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

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CHAPTER 1

General introduction

"Circular insanity varies in intensity and in duration as a whole and in each of its phases, whether it be among various patients or among various episodes in the same patient. At times, the circle is complete in 3 weeks or a month; sometimes it takes many months or years. Still, whether the course is slow or rapid, the tempo of the disorder does not alter its essential nature: the disease remains the same in its general features as well as in its principal details"

— Falret JP, 1854. Memoire sur la folie circulaire. Bulletin de l'Académie de Médecine, 19: 382-415 (1)

This text originates from the 19th century psychiatrist Jean-Pierre Falret, who was one of the first to extensively describe 'la folie circulaire', or what we today know as bipolar disorder (BD). This description of the disorder illustrates that 130 years ago the notion already existed that the disease course of BD is characterized by both recurrences within patients and a strong variability between patients. The circularity in Falret's description of the disorder refers to the circular occurrence of both manic and depressed mood episodes. However, clinically it seems evident that this circularity is not only restrained to the bipolar mood episodes, but seems to include all facets of the lives of bipolar patients. Typical patterns in the life course of bipolar patients are those of increasing (subjective) professional or interpersonal achievements in periods of hypomania and a typical decline of all these facets when mania becomes more severe or when depression arises. This erosion of important

life domains as a consequence of the disorder presumably will enhance the risk for relapse into new mood episodes. However, to what extent the disorder and adverse environmental factors negatively interact with each other is unknown, since most previous research mainly focused on unidirectional associations between the disorder and the psychosocial environment. Thus, the effect of environmental factors, such as life stress and support, on the disease course has been studied, but the opposite direction, the effect of the disorder on the psychosocial environment, is hardly investigated within BD samples. With the growing interest and need for effective psychosocial interventions for bipolar patients (2, 3), a better understanding of the complex interactions between the illness and associated psychosocial factors is of great importance. The major purpose of this thesis is to find 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 obtain more understanding of the complexity of BD and its mood course, one should use other approaches than cross-sectional and unidirectional methods.

1.1 Bipolar disorder

BD is a common mood disorder, which is characterized by periods of major depression alternated with periods of hypomania (BD II) or mania (BD I) (see Figure 1.1). Depression is characterized by low mood, lack of energy, lack of interest, changes in sleep and appetite, and negative thoughts about the self, the world and the future. Mania can be perceived as the total opposite of depression, leading to a supra-normal state with increased energy, little need for sleep, racing thoughts, elevated mood, and positive perceptions of the self, the world and the future (4). When the manic state does not lead to functional impairment and lasts at least 4 days we speak of a hypomanic state. When functioning is impaired and symptoms last for 7 days we speak of a manic state.

The life time prevalence of BD is estimated around 1% for BD I and between 1%–2% for BD II (5–7). The highly disabling character of the disorder is well reflected by the fact that it is responsible for the loss of more disability-

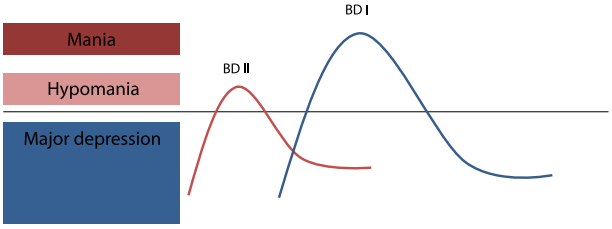

Figure 1.1 | Bipolar type I and II disorder.

adjusted life-years (DALYs) than all forms of cancer or major neurologic disorders such as Alzheimer's and other dementias (8). Further, BD is associated with premature mortality, both resulting from higher prevalence proportions of several medical conditions like cardiovascular disease and diabetes mellitus, as well as from suicide (9). Suicide rates are estimated to be 20 to 30 times higher than for the general population (10), with up to one half of the BD patients attempting to commit suicide during their life (11).

Both the high recurrence rates of mood episodes and the relatively early age of onset of the disease are responsible for the high burden of BD. The natural course of BD is characterized by a constant risk of recurrence, even when patients receive optimal treatment, according to official practice guidelines (12, 13). Over 90% of patients with BD relapse into new mood episodes during their lifetime (14). The recurrence risk in BD is about twice as large as in major depression and the risk of having mood episodes remains relatively high for at least 30 to 40 years after onset (15). Moreover, while symptomatic recovery is reached by 90% of the patients within 2 years after a severe episode, only 30% attain full functional recovery (16).

Furthermore, the average age of onset is estimated around age 25 years (17) with a majority of the patients reporting an age of onset before the age of 20 years (18). This indicates that BD is a disease of young adults, striking them in a critical period in their lives and affecting both personal and professional development.

1.2 The longitudinal bipolar mood course and its (psychosocial) predictors

Because of the high recurrence rates in bipolar patients, monitoring of the longitudinal disease course is highly valuable both in clinical and research settings. Monitoring of the course provides the opportunity to evaluate treatment efficacy and the effects of a variety of factors on increasing or decreasing symptom severity. Systematically monitoring of the longitudinal bipolar mood course originates from 1921 when Kraepelin developed a scheme for charting fluctuations in manic and depressive mood (19). This scheme was modified over the subsequent years and resulted in the The National Institute of Mental Health's Life Chart Method (NIMH LCM)(20). This method includes both a retrospective technique using monthly ratings (21) and a prospective version using daily ratings (20). A systematic analysis of the literature showed that over the last decades both retrospective and prospective NIMH life chart data have been used in over a 100 scientific papers, illustrating the wide use of this tool (Chapter 2).

The systematic monitoring of the bipolar disease course in large longitudinal cohort studies (e.g. 22, 23, 24) led to valuable information about the bipolar disease course and its possible predictors. It appeared that individual patients vary strongly in cycling pattern and severity and polarity of episodes. Some of this variability is associated with the different BD I and II subtypes. For instance, BD II is associated with a more chronic course with more frequent episodes compared to BD I (25–27). However, the BD subtype classification does not fully reflect the wide variety in course patterns among BD patients (26–28). Therefore numerous studies attempted to find correlates or predictors of the longitudinal bipolar mood course. These studies showed that the strongest predictors of the future disease course are disease characteristics itself, such as the predominant polarity of previous episodes (29), the previous number of episodes (30), and the number of residual mood symptoms (12). However, also environmental factors such as stressful life events (31) and lack of social support are associated with a more unfavourable disease course. In prospective studies, the occurrence of negative life events (31–33) and low social support support (34) are predominantly as-

sociated with more depressive symptomatology, and less with increases in manic symptomatology. It remains however unclear whether there is truly no association between environmental stress and mania or whether it is due to the mainly cross-sectional designs of previous studies. The short follow-up times and the infrequent occurrence of manic symptomatology in the bipolar samples that were included may explain the lack of an association of environmental factors with manic symptoms. A study by Johnson et al. (31) showed that mania is not trigged by negative events, but specifically by goal attainment life events. This may indicate that manic versus depressive symptoms are trigged by different environmental factors.

In the last decades, cognitive impairment has also been linked to BD in several studies. Ample evidence indicated that bipolar patients suffer from cognitive impairment, even in euthymic state (35). Attention problems, slowing of processing speed, deficits in visual and working memory, and executive disfunctioning were the most consistent observations (36). A growing number of studies found evidence for the hypothesis that cognitive impairments persist in the euthymic state (37–39), giving rise to the idea that cognitive impairments may represent a trait or an endophenotype of the disorder (40). Although it is widely suggested that cognitive performance is affected by mood symptoms, studies investigating this association are rather scarce and limited by cross-sectional design and small sample sizes. The few longitudinal studies that have been performed show that especially depressive symptomatology was associated with poorer cognitive functioning in bipolar patients, whereas no specific associations were found with mania (41, 42). We hypothesize that the failure to find effects of manic mood on cognitive performance might be due to the fact that these association are non-linear instead of linear (43). This means that mild manic symptoms might increase cognitive performance until they become increasingly severe and cognitive performance will decline, following a reversed U-shaped association. This is in line with findings suggesting that low levels of manic symptoms are related to reports of mental alertness, goal directed activity, increased self-confidence and increased self-efficacy in non-clinical samples (44, 45). In Chapter 5 of the current thesis these specific association between depressed and manic mood and cognitive performance will be investigated.

1.3 Causation and the bipolar disease course

As the previous sections illustrate, BD research has focused primarily on the identification of predictors of relapse into new mood episodes. The assumption is that once the triggers are identified, it will be possible to target these triggers with (psychotherapeutic) treatment strategies. This suggests that clear cause-and-effect mechanisms can be identified. However, how to approach causality in general, and in psychology or behavioural sciences specifically, is still debated among philosophers and scientists (46, 47). In BD the assumed multifactorial etiology and chronicity of the disorder makes it highly difficult to define a starting point of both the disorder itself and of the recurrent episodes. Consequently, cause and effect are equally complex to disentangle. Especially interactions between the social environment and symptomatology are highly dynamic and are more likely to be bidirectional or circular than unidirectional.

Moreover, in the unipolar depression literature there is ample evidence that suggests that the depressed person creates its own unfavorable psychosocial environment, which is known as the 'stress generation theory' (48, 49). Moreover, this generation of life stressors may also play an important role in the maintenance and recurrence of depressive episodes. Although it seems plausible that such a mechanism may even more strongly apply to BD, because of its chronic and recurrent character, it has hardly been studied in bipolar samples. To our knowledge, only one small prospective study (50) to date investigated reciprocal associations of life events in BD. However, because of the small sample size and short follow-up time, these results should be interpreted with caution. Other longitudinal studies on the association between psychosocial factors like social support and life events, only tested whether psychosocial factors preceded increases of bipolar symptomatology, but failed to test for the opposite temporal direction. Thus, although bidirectional associations between environmental stressors and the course of BD are assumed to exist, this issue received very little scientific attention within bipolar samples. In our view, this means that the complexity of the interaction between the BD and its environment has not been fully acknowledged in theoretical and statistical models that were tested in previous studies. We

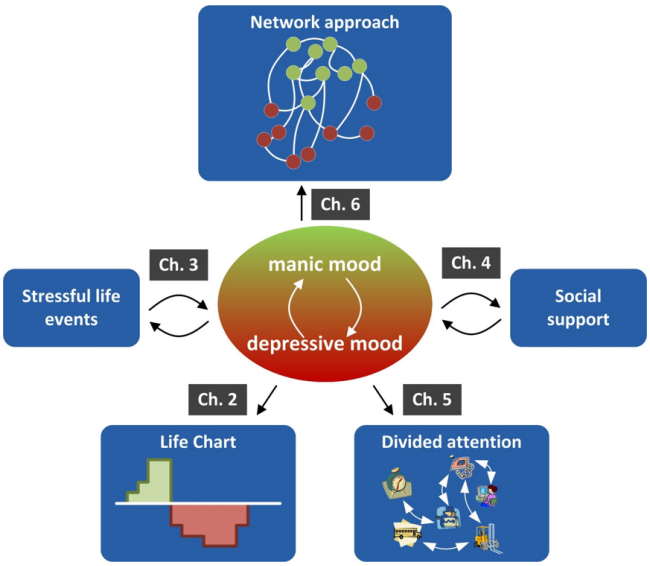

Figure 1.2 | Schematic representation of chapter content.

assume that there exists an ongoing vicious cycle in which bipolar mood symptoms are triggered by adverse life events and low social support, and the mood symptoms in turn will lead to the occurrence of more adverse events and erode the social support system (Figure 1.2) (Chapter 3 and 4).

1.4 Network approach

In addition to a bidirectional approach to longitudinal bipolar data there is a novel approach in psychopathology research, called the network approach. Within this approach the symptoms of the disorders and their associations are proposed as the central focus of attention and as the source of more profound understanding of psychiatric diseases (51). One of the important aims of this approach is to study psychiatric disorders less categorical than they are now presented by the diagnostic boundaries of the diagnostic handbooks (4).

For example, in a recent study Goekoop et al. (52) the authors show that within an unselected group of psychiatric patients, symptoms of a wide vari-

ety of disorders are all interconnected, with particular groups of symptoms clustering together into 6 distinct psychiatric syndromes. In the bipolar field, we also become more aware of the fact that diagnostic categories do not always reflect what we observe in the clinical reality. For instance, the fact that the 'mixed specifier' category is incorporated in the new DSM 5 reflects the need for less strict distinction between manic and depressed mood states. Within a network approach, one would be able to study in what way manic and depressed symptoms are interconnected, and possibly reinforce one another.

Additionally the way symptoms are interconnected and mutually reinforce one another might provide more insight in how specific course patterns in bipolar patients evolve, apart from all sorts of external factors that might affect the disease course (Chapter 6).

1.5 Aims and outline of this thesis

Given the severe disease course in terms of chronicity, recurrence rate, and high burden of BD it seems likely that the associations between psychological factors and the disease course are complex and reciprocal in nature. However, most previous research used unidirectional approaches when studying the association between the disorder and the psychosocial environment. Therefore the overall aim of the current thesis is to critically investigate previously reported associations between psychological factors and the bipolar disease course from a novel theoretical and statistical angle. We investigated this in the context of the 'Bipolar Stress Study'. This cohort contains 173 BD I and II patients who were followed over a 2-year period. Previously, Spijker et al. presented the first findings from this study (53–55), mostly focusing on genetic and biological vulnerabilities in BD patients. In the current dissertation, the focus is on the psychosocial vulnerabilities associated with the longitudinal mood course. For this aim, mood, positive and negative life events and levels of social support were measured repeatedly over a 2-year period, which allows for the testing of potential bidirectional associations within the longitudinal mood course. Figure 1.2 summarizes the associations that will be investigated within the different chapters of the current thesis.

In Chapter 2 the complexity of interpreting longitudinal mood data obtained from the prospective NIMH life chart method will be addressed. In this systematic review we will give an overview of different methods to handle the data and calculate different outcome measures. Subsequently, the aims of chapter 3 and 4 is to critically examine the issue of bidirectionality in the bipolar disease course. In Chapter 3 bidirectional associations between positive and negative life events and the longitudinal course of manic and depressive symptomatology are investigated, including differences in these associations between bipolar I and II patients. In Chapter 4 temporal, bidirectional associations between longitudinal manic and depressive symptomatology and different forms of social support are examined.

In Chapter 5 we will address one part of the dispute about whether cognitive impairments are considered as trait characteristic of BD or rather as a consequence of state dependent mood symptoms. Therefore we will thoroughly investigate divided attention (DA) performance variability over time within patients, and the association of this performance with the fluctuating mood states. We will also assess potential non-linear relationships between level of manic symptoms and cognitive performance.

In Chapter 6 we will focus on the phenomenon that regardless of which factors triggered new mood episodes, the longitudinal course displays rather consistent patterns of time. As previously mentioned, the previous mood course is one of the strongest predictors for the future polarity and severity of the disease course (12, 56, 57). This means that when a patient displays a specific course pattern in the early stage of the disease, it is more likely that the patient will also display this pattern in the future. The potential existence of this vulnerability for developing specific symptom patterns is acknowledged within the previously described network approach of psychopathology (51). By using this approach we aim to identify specific symptom patterns for bipolar patients with different longitudinal course types.

