specific course type may be a result of different underlying symptom patterns.

Conclusion and discussion

One of the main findings of the current thesis is the fact that psychosocial factors such as life events and low social support are not primarily predictors of subsequent mood symptoms, but also seem to occur as a result of mood symptoms. Over the last decades longitudinal studies have proven their great value for research in BD. These studies provided ample knowledge about the bipolar disease course and its associated factors. The current study contributed to this knowledge by adding different research approaches to analyse and interpret these complex longitudinal associations. These results implicate that it is difficult, and maybe not even very useful, to determine cause and effect when studying the ongoing interaction between the course of bipolar disorder and psychosocial factors. Consequently, models in which strict monocausal directions of causality are abandoned might lead to a closer approximation of the reality of the disorder and its complex interactions with the environment. The network approach may turn out to be a suitable statistical method to analyse and understand such complex associations.

The current results might also be of clinical value. First, adverse psychosocial circumstances might not only lead to a more unfavorable disease course,

but the disease itself could also have negative effects on the environment. Within psychotherapeutic interventions this reciprocity should be taken into account, for instance by involving significant others of the patients in the treatment. 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. Furthermore, careful monitoring of the mood state might also yield more insight in how mood symptoms are interconnected. In line with the network approach it might also help to identify core symptoms that strongly influence the emergence of other symptoms. These central mood symptoms might be identified as specific targets of (psychotherapeutic) interventions.

Also perceptions of patients might be important targets for (cognitive) interventions, since we showed that especially negative perceptions of social support are associated with an adverse disease course and not the actual amount of support received. Additionally, possibly not only perceptions about social support are important to target, but also perceptions about the self and one's own functional and/or professional capacities might be relevant. We showed that light hypomanic symptoms can lead to increased performance on a cognitive task. Treatment adherence might lead to a stable mood and therefore the loss of this supranormal level of functioning. This might result in feelings of failure and disappointment, and potential instable mood. So, discussing these issues might also be an important focus of psychotherapeutic interventions.

Finally, although we demonstrated that environmental factors play a role in the BD disease course, these factors only partly explained changes in mood symptoms. Therefore a multifactorial model including environmental, clinical and biological factors is needed for a more comprehensive understanding of the mechanisms involved in the disease course.