CHAPTER 2

The use of the prospective NIMH Life Chart Method as bipolar mood assessment method in research: a systematic review of different methods, outcome measures and interpretations

Koenders MA, Nolen WA, Giltay EJ, Hoencamp E, Spijker AT (2015). The use of the prospective NIMH Life Chart Method as bipolar mood assessment method in research: a systematic review of different methods, outcome measures and interpretations. Journal of Affective Disorders; 136 (1): 260-268

Abstract

The severity of bipolar disorder can be assessed using the daily prospective National Institute of Mental Health's Life Chart Method (LCM-p). Also for scientific research the LCM-p, has been used frequently. However, processing and analysing the LCM-p for research purposes, is challenging because of the multitude of complex measures that can be derived from the data. In the current paper we review the different LCM-p course variables (mood episodes, average severity, proportion of time ill and mood switches) and their definitions. Strengths and limitations and the impact of the use of different LCM-p course measures and definitions on the research results are described.

A systematic review of original papers on the LCM was conducted using 9 electronic databases for literature between January 1996 and January 2014. Papers using other prospective charting procedures were not evaluated in the current study. The initial literature search led to 1319 papers of which 21 were eventually selected. A relatively wide variety of definitions of LCM-p course variables was used across the studies. Especially for the calculation of number of episodes and mood switch no univocal definition seems to exist. Across studies several different duration and severity criteria are applied to calculate these variables. We describe which variables and definition are most suitable for detecting specific bipolar disease course characteristics and patterns. In the absence of a golden standard for the calculation of LCM-p course variables, researchers should report the exact method they applied to their LCM-p data, and clearly motivate why this is their method of first choice considering their research aim.

2.1 Introduction

Bipolar disorder is a common mood disorder, with a life time prevalence of 2.4% (58). The natural course of BD is characterized by an always present risk of recurrences even when patients receive treatment according to contemporary practice guidelines (12). Over 90% of patients with bipolar disorder experience recurrences during their lifetime (14). Furthermore, while that symptomatic recovery is attained by 90% of the patients within 2 years after a severe episode, only 30% attain functional recovery (16), implicating the major impact the disorder has on functioning and daily life of bipolar patients.

For the monitoring of symptom severity there are several measures such as the Hamilton Depression Rating Scale (59) for depressive symptoms and the Young Mania Rating Scale (60) for manic symptoms. However these instruments only allow for a cross-sectional assessment of symptom severity and do not evaluate the longitudinal course.

The National Institute of Mental Health's Life Chart Method (NIMH LCM) (20) was developed as a tool for longitudinal monitoring of chronic cyclic affective disorders, such as bipolar disorder (BD) and enables patient and clinician to visualize and obtain insight in the mood course. Several variants of this Life Chart Method (LCM) are used in clinical practice and research, including clinician and self-rated versions taken retro- and prospectively at daily to monthly intervals. The prospective LCM (LCM-p) consists of a clinician version that is rated by the treating physician, and a self-rated patient version. In both versions scoring of severity of mania or depression is based on the level of mood (i.e. mania or depression) associated functional impairment, which is considered to simplify the process of rating. The LCM-p uses four levels of severity: mild, moderate low, moderate high, and severe. The LCM also gives the opportunity to score mixed mood states, when patients experience impairment caused by manic and depressed symptoms at the same time. The LCM proved its major clinical value by giving both clinician and patient an immediate graphical insight in the patient?s individual bipolar mood course over longer periods of time. Both the clinician and patient version of the LCM-p have now been validated, showing that the daily assess-

ment of mood and episode severity based on the degree of mood associated functional impairment correlated highly with cross-sectional measurements of mood symptoms and global functioning (61-63). The retrospective LCM (R-LCM) has not yet been validated.

Also for scientific research on the course of illness, the LCM-p, especially the daily version, has been used frequently. However, processing and analysing the LCM-p for research purposes, is challenging because of the multitude of complex measures that can be derived from the data. The largest benefit of the LCM-p is that it summarizes the course of mania or depression associated functional impairment over time without diagnostic bias as to what constitutes for example a manic or depressive episode. However, to interpret these complex data, researchers need to transform the raw LCM-p data into course variables. The main course variables that are derived from the LCM are: number of episodes (e.g. 64), number of mood switches (e.g. 65), average mood severity over time (e.g. 30) or proportion of time impaired (66). Although clinical definitions of several bipolar course variables (e.g. recurrence, relapse, remission, response) are previously described by a taskforce of the International Society of Bipolar Disorders (ISBD), criteria to derive these course variables from the LCM were not always clear and differed across studies. For example, for the definition of an episode some researchers have used the Diagnostic and Statistical Manual IV (DSM-IV) (4) duration criteria (e.g. 67) while others used more strict criteria (e.g. 62). One reason for these differences is the fact that different aspects of the mood course are relevant for different research questions. Another reason might be that there is a lack of concise and unequivocal criteria for the calculation of p-LCM course variables.

The aim of the current paper is to review the four main course variables utilized across studies that use the daily LCM-p. We will first describe definitions of these LCM-p course variables and the impact of definition differences on the research results. Subsequently we will amplify on the strengths and limitations of the different LCM-p course measures with respect to specific research aims. We will further suggest recommendations that may help with the interpretation and analysing of life charts.

2.2 Method

To create an overview of the different interpretation methods of the LCM-p across the literature, we conducted an electronic literature search in several databases that all let to unique hits (unique hits are presented between brackets): ScienceDirect (396), LWW (333), Academic Search Premier (294), PubMed (169), PsycINFO (68), Wiley (61), Embase (22), Cochrane (5), Web of Science (4). We selected documents containing the following descriptors in title, abstract or free text: ("Bipolar Disorder" OR "bipolar disorder" OR "bipolar disorders? OR "Mania" OR "Manias" OR "Manic State" OR "Manic States" OR "hypomania OR "Bipolar Depression" OR "Manic Disorder" OR "Manic Disorders" OR "bipolar" OR bipolar* OR "manic depressive" OR "manic depression" OR "manic" OR "Manic-Depressive Psychosis" OR "Manic Depressive Psychosis" OR "Bipolar Affective Psychosis" OR "Manic-Depressive Psychoses" OR "Cyclothymic Disorders" OR "Cyclothymic Disorder" OR "Cyclothymic Personality" OR "Cyclothymic Personalities" OR Cyclothym* " OR "hypomanic" OR "Affective Disorders, Psychotic" AND ("life chart" OR "life charts" OR "life charting" OR "lifechart" OR lifechart* OR "mood chart" OR "mood charts" OR "mood charting" OR "moodchart" OR moodchart* OR "NIMH-LCM-p" OR "LCM" OR "mood rating" OR "mood ratings").

Abstract and titles were used to determine the relevance of the reference. When potentially relevant, full texts were retrieved to assess the article for inclusion. The search was limited to studies published in peer reviewed journals in English available between January 1996 and December 2014. The articles were selected if they met the following criteria: original paper, use of the original daily prospective NIMH-LCM, within adult bipolar I and/or II sample, $N \geq 30$, follow-up time ≥ 3 months. Articles that missed a description of the use and interpretation of the NIMH-LCM were excluded, as well as studies that modified the LCM data by anchoring the life-chart data to other measures such as cross-sectional mood questionnaires (e.g. 68, 69-71) or to other functioning scales (e.g. 72). The initial literature search led to a total of 1352 hits. Figure 2.1 shows the flow chart of the selection process, which led to 21 original articles (presented in Table 2.1) that met our inclusion criteria.

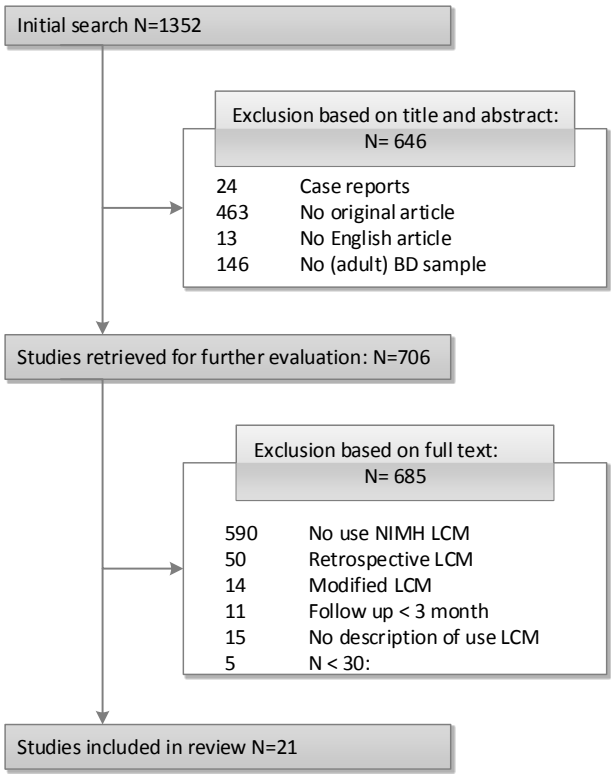

Figure 2.1 | Flow chart of systematic article selection.

Study	N	Follow-up period	LCM	Study aim	Outcome measure	Compliance
Denicoff et al., 1997a	52	1 year	Clinician and patient version	Efficacy psychotropic drugs	- episodes (leapfrog) - proportion of time impaired - average severity	83% compliance to 1 year treatment intervention (no specific LCM compliance information)
Denicoff et al. 1997b	30	2 year	Clinician and patient version	Validation of the prospective clinician NIMH-LCM	- episodes (leapfrog) - average severity	unknown
Denicoff et al. 2000	270	6 months	Clinician and patient version	Validation of the prospective clinician NIMH-LCM	- average severity	27% incomplete data
Post et al., 2001	64	1 year	Clinician and patient version	Effect of antidepressant on induction of mania	- episodes (DSM-IV and shorter 'episodes') - switch rate	unknown
Denicoff et al., 2002	52	1 year	Clinician and patient version	Utility of LCM in clinical trials	- episodes (no definition) - proportion of time impaired - average severity - switch rate	unknown
Joffe et al., 2002	69	1 year	Unknown	Effect of antidepressant on induction of mania	- episodes (DSM-IV) - switch rate	unkown
Post et al., 2002	258	1 year	Clinician and patient version	Ratio depression and mania	- episodes (leapfrog) - proportion of time impaired	unkown
Post et al., 2003	258	1 year	Clinician and patient version	Clinical predictors of mood course	- episodes (DSM-IV + leapfrog) - proportion of time impaired - average severity	unkown
Nolen et al., 2004	258	1 year	Clinician and patient version	Clinical predictors of mood course	- episodes (leapfrog) - average severity	unknown

Table 2.1 | Selected studies using the prospective NIMH LCM.

Kupka et al., 2005	539	1 year	Clinician and patient version	Risk factors for rapid cycling	- episodes (DSM-IV + leapfrog) - proportion of time impaired - average severity	unknown
Leverich et al., 2006	159	1 year	Clinician and patient version	Effect of antidepressant on induction of mania	- episodes (DSM-IV and shorter 'episodes') - switch rate	unknown
Kupka et al., 2007	507	1 year	Clinician and patient version	Ratio depression and mania	- episodes (DSM-IV + leapfrog) - proportion of time impaired - average severity	unknown
Leverich et al., 2007	480	1 year	Clinician and patient version	Age of onset and course severity	- episodes (DSM-IV) - proportion of time impaired - average severity	unknown
Goldberg et al., 2008	182	6 months	Patient version	Effect of lamotrigine on mood stability	- proportion of time impaired	>90% drop out
Langosch et al., 2008	38	1 year	unknown	Effect of quetiapine and sodium valproate on rapid cycling	- proportion of time impaired - switch rate	unknown
Shivakumar et al., 2008	41	3 months	Clinician and patient version	Effect of menstrual cycle on bipolar mood course	- average severity	66% drop out
Born et al., 2009	49	1 year	Clinician and patient version	Comparison of the BD I and II mood course	- proportion of time impaired	unknown
Post et al., 2010	529	1-4 year	Clinician and patient version	Age of onset BD and longitudinal course	- episodes (DSM-IV) - proportion of time impaired - average severity	91% finished year 1, 55% year 2, 34% year 3, 26% year 4.
Zaane et al., 2010	137	1 year	Patient version	Effect of Alcohol use on course of bipolar disorder	- episodes (DSM-IV + leapfrog) - proportion of time impaired - average severity	34% drop out

Table 2.1 | Selected studies using the prospective NIMH LCM (cont.)

Zaane et al., 2014	137	1 year	Patient version	Effect of Alcohol use on course of bipolar disorder	- average severity - switch rate	34% drop out
Born et al. 2014	108	1-4 year	Patient version	Validation of the prospective patient NIMH-LCM	- average severity	unknown

Table 2.1 | Selected studies using the prospective NIMH LCM (cont.)

2.3 Results

Of the 21 selected articles 12 studies used the LCM-p to investigate the bipolar mood course and the effect of clinical predictors (e.g. age of onset, alcohol use, bipolar subtype, menstrual cycle) on the course, 6 studies investigated medication effects on the mood course, and 3 studies investigated the utility/validity of the LCM-p in clinical trials. These 21 studies are based on (subsets of) data collected in 7 different study populations.

A combination of the clinician and patient version of the LCM-p was most often used in the selected studies (76%). In studies using both versions the clinician version of the LCM-p was based on the patient self-rated LCM-p and only the data from the clinician version were used in the main analyses. Further in the majority of the studies the compliance was not reported, however based on the ones that did report this it became clear that compliance rates over the observed period varied strongly between 10% and 91% (Table 2.1). Goldberg et al. (73) mentioned worsening of affective symptoms as a reason for drop-outs. In the study by van Zaane et al. (74) reasons for drop-outs are well documented and reported, with the most important reason being aversion against daily registration of the LCM-p. Further, it is notable that studies that reported higher drop-out rates used the patient version (self-report) rather than the clinician version of the LCM-p (73-75).

In Table 2.1 the different LCM-p course variables used in the different studies are also depicted. Table 2.2 describes the 4 most frequently used course variables of the LCM-p data across the included 21 studies, and the most common definitions of these variables. Most studies used several different course variables within one study. In the subsequent sections, we will describe the use of these variables in detail, as well as their advantages and disadvantages. Figure 2.2 (a fictitious life chart mood course) aims to illustrate the effects of different course variable definitions.

	Used in studies N (%)	Most commonly used definition	Advantages	Disadvantages
Number of manic and depressed episodes (DSM criteria)	9 (43%)	Depressed episode requires a duration of 2 weeks, a hypomanic episode requires at least 4 days without functional impairment, and a manic episode requires 1 week with functional impairment.	Represents global cycling pattern Can be used to distinguish different course types	May underestimate the number of episodes Short episodes with clinical relevance are missed No specific criteria for euthymia duration between two mood episodes of same polarity
Number of manic and depressed episodes (leapfrog rule)	8 (38%)	A manic episode requires 1 day of moderate or severe mania, a hypomanic episode requires 2 days of mild mania, and a depressive episode requires 2 days of moderate depression or 1 day of severe depression. Episode ends at switch or 2 week euthymia.	Prevents counting false-positive episodes after ultra-brief periods of euthymia Represents detailed cycling pattern, with shorter episodes Can be used to distinguish different course types	May overestimate the number of episodes due to short duration criteria for episodes.
Proportion of time impaired	12 (57%)	Number of days or percentage of time with mania/depression related impaired during the observed period.	Little data manipulation Represents disorder impact over specific period Consistent definition across literature	No consensus in handling of mixed states Does not provide information on cycling pattern
Average severity	14 (66%)	Mean level of severity of depression and mania during the observed time period.	Little data manipulation Represents impairment severity over specific time period Consistent definition across literature	No consensus in handling of mixed states Does not provide information on cycling pattern
Mood switch	6 (29%)	Either any switch into a sustained mood period, or any crossing of the midline on the LCM.	Represents mood instability Identification of rapid cycling patterns	No consensus about definition of switch Switches into very brief periods of mood episodes might be clinically less relevant

Table 2.2 | NIMH Life Chart outcome variables.

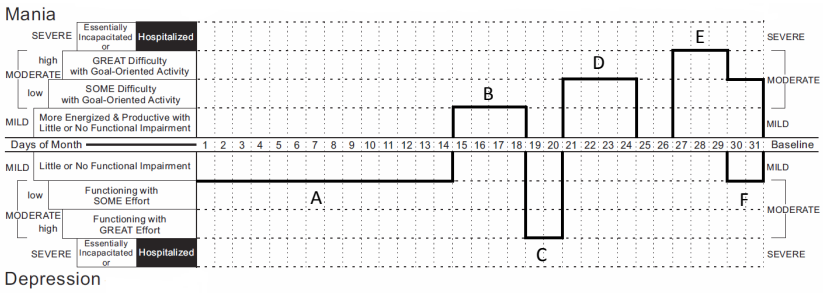

Figure 2.2 | Fictitious mood course on the prospective LCM.

2.3.1 Course variable: number of mood episodes

The number of episodes over the observed period is the most often used LCM-p course variable. However, the criteria for a LCM-p depressive and manic mood episode are not consistent across the literature. Basically there seem to be two different methods to define an episode, the first follows the DSM (DSM-III-R of DSM-IV) duration criteria and the second is the so called 'leapfrog rule' (62). In total 13 studies used number of episodes as an course variable, with 5 studies applying the DSM-IV criteria (76-80), 4 studies the leapfrog rule (30, 62, 81, 82), and 4 studies both the DSM-IV and the leapfrog criteria (64, 67, 74, 83).

Mood episodes based on DSM criteria

The DSM based method (DSM-III-R or DSM-IV) is the most frequently used method. However the scoring of the LCM-p is not based on DSM bipolar episode criteria, but on the severity of mood associated functional impairment. This means it is not possible to define a truly DSM defined bipolar mood episode from the LCM-p. Therefore researchers combined the DSM criteria for the duration of mania, hypomania or depression with severity criteria derived from the LCM-p ratings. However, the actual criteria that have been used across the studies are somewhat different as is depicted in Table 2.3. Further, not all authors specified how they exactly applied DSM criteria to the LCM data (77, 79).

According to the DSM-III-R or DSM-IV duration criteria, a depressive epi-

Study	Depression	Hypomania	Mania	
Kupka et al., 2005; Kupka et al 2007; Post et al. 2010; Zaane et al. 2010	≥ 2 weeks ≥ low moderate	≥ 4 days mild	≥ 1 week ≥ low moderate	
Post et al. 2003	≥ 2 weeks ≥ low moderate	≥ 4 days mild	unclear	
Post et al. 2001	-	≥ 1 week mild	'Sustained period' ≥ low moderate	Additionally distinguished shorter duration (hypo-) manias
Leverich et al., 2006	-	≥ 1 week mild	≥ 2 days ≥ low moderate	Additionally distinguished shorter duration (hypo-) manias

Table 2.3 | Applied duration and severity criteria for DSM definitions of mood episodes.

sode has a duration of at least 2 weeks, a hypomanic episode at least 4 days and a manic episode of at least 1 week. Further, the DSM-IV requires that a hypomanic episode is not accompanied by functional impairment (comparable with severity level 1 (mild) on the LCM-p), while manic and depressed episodes do affect functioning (comparable with severity level ≥2 (low moderate) on the LCM-p). So applying the criteria for a depressed episodes (≥ 2 weeks with ≥ mild moderate symptoms) period A is not considered a true DSM defined depressive episode, as the severity criterion is not fulfilled.

Most authors (64, 74, 80, 83) applied the above mentioned DSM criteria to calculate mood episodes. However, in the studies by Post et al. (76) and Leverich at al. (78) different duration criteria are applied to hypomanic and manic episodes. Both studies investigated the effects of antidepressants on mood changes from depression into (hypo-)mania. For this purpose also more subtle and brief periods of hypomanic symptoms of at least 1 day were relevant to evaluate based on a method previously proposed by Angst et al. (84). To be able to clearly distinguish the brief hypomanic episodes from full duration episodes, the duration criteria for a true hypomanic episode were set at 7 days instead of 4 days. Further, in these two studies manic episodes are rather based on severity criteria (≥ low moderate) than on strict duration

criteria.

So when these different criteria are applied to the mood course in Figure 2.2, the period B would be defined as a true DSM hypomanic episode by the studies that applied the 4 days criteria but would not be counted as such in the studies by Post et al. and Leverich at al. in which this would be counted as a brief hypomania. Additionally, because of the shorter duration criteria of Post and Leverich period E in Figure 2.2 would be counted as a manic episode, while according to the DSM duration criteria this short period with substantial manic symptoms and clinical relevance would not be counted as a true DSM manic episode.

Mood episodes: the leap-frog rule

Besides using the DSM-IV duration criteria as a method for defining episodes, another method has also been widely used. This method is called the 'leapfrog rule', which is suitable only for the daily LCM-p (62). This method does not only set a duration criterion, but also a severity criterion. According to this rule, mood fluctuations are not counted as an episode unless one of the following criteria are met:

1. a *manic* episode requires at least 1 day of moderate or severe mania;
2. a *hypomanic* episode requires at least 2 days of mild mania;
3. a *depressive* episode requires at least 2 days of moderate depression or at least 1 day of severe depression.

   This means that LCM ratings of mild depressed mood in the absence of ratings of at least moderate depressed mood within the same episode as depicted in period A in Figure 2.2 are not counted as an episode, while two days of moderate depressed would be considered an episode as depicted in period C.
4. In addition to the above, an episode is considered ended when the patient switches polarity or when there are 2 weeks of euthymic mood. In case of fewer than 2 euthymic weeks but longer than the longest contiguous duration of the adjacent mania or depression, the episode is

> also considered ended. Consequently, if the euthymic period is less or equal to the longest duration of adjacent depression or mania ratings, then the episode length is extended from the previous episode into the subsequent one, but only when the set of mood ratings does not change in polarity. This prevents false positive episodes when there are only (ultra-)brief periods of euthymia.

So when applying this rule to Figure 2.2, period D and period E should be considered as one single manic episode. By applying this last euthymia duration criterion, the leapfrog rule claims to be more conservative and prevent overestimation of the number of episodes in comparison to applying only the DSM-IV duration criteria.

Differences in course between DSM-IV duration criteria and leapfrog rule

Applying different definition criteria for LCM-p episodes can lead to differences in the number of episodes. Kupka et al. (83) and Van Zaane et al. (74) used in their studies both the leapfrog rule and the DSM duration criteria and reported the differences in course. For the DSM episodes they used the following criteria: a manic episode of at least 7 days and at least (low) moderate severity or hospitalization, a hypomanic episode of at least 4 days and mild severity, and a depressive episode of at least 14 days and at least (low) moderate severity or hospitalization. Their results clearly illustrate the differences between the two methods. In Kupka's study, in which the mood courses of rapid cyclers and non-rapid cyclers were compared, it is demonstrated that applying the leapfrog rule resulted in the detection of on average 9 additional (in addition to DSM defined episodes) mood episodes in the rapid cycling group. In Van Zaane's study applying the leapfrog rule resulted in 2.5 more depressive episodes, 1.5 more hypomanic episodes and 6.4 more manic episodes compared to the number of the DSM defined episodes. This does not support the widely assumed assertion of the leapfrog rule to being more strict and preventing overestimation of the number of episodes (62), but this method does seem to detect more subtle and short mood changes which remain undetected when DSM criteria are applied.

Conclusion number of episodes

In light of the absence of a gold standard methodology, it remains unclear whether the lenient duration criteria of the leapfrog method likely overestimate the number of episodes, or whether the more strict DSM-IV criteria underestimate the number of episodes. What is clear is that the two methods give different perspectives with respect to frequency ratios of the occurrence of different mood states. Based on the research question at hand researchers should decide whether DSM mood episodes are informative or that also brief episodes and subtle mood changes are relevant, for instance when studying (ultra-) rapid cycling patterns (e.g. 82, 83) or when studying the short term (hypo-)mania inducing effects of antidepressants (76, 78).

2.3.2 Course variable: proportion of time ill/impaired

A second indicator of course severity that is used across the literature is the proportion of time ill or impaired. This is defined either as the number of days ill/impaired or the percentage of time ill/impaired during the observed period. Methods of calculating these two course variables are used rather consistently across the literature and simply consist of counting the number of days or the percentage of time (number of days with reported impairment divided by number of days observed) for manic or depressed mood state separately. When calculating the proportion of time impaired for the mood course in Figure 2.2, this results in 13 of the 31 observed days with mania related impairment (proportion 42%) , 18 of the 31 observed days with depression related impairment (proportion 58%), or a total proportion of overall time impaired of 29 days (proportion 93.5%). In some studies the percentage of time impaired was presented for every severity level of the LCM (e.g. 64, 67, 82).

Only when scoring mixed mood states (see Figure 2.2, period F) some inconsistency emerges. The NIMH Life Chart Manual (85) states that in case of mixed mood states the rated mania score is included in the average mania score and the depression score in the depression average. However, Denicoff et al. (86) used the rule that when patients experienced manic and depressive symptoms simultaneously, and met DSM III-R criteria for mania or

hypomania, the day was rated as manic. This means that the rated depressive symptoms of the mixed mood state are not included in the proportion of time impaired calculations.

There are several advantages when using this course variable. First, it provides insight in the long term impact of the disorder in terms of proportion of time that the patient is disabled by the disorder, regardless of whether there occurred strict DSM-IV episodes. Second, methods to calculate these variables are consistent across studies, which improves comparability of these studies. Third, it provides a clear picture of the longitudinal impact of the disorder on daily functioning. There are also some disadvantages however. The cycling pattern is not reflected in this variable, since patients with rapid mood switches cannot be distinguished from patients with prolonged mood episodes when both are impaired for the same proportion of time. However, in some studies the proportion of time ill/impaired is used as a method to distinguish different course types within the patient groups. Post et al. distinguished three different course types (minimally impaired, episodically ill, and chronically ill) based on proportion of time ill/impaired on the LCM-p in combination with a description of their specific cycling pattern (67, 82). Still, this method is most suitable for a more global descriptions of course severity, for instance when long term medication effects are measured (73, 81) or when the effects of specific clinical predictors on overall course severity is measured (e.g. 66, 74, 80, 87).

Conclusions considering proportion of time ill/impaired

Considering the fact that this method requires little manipulation of the LCM-p data and relative consensus exists about the calculation of number of days or percentage of time impaired, this method allows for comparison with previous studies that used this method. Reporting of percentage of time ill/impaired might be preferred over reporting number of days impaired, since it is easier to interpret for the reader. Reporting the proportion of time impaired reflects a more global measure of disease severity, but does not provide specific information about cycling patterns.

2.3.3 Course variable: average severity of illness

The LCM-p assesses the severity of functional impairment due to mood symptoms for a certain day. In research settings, measuring/reporting of illness severity over longer periods of time is required. Calculation of this variable seems rather consistent across the literature. The average of the weighted severity measured of the reported impairment over an certain time period of the LCM-p is used according to the following formula based on Denicoff et al. (62):

[(no. days of severe depression × 10) + (no. days of moderate high × 7.5) + (no. days of moderate low depression × 5) (no. days of mild depression × 2.5)] / # of days observed.

[(no. days of severe mania × 10) + (no. days of moderate high mania × 7.5) + (no. days of moderate low mania × 5) + (no. days of mild (hypo)mania × 2.5)] / # of days observed.

For the mood course in Figure 2.2 this would lead to the following calculation for depression:

(0 × 10) + (2 × 7.5) + (0 × 5) + (16 × 2.5) = 55/31 = 1.8

and for mania:

(0 × 10) + (3 × 7.5) + (6 × 5) + (4 × 2.5) = 62.5/31 = 2.0 Other studies not only evaluated mean LCM-p severity scores for each pole (manic/depressed), but also overall impairment scores by averaging the scores of both poles (30, 74). Furthermore, averages can be calculated over the total observed period, or over specific time periods, such as weekly or monthly averages (62, 63). Regarding mixed episodes, Denicoff et al. (86) used a different method (as described in section 3.2) than was proposed in the NIMH LCM manual. As is described before, when patients experienced manic and depressive symptoms simultaneously, those days should be rated as mania but not depression.

Conclusions considering average severity

Calculating the average severity requires little manipulation of the LCM-p data and calculation methods are consistent among studies. Besides, this

method also allows for a clear representation of the severity of impairment over an observed period and allows for a distinction between impairment severity among patients. This method is comparable to the proportion of time ill/impaired in the sense that it provides a more global severity measures of the disease course. However, again this method does not allow for determining cycling patterns.

2.3.4 Course variable: mood switches

Some researchers were especially interested in the number of mood switches, defined as an immediate change from a depressive episode into a hypomanic or manic episode or vice versa (75, 76, 78). This course variable is mainly used in studies that focussed on the potential risk of antidepressants to induce switches form a depression into hypomania or mania (76, 78). A difficulty in these studies is how to define switch, i.e. how to define an episode from the LCM-p data as discussed above.

This is nicely illustrated by the study of Leverich et al. (78). In addition to switches into full manic episodes (hypomania: ≥7 with mild severity; mania: ≥ 2 days with ≥ moderate severity), they also looked at switches into shorter duration episodes (brief hypomania: ≥ 1 day mild severity). This allows for a distinction in severity of switch (e.g. subthreshold switch into brief episodes versus threshold switches into full duration hypomania or mania) and for a detailed representation of mood instability.

In the study by Post et al. (76) the above mentioned criteria were also applied. They reported that 14% of the patients had switches into full hypomanic or manic episodes, but an additional 18% had ultradian switches or switches into brief hypomanic episodes. This illustrates the additional information about mood instability that can be gained by including subthreshold switches.

Further, besides switch into DSM episodes or shorter episodes a third definition of switch is used, which is any change in mood polarity or any crossing of the midline on the LCM-p (not including ultradian switches) (65, 75, 86).

The different used duration criteria obviously will lead to different numbers of switches within the same course. When the full episode criteria for hypo-

mania and mania of Leverich et al. and Post et al. are applied to Figure 2.2, there is no mood switch in this course. However, when the shorter duration criteria are applied, there are two switches into hypomania: from period A (depression) to period B (hypomania) and from period C to period D. When a switch is defined as any crossing of the midline and also switches into depression are included, three switches in Figure 2.2 can be identified (from period A to period B, from period B to period C, from period C to period D,), indicating that applying different criteria also lead to different number of switches within the same patient.

Conclusions considering mood switches

Switch rate is a course variable that is mainly used in studies measuring medication effects on the clinical BD course. In general, for the calculation of switches different criteria than DSM criteria are used. However, no consensus seems to exist over what exactly should be considered a mood switch. Very rapid mood changes (any crossing of the midline) might be a good indicator of mood instability and rapid cycling patterns. But, as Leverich et al. (78) already mentioned, mood switches into a more sustained period of mood symptoms might be clinically more relevant, since very brief switches might be considered less problematic since their impact on daily functioning might be minimal.

2.4 Discussion

This review reveals the challenging issues when using course variables derived from the NIMH LCM. These course variables can be used in research, but also when interpreting the rich data provided by this chart in clinical care. The NIMH LCM is first and foremost an important clinical tool for monitoring the bipolar mood course and a valuable resource for both clinician and patient to gain more insight in the longitudinal mood course of the patient and its possible correlates. The current review shows that this tool is also widely used in research.

Both the clinician rated version of the LCM-p and the patient rated version are now well-validated (61, 88). Both version are suitable for long-term mon-

itoring of the mood course and both have their advantages and disadvantages. The benefits of the clinician version is that clinicians can perform the prospective ratings every time they see the patients, and irrespective of whether or not patients have completed their own ratings. Consequently, clinician ratings are more likely to be complete, although probably less reliable when not using the ratings by the patients themselves, especially in cases with the rating of longer intervals. However, rating of the clinician version is time-consuming and therefore costly in both clinical and research settings. With respect to the patient version, a recent validation study (88) shows good validity and reliability of this version, suggesting this version to be a good alternative to the clinician version. However, especially daily self-rating might be rather burdening to patients and may lead to higher drop-out rates than the clinician version (89). Alternatively, electronic versions of the life chart might lead to more compliance (90).

Further, the main issue we address in this review is the fact that the LCM-p is used to measure different course variables which are differently defined. The most commonly used measures are: number of mood episodes, proportion of time impaired, average severity of impairment, and number of mood switches. In most studies a combination of these course variables are used.

The course variables which have the most consistent definitions across the literature are: proportion of time impaired/ill and average severity of illness. Calculating these course variables requires minimal manipulation of the raw LCM-p data and they reflect global impact and severity of the disorder over an observed period of time. A benefit of the calculation of proportion of time ill is that it allows for a distinction between patients that have an equal number of episodes, but very different duration of time in certain mood states. A disadvantage of these variables is that they do not reflect cycling patterns or overall mood instability. Both average severity and proportion of time ill/impaired are therefore often used in combination with other LCM-p variables, such as number of episodes or switch rates.

Number of episodes based on the LCM-p is the most frequently used variable across the reviewed literature. However, at the same time several different definitions are used to calculate the number of episodes. Especially on the duration criteria for episodes no strict consensus exists. Most studies used

duration and severity criteria based on the DSM-III-R or DSM-IV. However, also other criteria are used such as the leapfrog rule and the modified duration criteria (76, 78) of Angst. These two methods use shorter duration criteria for episodes, leading to higher numbers of episodes counted. The relevance of additionally including brief mood episodes is demonstrated by the studies of Angst et al. (84, 91) showing that brief episodes are part of the clinical reality of the course of bipolar disorder and that the occurrence of episodes is not restricted to DSM duration criteria. Consequently, DSM duration criteria might be useful to detect more general cycling patterns and full-duration episodes, with the risk of underestimating number of mood episodes. As such, the shorter duration criteria are suitable for the detection of rapid cycling patterns, with the risk of overestimating the number of episodes. The leapfrog rule might be most suitable for the detection of brief episodes, since it minimalizes the risk for overestimation of number of episodes by setting more strict criteria to what constitutes an euthymic period.

For the calculation of number of switches the same problems arise which apply to the calculation of mood episodes. Again, when very rapid switches are included, mood instability might be overestimated. However when stricter duration criteria are applied, clinically relevant mood changes might be overlooked.

The current review has several (potential) limitations. While effort was made to uncover all relevant publications on the LCM in the English language, some relevant studies may have been missed. Moreover, this review was limited to an evaluation of the prospective NIMH LCM and did not include an overview of the use of the retrospective LCM as well as other charting methods. The strengths of the current review is that it is the first to describe the different interpretation methods of the LCM-p when using it as an course measure which may help to increase comparability across future studies.

In conclusion, our systematic review showed that the LCM-p is not only a clinical useful tool (not discussed as such in this paper), but is also a challenging but invaluable and widely used method in longitudinal research. Strict recommendations on how to use the LPM-p in course research are hard to give. Since there exists strong variety in methods to analyse and report LCM-

p data it is important that researchers report the exact method they applied to their LCM-p data and motivate why this is their method of first choice.

CHAPTER 3

Stressful life events in bipolar I and II disorder: cause or consequence of mood symptoms?

Koenders MA, Giltay EJ, Spijker AT, Hoencamp E, Spinhoven P, Elzinga BM (2014). Stressful life events in bipolar I and II disorder: cause or consequence of mood symptoms? Journal of Affective Disorders; 161:55-64.

Abstract

Life events are assumed to be triggers for new mood episodes in bipolar disorder (BD). However whether life events may also be a result of previous mood episodes is rather unclear. In the current study 173 bipolar outpatients (BD I and II) were assessed every three months for two years. Life events were assessed by Paykel's self-report questionnaire. Both monthly functional impairment due to manic or depressive symptomatology and mood symptoms were assessed.

The results show that negative life events were significantly associated with both subsequent severity of mania and depressive symptoms and functional impairment, whereas positive life events only preceded functional impairment due to manic symptoms and mania severity. These associations were significantly stronger in BD I patients compared to BD II patients. For the opposite temporal direction (life events as a result of mood/functional impairment), we found that mania symptoms preceded the occurrence of positive life events and depressive symptoms preceded negative life events.

The use of a self-report questionnaire for the assessment of life events makes it difficult to determine whether life events are cause or consequence of mood symptoms. Second, the results can only be generalized to relatively stable bipolar outpatients, as the number of severely depressed as well as severely manic patients was low.

Life events appear to precede the occurrence of mood symptoms and functional impairment, and this association is stronger in BD I patients. Mood symptoms also precede the occurrence of life event, but no differences were found between BD I and II patients.

3.1 Introduction

The course of bipolar disorder (BD) is assumed to be the result of a complex interaction between genetic and biological vulnerability and environmental factors (92-94). The severity and frequency of the occurrence of (hypo-) manic and depressed episodes is highly variable and unpredictable among BD patients. In order to improve treatment effect and disease outcome, more insight is needed in factors predicting and contributing to relapse into mood episodes. Stressful life events play an important role in the course of BD. The occurrence of major events in the life of BD patients has been associated with an increased risk of relapse into mood episodes (95, 96) and increased time until recovery (97). Especially negative life events seem to be more common in the months prior to both depressive (31, 32, 98-101) and manic episodes (102-107). One of the more recent studies, and the largest follow up study on life events in BD to date, shows that negative life events especially precede depressive symptoms and life events involving goal attainment precede manic symptoms (108). However both for depression (107, 109) and mania (31, 32, 98, 109) findings are inconsistent, and the exact nature, strength and direction of the associations are still unclear.

Further, it has been suggested that life events may also occur as a consequence of the disorder. The so-called 'stress generation theory' in unipolar depression (110) states that individuals with depressive symptomatology may generate stressful events, (for example, marital problems, or loss of a job) due to their depressive symptoms. There is a substantial amount of evidence that supports this relationship in unipolar depression (49), and hence, whether this also holds for BD patients remains unclear, since only one prospective study (50) to date examined this association and found that hypomanic symptoms predicted increases in both negative and positive life events and depressive symptoms appeared to be less stronger predictors of subsequent life events.

There are several factors that complicate examining the association between life events and mood, which may have contributed to inconsistent results. One of the factors that may explain part of the inconsistencies may relate to the BD subtypes that have been studied, as previous studies strongly differ

in terms of the specific BD diagnosis. Some studies examined samples including all BD subtypes (32), others only included cyclothymic and BD II patients (111) or only BD I patients (e.g. 31). This might contribute to inconsistent findings, since growing evidence indicate that BD I and II differ on both clinical (112), genetic (25, 113) and neurocognitive characteristics (114, 115). For instance, compared to BD I, BD II is associated with more comorbidity of psychiatric illnesses (116, 117). Further, BD II is associated with a more chronic course with more frequent episodes (25-27) which may lead to the process of 'kindling' (93), meaning that in time mood episodes may appear more easily without being triggered by any environmental stressor. It is however unclear to what extend kindling is involved in BD in general and in patients with BD II in particular.

A second factor that may have contributed to inconsistent findings, is the fact that most prospective studies rely on rather small sample sizes, ranging from N=41 to N=56 (32, 98, 109, 118) and short follow-up periods. They therefore may have lacked statistical power to detect a consistent association between life events and mood symptoms. To date, only Johnson et al. (31) studied the effect of life events on bipolar mood in a prospective study with both a large sample size (N=125) and a relatively long follow-up period (27 months).

Third, it remains difficult to determine whether life events are a cause or a consequence of bipolar mood episodes. Several studies tried to control for this by excluding those life events that were rated by the researchers as dependent of mood symptoms (e.g. losing a job due to a current depression), and only including life events rated as independent of mood symptoms (e.g. illness or death of a relative) (e.g. 31, 32, 95, 100). However, even though dependent life events may strictly speaking be consequences of the disorder, this does not mean that these events cannot have an adverse effect on the course of the disease as well, illustrating the difficulty in determining the temporal direction of the association.

In the current two-year prospective follow-up study among 173 BD patients we aimed to examine both temporal directions of the association between negative and positive life events and depressive and mania symptomatology and functional impact of mood disturbances. Additionally, to control for possible differences between BD I and II, we examined BD subtype as a pos-

sible moderator of the association between life events and mood symptoms and functional impact.

3.2 Materials and methods

3.2.1 Method

Participants

This is a 2-year prospective follow-up study among 173 bipolar outpatients with a diagnosis of BD I (N=121) or BD II (N=52) (also including BD not otherwise specified (N=2) and cyclothymia (N=1)) according DSM-IV-TR diagnostic criteria. All patients treated for BD by the Outpatient Clinic for Mood Disorders in The Hague (The Netherlands) were invited to participate in the study, either by letter or directly by their treating physician. After written informed consent was obtained, 173 patients were willing to participate and enrolled into the follow-up study. Participants were older than 18 years. Exclusion criteria in this study were schizo-affective disorder, neurological disease and substance abuse disorders.

Diagnoses of BD and psychiatric Axis I co-morbidities were based on DSM-IV criteria and were assessed with a standardized diagnostic interview developed by Sheenan et al. (119) using the Dutch version of the MINI International Neuropsychiatric Interview Plus (version 5.00-R; MINI-PLUS), with good interrater (kappa >.75) and retest reliability (kappa > .75) (119, 120) DSM-IV axis II comorbidity was not assessed. The Questionnaire for Bipolar Illness, Dutch translation (23, 121) was used to specify subtypes of BD, its course over time and detailed information about age of onset of first symptoms regarding hypomanic, manic, and depressive episodes.

Of the total sample, 90.2% of the patients (N=156) completed at least 1 year follow-up, eventually a cumulative number of 44 (25.4%) patients dropped out before the end of the study. The most common reasons for patients to quit prematurely were: being too unstable, being hospitalized, deeming the research too burdensome, discontinuing treatment at our outpatient clinic, and not showing up at an appointment more than 2 times. Figure 3.1 shows the flow-chart with the number of patients who dropped out at the different

time points.

Procedure

All patients signed informed consent before entering the study. After completing the baseline measurement with a psychiatric interview, assessment of current and past mood, and patient and disease characteristics, patients had face-to-face contacts with the research assistant at 3-, 6-, 9-, 12-, 15-, 18-, 21-, and 24- months follow-up. During these contacts manic and/or depressed mood, medication use and stressful life events during the past three months were assessed (see Figure 3.1). In order to increase accuracy of recall of mood severity in the past three months and the occurrence of life events, information from diaries, calendars, patient files or other anchor points were used.

3.2.2 Materials

Life events

The occurrence of life events was assessed every 3 months by Paykel's (122) self-report questionnaire consisting of 61 life events, which was independently completed by the patients. This instrument categorizes possible life events into 10 groups (i.e., employment, education, financial status, somatic health, loss, living place, relationship, criminality, family and social problems, and other events). Patients rated whether the events on the list occurred within the preceding 3 months, and if so they rated on a 5-point scale how upsetting the event has been to them.

The 61 single life event items were summarized into 2 main categories: the number of negative life events, and the number of positive life events. This led to a total of 39 negative life events, such as increasing arguments with the spouse, the end of a romantic relationship, business failure, serious illness of a family member, failure to an important exam, demotion at work, and unemployment for one month. A total of eleven positive life events consisted of events such as promotion at work, engagement, marriage , and a wanted pregnancy. A total of eleven life events, that could not be categorized as either positive or negative, were rated as neutral or ambiguous events (change of work field, change of work hours, moving) and were not included in the

current analyses. The categorization into negative and positive life events was determined a priori by the researchers regardless of patients ratings of the event. This method was chosen since patients ratings may be highly influenced by current mood state and in many previous studies categorization of life events (i.e. positive versus negative life events, dependent versus independent life events) was also based on a priori categorization by the researchers (i.e. 31, 32, 105).

For additional analyses of the effects of specific types of life events , life events were categorized into the above mentioned 10 life event categories.

Illness severity

Illness severity was assessed both in terms of symptoms severity and the functional impact of the mood disturbances. In order to assess mood severity based on number and severity of symptoms the Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR) (123), and the observer based Young Mania Rating Scale (YMRS)(60) was administered every 6 months. Both the QIDS (123) and the YMRS (60) have good (inter-) reliability and validity. The functional impact of mood disturbance was assessed by the NIMH monthly retrospective life chart method (LCM-r) (21, 124). This tool was used every up to eight assessment sessions, to measure medication use and monthly functional impairment arising from manic or depressed symptomatology of the previous 3 months. The advantage of this monthly tool over its daily counterpart could be the lowering of dropout rate as it demands fewer resources on the part of the clinicians and the patients. However, disadvantages are the fact that patients might not remember every minor episode, especially not when subdepressive or hypomanic symptoms are involved.

The retrospective life chart distinguishes four levels of severity for both mania and depression: mild, moderately low, moderately high, and severe. LCM rating is not based on number or severity of symptoms, but on the level of functional impairment arising from these mood symptoms. With 'mild' manic or depressive symptoms representing a distinct difference from normal mood, but with minimal or no functional incapacity, 'Moderately low'

manic or depressive symptoms reflecting some difficulty in usual roles and functioning, 'moderately high' reflecting much difficulty in usual roles and functioning, and 'severe' manic or depressive symptoms reflecting symptoms that essentially incapacitated the patient or resulted in hospitalization (85). Based on the life chart data, mean severity of functional impairment of depression and mania of every three-month period was calculated by averaging the monthly severity scores. A similar method has been used in previous research (62, 67). Medication use assessed with the life chart was categorized into a dichotomous variable. The psychotropic medication classes that were used most frequently, were coded according to the Anatomical Therapeutic Chemical Classification System (http://www.whocc.no/) and included Lithium (ATC code: N05AN01), anti-epileptics (ATC code: N03AF01, N03AG01, N03AX09, N03AX11), antipsychotic medication (ATC code: N05Ax with exclusion of N05AN01), benzodiazepines (ATC codes: N05BA, N05CD, N03AE01, N05CF), and antidepressants (N06A).

At the different time points during follow-up correlations between QIDS score and life chart depression score of the corresponding month varied between r=.52 and r=.65 (all significant at p<.001). Correlation between YMRS scores and life chart mania scores of the corresponding month varied between r=.40 and r=.65 (all significant at p<.001). This means that QIDS scores account for 28% to 43% of the variance of life chart depression, and YMRS scores account for 16% to 43% of the variance in life chart mania.

3.2.3 Statistical analyses

Sociodemographic and baseline characteristics were summarized as means (standard deviation [SD]) for continuous variable and as numbers (proportions) for categorical variables. Differences between subgroups were analyzed with independent sample t-tests, or chi-square analyses if appropriate.

Because data of this prospective study are nested (repeated measurements within an individual) and missings occurred because of dropouts, multilevel regression analyses (linear mixed-models) were used to analyze the associations between total number of positive and negative life events and mood states. A compound symmetry covariance structure was used consisting of

the time points (i.e. lower level) and the patients (i.e. higher level).

Life chart scores and QIDS and YMRS scores were analyzed separately, since life chart mood was assessed for up to 8 waves (every 3 months), and QIDS and YMRS for up to 4 waves (every 6 months) (see Figure 3.1). Throughout the analyses, we examined both life chart and QIDS and YMRS severity scores as continuous variables, instead of a dichotomous variable (i.e. presence/absence of mood episodes).

In the first set of models we explored to what extent positive/negative life events precede mood/functional impairment. For the first set of models we used the number of positive and negative life events of the last three months as the predictor variable and mood assessed at the subsequent time point (life chart, QIDS, and YMRS) as outcome variable. The direction of the association is shown by the arrows [1] in Figure 3.1. Associations were first assessed in a crude model, only adjusting for time and mood. Subsequently, we repeated multilevel regression analyses additionally adjusting for age, sex, level of education, medication use (adding 5 dichotomous variables).

In the second set of models we explored the reversed temporal relationship, that is to what extent mood /functional impairment precede life events. In these models mood severity (life chart, QIDS and YMRS) was used as predictor variable and positive and negative life events in the subsequent 3 months as outcome variables. This is indicated by the arrows [2] in Figure 3.1. Again, associations were first assessed in a crude model and subsequently in a model adjusting for age, sex, level of education, medication use, and total number of life events at time of assessed mood.

In an additional set of analyses we examined the interaction of BD subtype × (positive and negative) stressful life events for both temporal relationship, in order to determine whether effect of life events on mood/functional impairment and mood/functional impairment on life events were different for the two BD subgroups. All analyses were completed using SPSS for Windows (version 19.0; SPSS, Inc. Chicago, IL). All tests were two-tailed with $p<0.05$ denoting statistically significance.

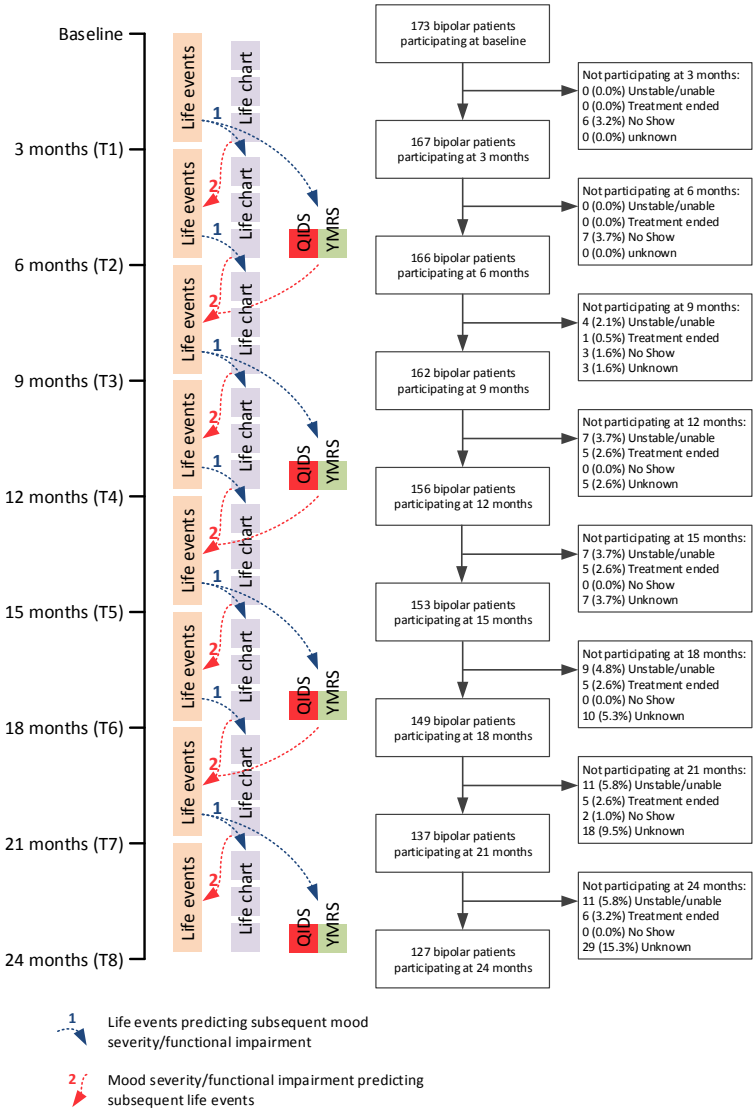

Figure 3.1 | Flow chart of follow-up measurements, direction of associations and drop-out rates.

3.3 Results

3.3.1 Demographics and clinical characteristics

Basic demographic and clinical characteristics of all patients who participated in at least one follow-up measurement (N=173) are summarized in Table 3.1. In total there were 1180 data points with complete data during 24 months of follow-up. The included subjects had a mean age of 49.9 years and were predominantly female (57.8%). Overall, mean score on the QIDS at study entry was 7.5, indicating mild depressive symptoms. Mean YMRS score was 1.7, indicating overall absent or low mania symptoms at study entry. During the duration of the study QIDS scores varied from 0 to 24, with mean scores of the total sample varying from 6.5 (SD=4.8) to 7.4 (SD =4.7). Individual YMRS scores varied between 0 to 39, with overall YMRS mean scores during follow-up varying from 1.5 (SD=3.7) to 2.1 (SD=4.8). During the two year follow-up, patients reported on the life chart functional impaired due to depressed mood 32.7% of the times, manic mood 12.2% of the times and stable mood 57.1% of the total follow up time.

A total of 8 (4.6%) patients reported no life events during the period of the study and individual number of total reported life events (positive and negative) during 3 months periods ranged from 0 to 14. Percentage of patients reporting life events over the eight follow up measurements were as follows: including the data of all timepoints (in total 1180 valid data points); in 76% (N=904) no positive life events were reported, in 16.3% (n=192) 1 positive life event was reported, in 4.8% (N=57) 2 positive life events were reported, and in 2.2% (N=26) 3 or more positive life events were reported. With respect to negative life events during 24-months follow-up, 28.9% (N=342) reported no negative life events, 22.8% (N=269) reported 1 negative event, 19.6% (N=231) reported 2 negative events, 11.7% (N=138) reported 3 negative life events, and 16.9% (N=200) reported 4 or more negative life events.

Between the group who participated until the end of the study (n=127) and the group that dropped out during the study (N=44) no significant differences in baseline demographic and clinical characteristics were found and during the study no differences in mood severity on the QIDS, YMRS and life chart were found. Moreover, number of admissions was the same in both

completers and dropouts, during the study as well as the first 3 months after dropping out.

	Total	BD I	BD II	P-value
Total N	173	121	52	
Male sex; n(%)	73 (42.2)	54 (44.6)	19 (36.5)	.323
Mean age; mean (SD)	49.9 (11.4)	50.6 (11.9)	48.3 (10.2)	.230
Level of education; N (%):				
- primary	39 (22.5)	30 (25.0)	9 (17.6)	.294
- secondary	50 (28.9)	32 (26.7)	18 (35.3)	.257
- higher	82 (47.4)	58 (48.3)	24 (47.1)	-
Clinical characteristics:				
Diagnostic information; N(%)				
BD1	121 (69.9)	-		-
Comorbidity	67 (38.7)	43 (35.6)	24 (46.2)	.169
Age of onset; mean (SD)				
Age of onset first (hypo-) mania	30.8 (10.1)	30.3 (9.9)	31.9 (12.1)	.419
Age of onset first depression	27.6 (10.1)	27.4 (9.9)	27.9 (10.4)	.767
Age of onset disease	27.0 (9.8)	26.9 (9.7)	27.2 (10.1)	.875
Number of episodes; median (IQR)				
No. of manic episodes	5 (8)	4 (8)	5 (18)	.028*
No. of depressive episodes	6 (16)	6 (7)	13 (45)	.001**
QIDS baseline; mean(SD)	7.5 (4.9)	6.4 (4.4)	10.1 (5.3)	<.001**
YMRS baseline; mean (SD)	1.7 (3.1)	1.4 (2.9)	1.9 (2.9)	.385
Medication use baseline; N(%)				
Lithium	119 (68.8)	89 (76.1)	30 (58.8)	.024*
Anti-epileptics	36 (20.8)	24 (20.5)	12 (23.5)	.661
Anti-psychotics	42 (24.3)	39 (33.6)	3 (5.9)	<.001**
Benzodiazepines	42 (24.3)	29 (25.4)	13 (25.5)	.994
Antidepressants	56 (32.4)	35 (30.2)	21 (41.2)	.165

* p-value < .05

** p-value <.001

Table 3.1 | Sociodemographic and clinical characteristics in 173 participants with bipolar disorder.

3.3.2 Stressful life events preceding mood symptom/functional impairment

Table 3.2 shows the results of the multilevel analyses considering the association between total number of negative and positive life events and sub-

sequent functional impairment and severity of mania and depression. Negative life events were strongly and consistently associated with increases in subsequent depression severity/functional impact on the life chart and QIDS and increases in mania severity/functional impact on the life chart and on the YMRS. These results remained unchanged in the multivariate adjusted model. In Figure 3.2 the association between the number of negative life events and life chart functional impairment, and YMRS and QIDS scores is depicted. There appears to be a threshold effect, since severity of both life chart functional impairment and depressive and manic symptoms strongly increases after the occurrence of 4 or more negative life events, whereas scores of one to three negative life events have minimal effects on life chart functional impairment and mood severity.

Positive life events were significantly associated with subsequent life chart and YMRS mania severity, also after multivariate adjustment, but no association was found with life chart and QIDS depression severity in the subsequent months.

Additional analyses showed that there were no differences in the effects of single life events items, suggesting all life events contributed rather equally to the results (data not shown). Also no specific effects were found of groups of life events occurring in certain life domains (e.g. interpersonal problems, work problems, financial problems) (data not shown).

3.3.3 Mood symptoms/functional impairment preceding stressful life events

Next, the opposite temporal direction, mood severity and functional impairment preceding life events, was investigated. The results of both the crude and multivariate adjusted analyses are summarized in Table 3.3. In the multivariate adjusted analyses a significant association was found for YMRS mania severity preceding number of positive life events (β=.124, p=.010), but not negative life events, and QIDS depression severity preceded number of negative life events (β=.151, p=.002). However life chart functional impairment was not significantly associated with subsequent negative or positive life events.

	No. of data points Life Chart	No. of data points QIDS/ YMRS	Mania symptoms				Depressive symptoms			
			Life chart data		YMRS		Life chart data		QIDS	
			Beta (SE)	P-value	Beta (SE)	P-value	Beta (SE)	P-value	Beta (SE)	P-value
Total no. of negative events:										
Crude[1]	978	385	.142 (.032)	< .001**	.152 (.049)	.002**	.087 (.033)	.009*[i]	.133 (.038)	< .001**
Multivariable adjusted [2]	961	362	.128 (.033)	< .001**	.157 (.053)	.003**	.084 (.033)	.012*[i]	.158 (.042)	< .001**
Total no. of positive events:										
Crude[1]	978	385	.087 (.031)	.004**	.243 (.057)	<.001**	-.009 (.014)	.723[i]	.024 (.037)	.519
Multivariable adjusted [2]	961	362	.071 (.031)	.021 *	.238 (.062)	<.001**	-.005 (.031)	.501[i]	.043 (.041)	.296

[1]: adjusted for time and mood

[2]: adjusted for time, gender, age, level of education, and medication use (antipsychotic, antidepressants, benzodiazepines, lithium, and anticonvulsive agents) and mood using multilevel regression analysis (i.e. mixed models).

* p-value < .05

** p-value <.001

Table 3.2 | Stressful life events preceding mood symptom/functional impairment at follow-up in 173 patients with BD.

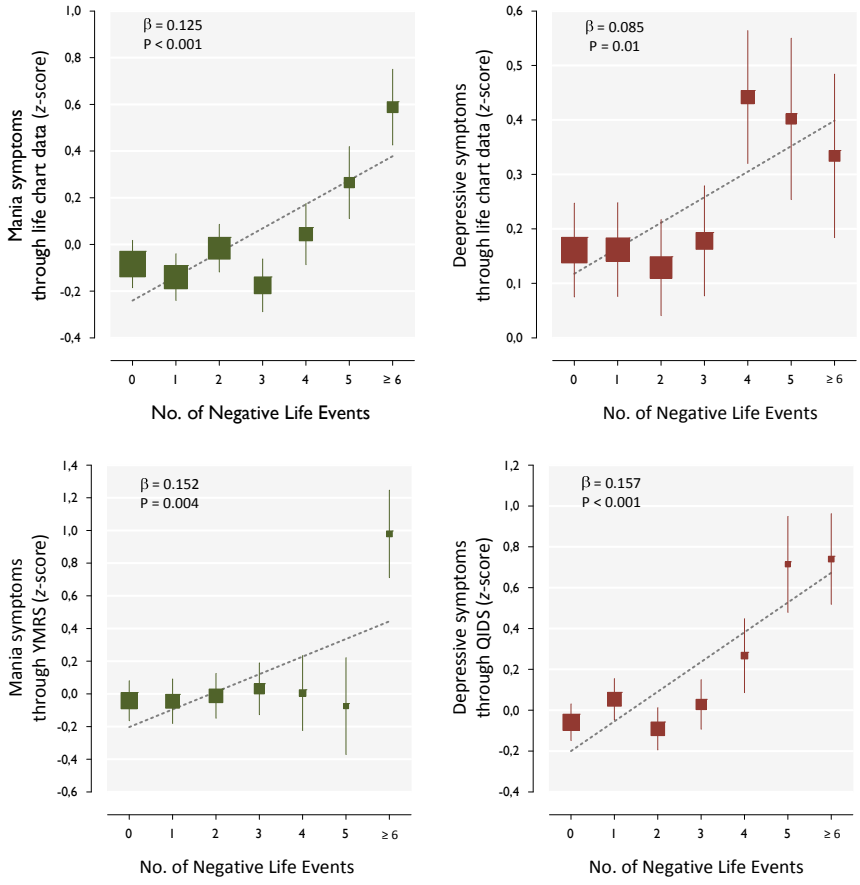

Figure 3.2 | Plots of the association between number of negative life events and the standardized score mood severity (QIDS/YMRS/Life Chart). The size of each square is proportional to the number of participants. Vertical lines indicate standard errors. Data are adjusted means by linear mixed models.

	No. of data points	Total number of negative life events		Total number of positive life events	
		Beta (SE)	P-value	Beta (SE)	P-value
Mania symptoms according to life chart method:					
Crude	992	.022 (.028)	.445	.014 (.032)	.673
Multivariable adjusted	932	.001 (.029)	.973	-.002 (.034)	.964
Mania symptoms according to YMRS:					
Crude	385	.079 (.047)	.094	.136 (.048)	.004*
Multivariable adjusted	374	.049 (.049)	.306	.124 (.048)	.010*
Depressive symptoms according to LCM:					
Crude	992	.043 (.029)	.140	.039 (.033)	.228
Multivariable adjusted	932	.051 (.031)	.088	.043 (.034)	.211
Depressive symptoms according to QIDS:					
Crude	386	.198 (.052)	<.001**	-.016 (.055)	.768
Multivariable adjusted	359	.151 (.049)	.002**	.005 (.056)	.926

[1]: adjusted for time and life events

[2]: adjusted for time, gender, age, level of education, and medication use (antipsychotic, antidepressants, benzodiazepines, lithium, and anticonvulsive agents) and life events using multilevel regression analysis (i.e. mixed models).

* p-value < .05

** p-value <.001

Table 3.3 | Mood symptoms/functional impairment preceding stressful life events at follow-up in 173 patients with BD.

The life chart data reflect mood dependent functional impairment of the past three months, the QIDS and YMRS reflects current mood, with the last measure being temporarily more proximal to the subsequently assessed life events (see Figure 3.1). However, also when life chart functional impairment of only the last month of the three life chart months was included in analyses, life chart severity neither preceded life events (data not shown).

Additional analyses showed that mood/functional impairment did not preceded certain types of life events or life event categories (data not shown).

3.3.4 Bipolar I versus bipolar II patients

Finally we examined BD subtype as a possible moderator of the relationship of life events with subsequent functional impairment and mood. First, differences between BD I (N=121)and II (N=52) at study entry were analyzed (Table 3.1). BD II patients reported significantly higher QIDS scores at study entry and more previous hypomanic episodes and depressive episodes. Further in the BD I group lithium and anti-psychotics were used significantly more often. With respect to the other variables at study entry no differences were found. During follow-up no differences were found in mean QIDS and YMRS scores, functional impairment based on the life chart, and reported total number of positive and negative life events.

Results of the moderation analyses are presented in Table 3.4. These results show that only in the BD I group negative life events are significantly associated with subsequent depression and mania severity on the lifechart, QIDS and YMRS. Moreover, the number of positive events was significantly associated with subsequent manic symptomatology and functional impairment in the BD I patients, but not in the BD II patients. Further, negative life events even seemed to have opposite effects in the two diagnostic groups, in the BD I group negative events are associated with increase in mania severity, whereas in the BD II group negative life events were associated with a decrease in mania severity.

In order to examine whether the differences in number of previous mood episodes between BD I and II might explain the difference in association between life events and mood, we additionally adjusted for number of previ-

	Mania symptoms				Depressive symptoms			
	Life chart data		YMRS		Life chart data		QIDS	
	Beta (SE)	P-value for interaction	Beta (SE)	P-value for interaction	Beta (SE)	P-value for interaction	Beta (SE)	P-value for interaction
Total no. of negative events:								
BD I	.197 (.043)	< .001**	.230 (.063)	.001**	.094 (.039)	.717	.216 (.049)	.036*
BD II and BD NOS	-.027 (.045)		-.201 (.082)		.081 (.063)		-.035 (.092)	
Total no. of positive events:								
BD I	.049 (.039)	.376	.329 (.081)	.019 *	.011 (.036)	.563	.008 (.049)	.410
BD II and BD NOS	.119 (.045)		.024 (.079)		-.049 (.064)		.071 (.081)	

Adjusted for time, mood, gender, age, level of education, and medication use (antipsychotic, antidepressants, benzodiazepines, lithium, and anticonvulsive agents) and mood using multilevel regression analysis (i.e. mixed models).

* p-value < .05

** p-value <.001

Table 3.4 | Effects of life events on mood state at follow-up in patients with BD I (N=121) versus BD II (N=52).

ous manic and depressed episodes in the moderation analyses. This did not lead to different results, suggesting that differences in stress vulnerability are unlikely to be due to differences in number of previous episodes (kindling) (data not shown). Since in the BD II group comorbidity was slightly more common, additional adjustments for comorbidity were made as well, but again this did not lead to different results. For the opposite temporal directions, mood preceding life events, no differences between BD I and II were found.

3.4 Discussion

The aims of the current study were to examine the strength of both temporal associations between life events and mood disturbances in bipolar disorder, with respect to both functional impairment as well as mood severity. Additionally, we aimed to examine possible differences in these associations between BD I and II patients. The most important findings were that negative life events preceded both (hypo-) manic and depressive symptoms and functional impairment, while positive life events predicted only (hypo-) manic mood and functional impairment due to mania. The significant associations were predominantly found in the BD I group and not in the BD II group. For the opposite temporal direction, we found that mania symptoms preceded positive life events and depressive symptoms preceded negative life events. Functional impairment did not precede life events and no differences be-

tween BD I and II patients were found.

3.4.1 Life events preceding mood symptoms and functional impairment

In the current study negative life events were significantly and consistently associated with subsequent depressive mood and depression dependent functional impairment, which is in line with previous studies (31, 32, 98). Further, positive life events preceded manic symptoms/functional impairment, which is somewhat in line with a recent longitudinal study among BD I patients showing goal attainment life events (events that involve striving, or achieving a goal) to be predictors of increases of subsequent (hypo) manic symptoms. As the present study did not assess goal attainment life events our results cannot be directly compared to previous studies reporting that especially life events involving goal attainments and not positive life events in general are predictors of manic symptoms (31, 111, 118). Nevertheless, life events involving goal attainments importantly overlap with our positive life events.

Interestingly, we found clear indications that negative life events also predicted mania severity and mania dependent functional impairment in the subsequent months. These findings are not reported in other prospective studies (31, 32, 98, 109). A possible explanation for the fact that we do observe this association, whereas other failed to do so, might be related to the fact we used continuous mood data, while previous studies evaluated the effect of life events on relapse (dichotomous) into full (hypo-) manic episodes (32, 98, 109). Assessing mood as a continuous variable in the present study may have led to increased statistical power to detect possible associations. In sum, our findings provided support for the notion that negative life events may also precede mild manic symptomatology.

Further, additional analyses showed that no specific single life events or categories of life events in specific life domains (e.g. interpersonal problems, financial problems) are associated with subsequent mood/functional impairment. However, there is a cumulative effect of life events on mood/functional impairment, with the occurrence of single life events causing small mood fluctuations, but when larger numbers of negative life events occur, severity

of mood symptoms and functional impairment increase quite dramatically in the following months. This is in line with Boland et al.(125), who stated that it may not be the specific type of life event that is important but the overall level of disruption caused by the event. It is likely that the occurrence of several different stressful events can highly disturb daily life and thus daily structure and social rhythms, while single life events might not have this disturbing effect. Since social rhythm disruptions are associated with manic and depressive symptoms (126, 127), this might be an additional explanation for the association we found between negative life events and mania. For positive life events not such a threshold effect was found. This may be due to the fact that positive life events are relatively underrepresented compared to the negative life events in the used questionnaire.

3.4.2 Mood symptoms and functional impairments preceding life events

Our results also provide support for the idea that mood symptoms induce life events in BD patients. Hypomanic symptomatology predicted positive events and depressive symptoms predicted negative events. However, mood dependent functional impairment assessed with the life chart was not associated with subsequent life events. The fact that the QIDS and YMRS are more appropriate for the detection of subclinical mood symptoms, than the more crude monthly life chart might explain the different findings, since the literature on unipolar depression indicates, is that both mood episodes as well as subclinical mood symptoms are predictors of life events (128, 129). Moreover, the life chart scores depended on the degree of functional impairment arising from the mood symptoms and does not assess mood symptoms itself. This indicates that increases in number and severity of symptoms is associated with an increase in the occurrence of subsequent number of life events, and that this association may be less strong for functional impairment. The current findings are partly in line with the only other prospective study on stress generation in BD (50), in which (hypo-) manic symptoms were also found to precede positive life events, but no association with depressive symptoms was found previously. Both the current and previous findings seem to indicate that bipolar mood symptoms may induce life events.

3.4.3 Bipolar I versus bipolar II

Another interesting finding is that life events predicted subsequent mood severity and mood dependent functional impairment in the BD I group only, and not in the BD II group. In previous studies BD I and II have already been implicated to be different disorders with respect to several clinical features. BD II compared to BD I is associated with a more chronic course with more frequent episodes (25, 26). This chronic course may indicate that mood symptoms in BD II occur more independently from external factors, such as life events. Further BD II is associated with more comorbidity of psychiatric illness (116, 130), making this a more heterogeneous patient group in which consistent associations between external factors and mood symptoms are more difficult to disentangle. In the current sample BD II patients also seem to have more frequent episodes, since they reported a significantly higher number of previous manic and depressed episodes at study entry compared to BD I patients. However, after additionally adjusting for number of previous manic and depressed episodes, results with respect to the effect of life events on mood remained unchanged. Also psychiatric comorbidity did not seem to account for the differences found between BD I and II. It should be taking into account however, that the BD II group was smaller (N=52) than the BD I group (N=121), hence, the lack of power in the BD II group may also account for the failure to find an association between mood and stressful life events.

Another difference found between BD I and II, was that negative life events seemed to have an opposite effects in the two diagnostic groups, in the BD I group negative events are associated with increase in mania severity, whereas in the BD II group negative life events were associated with a decrease in mania severity. This is in contrast with earlier findings by Johnson et al. (31) showing negative life events to be associated with decrease in mania severity in a group of only BD I patients. To what extent life events have different effects on BDI and II patients and whether the lack of associations found in the current study also hold in larger BD II samples has to be further explored.

3.4.4 Strengths and limitations

Strengths of our study include reliability due to a relative large sample size and internal validity as we were able to adjust for several important confounders. To our knowledge this study contained one of the largest bipolar samples up to date to prospectively investigate the association between life events and mood over a 2 year period of time. This study was also novel in investigating both temporal directions between life events and mood in the same sample and in distinguishing between BD I and II subtype. Further, although there were several dropouts during follow up, a relatively small number of patients dropped out in the first year of follow-up. More importantly, no significant differences were found between completers and study drop-outs.

However there are also some limitations to the current study. First, the largest limitation is the use of a self-report questionnaire for the assessment of life events. Previous reviews emphasized the superiority of life-events interviews over self-report lists (131-133). The most important limitations of self-report relate to patients subjective interpretation as to what counts as a certain life event and misdating of events, making it difficult to distinguish whether the life events are cause or consequence of mood symptoms. Moreover, certain life events may have caused other life events, which we could not take into account. Together with the relative longer periods between follow up measurements (three to six months) it is difficult to distinguish cause from effect. However, we tried to minimize this bias by the frequent assessment of life events and analyzing both directions of the temporal relationship. This has diminished the chance that we faulty indicated mood dependent life events as predictors of mood.

Second, the results can only be generalized to relatively stable bipolar outpatients, as the number of severely depressed as well as severely manic patients was low. Further the life events questionnaire oversamples negative life events compared to positive life events, which may have resulted in lack of power to detect threshold effects of positive life events.

3.4.5 Conclusive remarks

Bipolar disorder is a severe and disabling mood disorder, with a relatively unpredictable disease course that varies strongly among individuals. This study underlines that it is highly important that both positive and negative life events should be clinically evaluated, as they are associated with occurrence of manic and depressed symptoms and functional impairment. Moreover, clinicians should be aware that life events can also occur as a consequence of mood symptoms. To date, both psychoeducation programmes (134, 135) and specific psychotherapeutic treatments (136) already aim to diminish the impact and occurrence of life events and stress in BD patients to some extent. The importance of these therapies is emphasized by the current study. Further, BD I patients may be more vulnerable to life events than BD II patients and if these findings hold in replication studies, interventions addressing stress and life events may especially be important to BD I patients.

Finally, numerous factors may alter the strength of the association between life events and mood, such as clinical factors like BD subtype, subjective appraisal of the life event, social support, coping styles, personality, disease characteristics, and genetic or biological factors. Future research is needed to identify those factors that may amplify the effect that life events have on the bipolar mood course.

CHAPTER 4

The bidirectional impact of perceived and enacted support on mood in bipolar outpatients: A two-year prospective study

Koenders MA, Giltay EJ, Spijker AT, Hoencamp E, Elzinga BM, Spinhoven P. The bidirectional impact of perceived and enacted support on mood in bipolar outpatients: A two-year prospective study. Comprehensive Psychiatry; 60: 59-67.

Abstract

Bipolar disorder (BD) is a chronic illness, and a great need has been expressed to elucidate factors affecting the course of the disease. Social support is one of the psychosocial factors that is assumed to play an important role in the course of BD, but it is largely unknown whether the depressive and/or manic symptoms also affect the patients' support system. Further, the perception of one's social support appears to have stronger effects on disease outcomes than one's enacted or received support, but whether this also applies to BD has not been investigated. The objective of this study is to examine temporal, bidirectional associations between mood states (depression and mania) and both enacted and perceived support in BD patients. The current study was conducted among 173 BD I and II outpatients, with overall light to mild mood symptoms. Severity of mood symptoms and social support (enacted as well as perceived) were assessed every three months, for two years (1146 data points). Multilevel regression analyses (linear mixed-models) showed that lower *perceived* support during 3 months was associated with subsequent higher levels of depressive, but not of manic symptoms in the following 3 months. Vice versa, depressive symptoms during 3 months were associated with less perceived support in the following 3 months. Further, manic symptoms during 3 months were associated with less *enacted* support in the subsequent 3 months. The current study suggests 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. Clinical implications of the current findings are discussed.

4.1 Introduction

The longitudinal course of both bipolar disorder (BD) I and II is usually chronic and often characterized by permanent minor or subclinical mood symptoms and relapse into full mood episodes (64, 137). The treatment of BD focusses on stabilizing acute mood episodes and preventing relapse when euthymia is established. To this end, pharmacotherapy has generally been the main treatment strategy, but over the last decade, the additional value of psychotherapeutic interventions in the treatment of bipolar patients has become increasingly evident (138, 139). Evidence based psychotherapies for BD are psycho-education (preferably with a significant other), family focused therapy (FFT), interpersonal social rhythm therapy (IPSRT) and cognitive behavioral therapy (CBT) (2). The majority of these therapies put substantial emphasis on the psychosocial context of the patient, since contextual factors like negative life events (31, 140) and family distress (141, 142) are consistently associated with increased relapse risks in BD. Inversely, bipolar patients with supportive relationships seem to have a more favorable course than patients that lack this support (34). Based on these findings, it seems plausible that the promotion of supportive interpersonal relationships will lead to a more favorable course of the disease. However, so far the number of studies are limited, and more specific data regarding the influence of the different kinds of support are needed. The different kinds of support can roughly be divided into *enacted* or *objective* supportive interactions on the one hand and *perceived* or *subjectively felt* social support on the other hand. Although this distinction might seem rather arbitrary, numerous studies among different non-bipolar populations, including patients with unipolar depression, consistently found that perceived support, rather than the enacted social support, affects psychiatric and general health outcomes (143-145). In these studies perceived support is generally defined as the subjective perception that support is available, adequate and sufficient, while enacted support refers to the actual received support within a specific time frame (145, 146).

Besides the fact that low levels of perceived support may lead to a more unfavorable course of the disease, it is also plausible that a persons' mood symptoms might affect the available support or the way support is perceived (147).

For example, people with depressed symptoms also tend to generate more strain in their relationships and thereby weaken their social support system (49, 110). To our knowledge, only Eidelman et al. (148) investigated bidirectional effects of social interactions in a bipolar sample over two time points with a relative short follow-up time (28-days). They found that both manic and depressed symptoms were related to more subsequent social strain. No evidence was found for associations in the opposite direction (social strain predicting mood changes), nor for associations between social support and mood symptoms.

In sum, there might be specific and bidirectional associations between perceived and enacted social support and the bipolar mood course, although this has not been studied in BD samples specifically. In order to improve the effectiveness of psychosocial interventions for bipolar patients, a better understanding is needed of the associations between social support and mood and potential differential effects of perceived and enacted support. The current prospective study is thus the first to investigate the lagged effects of social support (perceived as well as enacted) on mood state and vice versa in a large sample of patients with bipolar disorder.

4.2 Method

4.2.1 Participants

This is a 2-year prospective study among 173 bipolar I and II outpatients of the Outpatient Clinic for Mood Disorders in The Hague (The Netherlands). All patients were treated in accordance to the contemporary guidelines for bipolar disorder. Patients were invited to participate in the study either by letter or by their treating physician. After written informed consent was obtained, 173 patients were willing to participate and enrolled into the study and completed at least 2 consecutive waves. Participants were older than 18 years and exclusion criteria in this study were schizo-affective disorder, neurological disease and substance abuse disorders.

Diagnoses of BD were based on DSM-IV criteria and were assessed by trained research assistants, with a standardized diagnostic interview (119) using the

Dutch version of the MINI International Neuropsychiatric Interview Plus (version 5.00-R; MINI-PLUS). DSM-IV axis II comorbidity was not assessed. The Questionnaire for Bipolar Illness, Dutch translation (23, 121) was used to specify subtypes of BD and detailed information about disease characteristics (e.g. age of onset, number of previous episodes).

Figure 4.1 shows the flow-chart of the participation rate of the patients at the different time points. In total there were 1146 data points with complete data during 24 months of follow-up. Of the total sample, 83.8% of the patients (N=145) completed at least 1 year follow-up, with a cumulative number of 50 (28,9%) patients dropping out before the end of the study. There were no significant differences in baseline demographic and clinical characteristics between the group who participated until the end of the study (N=123) and the group that dropped out during the study (N=50). Moreover, during the study no differences in course severity were found among these two groups, and the number of hospital admissions was the same in both completers and dropouts, during the study as well as in the first 3 months after dropping out (based on file study).

4.2.2 Procedure

After completing the baseline assessment, patients had face-to-face contacts with trained research assistants at 3-, 6-, 9-, 12-, 15-, 18-, 21-, and 24- months follow-up. During these contacts, mood based functional impairment (Life Chart), medication use and social support were assessed (see Figure 4.1). The study protocol was approved by the local Ethical Committee, and was carried out in accordance with the Declaration of Helsinki.

4.2.3 Social Support List

The Social Support List (SSL) (149) was used to assess social support every 3-months during the 2 year study. The SSL is a commonly used scale (150-152) to assess different domains of social support. The test-retest reliability and convergent validity yield satisfactory indexes (149, 153). This 41-item list is developed in the Netherlands and distinguishes three separate dimensions: Enacted social support, perceived social support and negative interactions.

The negative interactions dimension is beyond the scope of the current study and therefore not included.

(i) Enacted social support

This subscale reflects the enacted amount of supportive interactions a person experiences. This part of the questionnaire starts with the question 'Does it ever happens that someone….', followed by 34 statements such as: 'calls you for a chat', 'visits you', 'cheers you up', 'asks you for help', etc. These items have a 4-point Likert scale: (1) 'rarely/never', (2) 'sometimes', (3) 'often', (4) 'very often'. The total score on this subscale ranges from 34 through 136 with higher scores reflecting more enacted social support. The Cronbach's alpha in the current sample of this enacted social support subscale was .83.

(ii) Perceived social support

This subscale reflects the discrepancy between the above mentioned amount of enacted social support interactions and the desired amount of social support. It contains the same 34 items that are stated in the enacted social support subscale, but with different response categories: (1) I miss it; (2) I don't really miss it, but I prefer more; (3) exactly the right amount; (4) it happens too often. The items scores of this domain as described in the manual of the SSL (149) (recoded as: 1=3, 2=2; 3=0) are summed, in order to create a score that reflects the perceived social support. The category 'it happens too often' was not included, since this reflects over involvement instead of support. The total scores on this domain ranges from 0 to 102, but were subsequently inverted in order to let higher scores reflect more perceived social support. Cronbach's alpha of this subscale in the current sample was .98.

4.2.4 Symptoms severity, functional impairment and medication use

Illness severity was assessed both in terms of symptoms severity and the functional impact of the mood disturbances. In order to assess mood severity based on number and severity of symptoms the Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR) (123) and the observer based Young Mania Rating Scale (YMRS) (60) were administered every 6 months. Both the QIDS and the YMRS have good (inter-) reliability and validity (60, 123). The functional impact of mood disturbance was assessed by the NIMH

monthly retrospective life chart method (LCM-r) (21, 124). This tool was used at every session, up to eight assessment sessions, to measure medication use and monthly functional impairment arising from manic or depressed symptoms of the previous 3 months. LCM-r rating distinguishes four levels of severity for both mania and depression: mild, moderately low, moderately high, and severe (85). Based on the LCM-r data, mean severity of functional impairment of depression and mania of every three-month period was calculated by averaging the monthly severity scores. A similar method has been used in previous studies (62, 67).

Medication use over the 24-months was assessed at all 8 time points with the life chart. Medication use was categorized into 5 dichotomous (use/no use) variables and included the categories lithium, anti-epileptics, antipsychotic medication, benzodiazepines, and antidepressants.

4.2.5 Statistical analyses

All analyses were performed using IBM SPSS for Windows (version 21.0; SPSS, Inc. Armonk, NY). Since we perform multiple tests, we considered results as significant findings when p-values were below .01.

Fluctuation of social support over time was estimated, using intra-class correlation analyses (ICC) for absolute agreement with a two-way random effect model for single measures.

Because of nested data (repeated measurements within an individual) and attrition resulting in missing data, multilevel regression analyses (linear mixed-models) were used to analyze the longitudinal associations between social support and mood state. A compound symmetry covariance structure was used consisting of the time points (i.e. lower level) and the patients (i.e. higher level). Mood scores on the QIDS, YMRS and life chart were right-skewed and therefore log-transformed before the analyses. Baseline associations between sociodemographic variables and social support were analyzed using univariate regression analyses.

The directions of the prospective associations tested by the mixed model analyses are depicted by the arrows in Figure 4.1. In order to investigate both temporal associations multilevel analyses were employed as follows:

1. Social support variables of the last three months were the predictor variables and mood/functional impairment assessed at the subsequent time point were the outcome variables (see blue arrows [1] in Figure 4.1). Associations were first assessed in a crude model (adjusting for time and mood state and functional impairment at the predictor time point) and subsequently additionally adjusted in a second model (adjusting for age, sex, level of education, and medication use (using 5 dichotomous variables, measured at 8 time points)).

2. The opposite temporal direction was assessed with mood state and functional impairment as predictor variables and subsequent reported social support variables as outcome variables (red arrows [2] in Figure 4.1). In the crude model, we adjusted for social support at the predictor time point, and in the adjusted model we additionally adjusted for age, sex, level of education, and medication use.

For all analyses we adjusted for the outcome variable at the predictor time point in order to adjust for the cross-sectional correlation between mood and social support and to prevent actually measuring an association between mood and subsequent mood or social support and subsequent social support.

The same method has been used before by our own group (140) and in other studies (154) for investigating bidirectional associations in a longitudinal sample with a within-subject repeated measures design. Moreover, a multilevel approach is suggested to be a suitable method to analyze complex reciprocal associations in prospective studies (155, 156).

4.3 Results

4.3.1 Demographics and clinical characteristics

Basic demographic and clinical characteristics of all patients who participated in at least one follow-up measurement (N=173) are summarized in Table 4.1. The included subjects had a mean age of 49.9 (SD=11.4) years and were predominantly female (58%). Overall, mean score on the QIDS at study

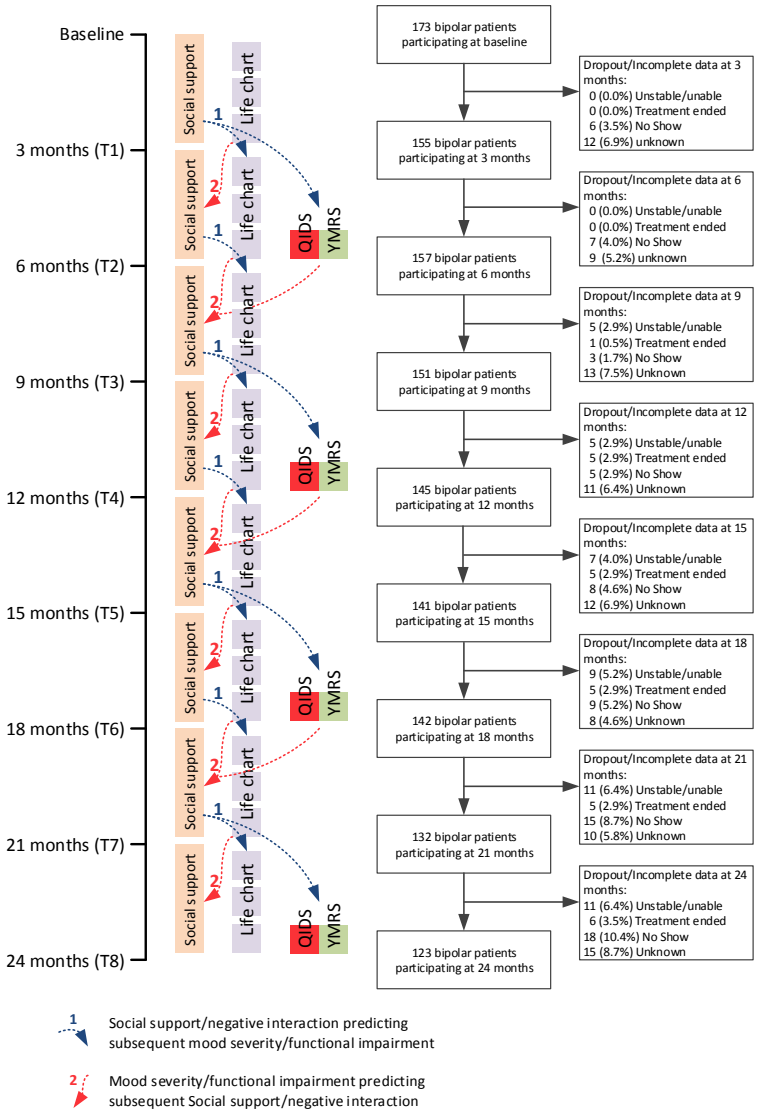

Figure 4.1 | Flow chart of follow-up measurements, direction of associations and drop-out rates/incomplete data.

entry was 7.5 (SD=4.9). During follow up QIDS mean scores varied between 6.5 and 7.5 (SD varied between 4.7 and 5.2) indicating overall mild depressive symptoms. Mean YMRS score at baseline was 1.7 (SD=3.1). During follow YMRS mean scores varied between 1.5 and 2.5 (SD varied between 3.7 and 5.0) indicating overall subclinical or low severity of mania symptoms. During the two year prospective study, patients reported life chart functional impairments due to depressed mood in 32.7% of the time points, and manic mood in 12.2% of the time points, whereas they reported a stable mood in 57.1% of the time points.

The associations between the variables in Table 4.1 and the social support variables were analyzed using regression analyses (data not shown). Older age was significantly associated with less enacted social support ($p<.001$). None of the other demographic and disease characteristics shown in Table 4.1 were significantly associated with any of the social support variables at baseline.

4.3.2 Social support variables over time

Means of reported perceived and enacted social support at baseline are presented in Table 4.1. Fluctuation of social support over time was estimated. ICCs of perceived social support between different time points varied between 0.67 and 0.85, for enacted social support ICCs varied between .57 and .82. The overall mean ICC (for 127 patients with complete data on all time points) for enacted social support is .73 and for perceived social support .77. This indicates moderate to high stability over time for both enacted and perceived social support over two years.

Subsequently, correlations between enacted and perceived support were investigated. Correlation between the two support constructs varied from .287 to .454 over the 8 time points. This indicates that enacted and perceived support were only weakly correlated in the current sample.

Baseline	
Male sex; n(%)	73 (42.2)
Mean age; mean (SD)	49.9 (11.4)
Level of education; N (%):	
- primary (ref.)	39 (22.5)
- secondary	50 (28.9)
- higher	82 (47.4)
Clinical characteristics:	
Diagnostic information; N(%)	
BD1	121 (69.9)
Age of onset; mean (SD)	
Age of onset first (hypo-) mania	30.8 (10.1)
Age of onset first depression	27.6 (10.1)
Number of episodes; median (IQR)	
No. of manic episodes	5 (8)
No. of depressive episodes	6 (16)
QIDS baseline; mean(SD)	7.5 (4.9)
YMRS baseline; mean (SD)	1.7 (3.1)
Medication use; N(%)	
Lithium	119 (68.8)
Anti-epileptics	36 (20.8)
Anti-psychotics	42 (24.3)
Benzodiazepines	42 (24.3)
Antidepressants	56 (32.4)
Social support baseline; mean (SD)	
Enacted social support	70.4 (12.9)
Perceived social support	- 28.1 (25.3)

Table 4.1 | Baseline characteristics of 173 bipolar patients.

4.3.3 Association between enacted and perceived social support and subsequent mood/functional impairment

Results from the mixed model analyses on the association between perceived and enacted social support and subsequent functional impairment and mood symptoms, adjusted for mood symptoms/functional impairment at the predictor time point. Direction of these associations are also depicted by arrows [1] in Figure 4.1 and results are summarized in Table 4.2 and Figure 4.2. Results show that lower perceived support was associated with more depression

related functional impairment on the LCM during the subsequent 3 months (β=-.16, p=<.001). Similarly, lower perceived social support was associated with more depressive symptomatology at the subsequent time point (β=-.14, p=.001). After additionally adjusting for demographic variables and medication use (model 2) results remained significant. Enacted social support in the last three months was not significantly associated with subsequent depressed mood symptoms or functional impairment. Further, no significant associations between (enacted and perceived) social support and manic symptoms and impairment were observed.

Analyses were also performed for BD I and II groups separately, but no differences in associations were observed (data not shown).

	Life Chart Depression		QIDS		Life Chart Mania		YMRS	
	Beta (SE)	P-value	Beta (SE)	P-value	Beta (SE)	P-value	Beta (SE)	P-value
Model 1 Enacted SS	-.05 (.04)	.178	-.06 (.04)	.114	.03 (.03)	.397	.08 (.05)	.112
Model 2 Enacted SS	-.06 (.04)	.105	-.09 (.04)	.044	.02 (.04)	.657	.07 (.06)	.225
Model 1 Perceived lack SS	-.16 (.04)	<.001*	-.14 (.04)	.001*	-.05 (.04)	.156	.03 (.05)	.539
Model 2 Perceived lack SS	-.14 (.03)	<.001*	-.14 (.04)	.002*	-.06 (.04)	.112	.04 (.05)	.490

Model 1: adjusted for time and mood using multilevel regression analysis (i.e. mixed models).
Model 2: additionally adjusted for gender, age, level of education, and medication use (antipsychotic, antidepressants, benzodiazepines, lithium, and anticonvulsive agents) using multilevel regression analysis (i.e. mixed models).
* p-value < .05

Table 4.2 | Association between enacted and perceived social support and subsequent mood symptoms/functional impairment.

4.3.4 Association between mood symptoms/functional impairment and social support in the subsequent 3 months

Subsequently we investigated the opposite temporal association, that is the association between mood state/functional impairment and subsequent social support in the following 3 months, adjusted for social support at the predictor time point. Direction of these associations are also depicted by arrows [2] in Figure 4.1. Table 4.3 summarizes the results of the mixed model analyses of these associations. Patients with more depression related functional impairment reported less perceived social support in the subsequent

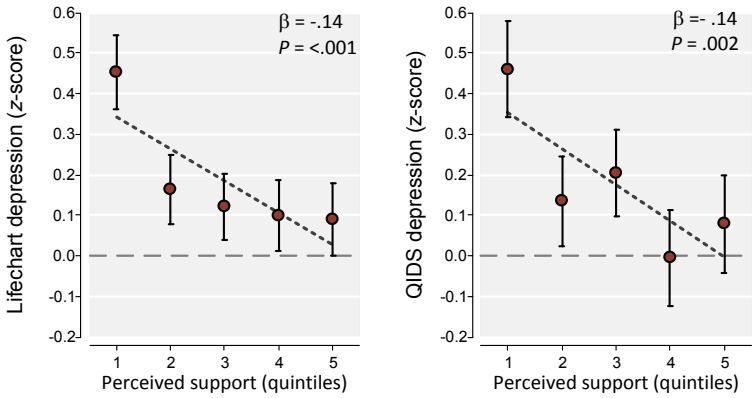

Figure 4.2 | Plots of the association between perceived social support and the standardized scores of mood severity and functional impairment (QIDS/YMRS/Life Chart). Vertical lines indicate standard errors. Data are adjusted means by linear mixed models.

three months (β=-.04, p=.002), while enacted social support was not significantly affected (β=-.04, p=.227). Finally more manic symptoms were related to less enacted social support in the subsequent months (β=-.09, p=.006).

Analyses were also performed for BD I and II groups separately, but no differences in associations were observed (data not shown).

4.4 Discussion

Our findings show that lower amounts of *perceived* support subsequently increase depressive symptoms and impairment. In turn, depression related impairment precede a decrease in the perception of social support, while manic symptoms lead to a decrease in enacted social support. These associations suggest that bipolar mood symptoms and social support reciprocally reinforce each other. Further, especially *perceived* support seems to be associated with the depressive mood course while *enacted* support appears to be of minor importance in terms of predicting subsequent mood changes. Further, in accordance with previous meta-analytic findings (157) we found that perceived and enacted support were only weakly correlated. Although described before, this is still an important finding that demonstrates that the

	Enacted SS		Perceived SS	
	Beta (SE)	P-value	Beta (SE)	P-value
Life Chart Depression				
Model 1	-.01(.02)	.806	-.04 (.01)	.002*
Model 2	-.03 (.02)	.227	-.05 (.02)	.005*
QIDS				
Model 1	-.04 (.03)	.195	-.01 (.03)	.890
Model 2	-.04 (.03)	.221	-.01 (.03)	.719
Life Chart Mania				
Model 1	-.02 (.02)	.179	-.01 (.01)	.721
Model 2	-.04 (.02)	.207	-.01 (.01)	.885
YMRS				
Model 1	-.08 (.03)	.014*	-.01 (.03)	.616
Model 2	-.09 (.03)	.006*	-.03 (.03)	.328

Model 1: adjusted for time and social support using multilevel regression analysis (i.e. mixed models).

Model 2: additionally adjusted for gender, age, level of education, and medication use (antipsychotic, antidepressants, benzodiazepines, lithium, and anticonvulsive agents) using multilevel regression analysis (i.e. mixed models).

* p-value < . 05

Table 4.3 | Association between mood symptoms/functional impairment and subsequent enacted and perceived social support.

two variables should be considered differential constructs of social support.

4.4.1 Perceived social support and the bipolar mood course

Although a specific association of perceived support with subsequent health outcome has been consistently reported within other study populations (e.g. cardiac patients, depressed patients, schizophrenia patients, first responders) (143, 158-161) the current study is the first to show that this also applies to bipolar patients. The underlying mechanisms that account for the specific role of perceived support are not entirely clear. Obviously, the subjective experience that support is sufficiently available appears to be more important than the enacted amount of supportive interactions one experiences (144, 160). The assumption that subjective experiences and beliefs are more important in psychological well-being than the objective situation is widespread in the field of cognitive behavioral therapy (162, 163). It is likely that comparable mechanisms account for the importance of perceived support over enacted support. Further, we found that low levels of perceived support not

only preceded increases in depressive symptoms and impairment, but also the opposite association was found in which increases in depressive impairment in the previous months led to reports of lower perceived support in the following months. However, these associations were less consistent (no association with depressive symptoms, only with impairment) and less strong than association of the opposite direction. Still, these findings indicate that low perceptions of support put bipolar patients at risk for subsequent depressive symptoms, but that previous depressed symptoms also erode perceptions of support. That mood state affects the way people perceive the intensity and quality of social interactions is a known phenomenon (147). Another explanation for the bidirectional associations between mood and support might be that low perceived social support and depressive symptoms share the same underlying trait, that accounts for both increases in depressive symptoms and decreases in perceived support (e.g. personality, attachment style). Altogether, the current findings underline the significant role of perceived support in the bipolar mood course, and the complexity of the association of perceived support and mood.

4.4.2 Specific association for mania and depression

Results show that there is a bidirectional association between perceived support and depressed symptoms, but no association with manic symptoms. The polarity specific association between perceived support and depression in BD has been found in previous studies (33, 164, 165). An explanation for the bidirectional associations between perceived support and depressed symptomatology specifically might be found in the fact that low perceived support is linked to negative early life experiences, dysfunctional personality traits and low self-esteem (145). All these factors are especially associated with an increased risk of depression (166, 167). Besides, depressive mood states may also result in polarized thinking, catastrophizing, blaming and mislabelling, which may alter support perception. In line with this, Johnson et al. (168) demonstrated that self-esteem is an important moderating variable between low support and subsequent depressive symptoms in BD patients.

Further, we found that manic symptoms (but not manic impairment) in the

previous months were specifically associated with decreases in enacted support in the subsequent months. The previously mentioned study by Eidelman (148) already revealed that manic symptomatology is associated with more subsequent interpersonal strain. It is plausible that the often disturbing manic behaviour leads to more interpersonal conflict and therefore to a decrease in enacted support of significant others. Furthermore, manic symptomatology and impairment were not at all associated with perceptions of support in the current study, implying that low perceptions of support are exclusively related to depressive symptomatology.

4.4.3 Clinical implications

The currently revealed role of perceived support implicates that it might be an important target for psychosocial interventions in BD. This is supported by a recent study among unipolar depressed and anxious patients (169), that found that perceived support had a mediating role in symptom change after treatment interventions. In the current psychotherapeutic interventions that focus on the social network of patients, perceptions of support are not a central theme. Both the Interpersonal Social Rhythm Therapy (IPSRT) and Family Focussed Therapy (FFT) attempt to diminish interpersonal problems and increase support. However, improving perceived support is not accomplished by increasing the amount of enacted support (144). The perception of social support heavily depends on psychological factors such as personality, attachment styles, and the perceptions of others (170-172). In this light, interventions that aim to correct cognitive biases or dysfunctional schemata may be effective in altering support perceptions (173, 174). This means that (techniques from) psychotherapies such as cognitive behavioural therapy or schema therapy might be useful to change support perceptions and possibly decrease depressive symptomatology. Future interventions studies should shed more light on the exact importance of perceived support as a target for psychotherapeutic interventions in BD.

Furthermore, the reduction of enacted support after the occurrence of manic symptoms might very well be a result of the often detrimental effects that manic behavior can have on the environment. Psychoeducation programmes that inform significant others about the manic state might increase under-

standing and lead to the realization that the manic person cannot be (fully) blamed for the displayed behavior. Further, when severely disturbed, FFT might be useful to restore these relationships.

4.4.4 Strengths and limitations

Some strengths and limitations of the current study are worthy of note. This study is one of the first to repeatedly measure social support in a large sample of BD patients. This study was also novel in investigating both temporal directions between social support and mood symptoms in the same sample, and in distinguishing between perceived and enacted support. The large sample size and repeated measurements led to a higher precision of the effects estimates. Further, current findings rely on rather rigorous statistical analyses, in which we consistently adjusted the outcome variable for the predictor time-point in order to accurately measure changes within the time frames of 3 to 6 months.

There are also several limitations that need to be discussed. First, although the use of self-report inventories in social support research is appropriate for the assessment of perceived support, for the assessment of enacted social support a method that more objectively assesses enacted support (e.g. prospective scoring of supportive interactions) might be more appropriate. Second, the results can only be generalized to relatively stable patients or patients with subclinical symptoms, as the number of time points that patients were severely depressed or manic was very low. As a result, the strength of the presented associations may underestimate those for patients with more severe psychopathology, especially for those with more severe manic symptomatology. Third, although 3-months measurements are rather frequent in prospective bipolar studies, this frequency does not allow for the detection of subtle mood changes or of every minor episode. Fourth, personality traits and/or disorders were not assessed in the current study, whereas these are important factors in both the recurrence of depressive symptoms (175) and in the perceptions of support (176). Finally, no data was collected on psychosocial interventions during the course of the study, while this is likely to be a factor that accounts for changes over time in both mood and social support.

4.4.5 Conclusions

The current findings reveal that low perceived quality of support might have stronger negative effects on the bipolar mood course than lower amounts of *enacted* support. Further, perceived support is especially related to depressive symptoms in a bidirectional way, while mania is specifically associated with a subsequent loss of enacted support. This indicate that social support variables and bipolar mood are strongly intertwined, indicating a vicious circle in which cause and effect are difficult to disentangle. Still, the current findings suggest that perceived support might be an additional target within the existing psychosocial and psychotherapeutic interventions for patients with a bipolar disorder.

CHAPTER 5

Effects of mood state on divided attention in patients with bipolar disorder: evidence for beneficial effects of subclinical manic symptoms

Koenders MA, Spijker AT, Hoencamp E, Haffmans PM, Zitman FG, Giltay EJ (2014). Effects of mood state on divided attention in patients with bipolar disorder: evidence for beneficial effects of subclinical manic symptoms. Psychiatry Research; 220: 302-308.

Abstract

A relative small number of studies have been dedicated to the differential effects of the current mood state on cognition in patients with a bipolar disorder (BD). The aim of the current study was to investigate the effect of current mood state on divided attention (DA) performance, and specifically examine possible beneficial effects of the (hypo-) manic state. Over a maximum period of 24 months, medication use, divided attention test (a subtest of the Test for Attentional Performance (TAP)) was assessed every 6 months in 189 outpatients with BD. Data were analyzed with multilevel regression analysis (i.e. linear mixed models).

DA performance varied considerable over time within patients. Corrected for psychotropic medication a significant quadratic relationship between manic symptoms and DA performance was found, with mild hypomanic symptoms having a positive influence on divided attention scores and moderate to severe manic symptoms having a negative influence. No association between depressive symptoms and DA performance was found. In future research on mania and cognition as well as in the clinical practice both the beneficial and negative effects of mania should be taken into account.

5.1 Introduction

Bipolar disorder (BD) is an 'episodic illness' which is characterized by alternating episodes of depression and (hypo-) mania. Besides the recurrent mood disturbances numerous studies indicate that patients with bipolar disorder suffer from cognitive impairments (177-180). Attention problems, slowing of processing speed, and deficits in visual and working memory and executive functioning appear to be most consistently observed (36). A growing number of studies found evidence that cognitive impairments persevere in the euthymic state (37-39), giving rise to the ideas that cognitive impairments may represent a trait or an endophenotype of the disorder (40). However, it is also widely suggested that cognitive performance is affected by bipolar mood symptoms. Nevertheless, studies investigating this association are rather scarce and limited by cross-sectional designs and small sample sizes. We are aware of only two longitudinal studies on the effects of bipolar mood on cognition, performed by Malhi et al. (41) and Arts et al. (42). Mahli et al. investigated 25 bipolar I patients for a maximum of 30 months and found that compared to the euthymic state of the patients, verbal memory was more impaired during the depressive state. No significant effect of manic state (mean YMRS score > 10) on cognition was found after adjusting for confounders, but a manic state only occurred in 12 patients. Arts et al. (42) included a total of 76 bipolar I and II patients, who were neuropsychologically assessed every two months, for a period of 2 years. In this study cognitive functioning varied substantially over time and depressed mood had a negative impact on performance in several cognitive domains but no relation was found with mania.

It is rather remarkable that in the above described longitudinal studies no distinct association was found between (hypo) manic symptoms and cognitive performance, while a number of cross- sectional neuropsychological studies found cognitive impairment in (hypo) manic BD patients (181-183). The fact that longitudinal studies failed to find this association may be due to a) a lack of power because of the small number of currently (hypo)manic patients (41), or b) the occurrence of only subclinical or mild hypomanic symptoms, as seen in the study of Arts et al. (42) in which mean Young Mania Rating

Scale (YMRS) (60) scores were 1.6 during cognitive assessment. In contrast, the cross sectional studies (181-183) were able to examine cognitive functioning during mild to severe manic episodes (YMRS mean scores ranging from 18.2 to 23.6). Or c) that non-linear models better model the relationship between manic symptoms and cognitive functioning, as suggested by the findings of Kravariti et al. (43). In their cross-sectional study they found a non-linear association between mild manic symptoms and executive control and processing speed among 31 BD patients with mild manic symptoms. These results indicate that mild levels of mania are related to better cognitive functioning compared to moderate levels. This is in line with findings suggesting that low levels of manic symptoms are related to reports of mental alertness, goal directed activity, increased self-confidence and increased self-efficacy in non-clinical samples (44, 45). Further, creativity is known to be associated with hypomanic traits or hyperthymia (184), and hypomania (185), underlining the possibility of increased or special performance levels during hypomania. Recent studies found that adolescents developing BD premorbidly have already normal or even better than average cognitive abilities regarding intelligence quotient (IQ) and reading abilities compared to healthy controls (186, 187). It is widely suggested (188), but poorly investigated, that among talented people, BD is a well-known phenomenon. This suggests that manic symptoms may both enhance and worsen performance.

Another complicating factor in studying cognitive performance in patients with a bipolar disorder is the impact of medication use. There are indications that especially antipsychotics (189, 190), benzodiazepines (191), antidepressants (192), and the use of multiple types of medication (polypharmacy) (193) have a negative effect on cognition. The majority of the before mentioned studies failed to adjust for potential confounding by medication. However, separating the effects of mood fluctuation and (fluctuations in) medication use on cognitive performance in patients of whom almost all use some kind of psychotropic drug is a challenge.

In this current longitudinal study, we aimed to investigate the natural variability of divided attention (DA) performance in outpatients with bipolar disorder. In addition, we examined the association between mood state, including euthymia, depressive and (hypo)manic mood, with objectively as-

sessed DA performance adjusted for medication use.

There are several reasons studying DA in BD patients. First, DA is an essential component of everyday living (194) and is thought to be crucial for the ability to drive in traffic (195), to establish and maintain joint attention and to avoid confusion when confronted with unfamiliar situations. Second, with respect to bipolar and unipolar depression was found that the divided attention performance predicted response to treatment, remission of symptoms, and risk of relapse in depressed patients (196). Furthermore in longitudinal studies both impairments in executive functioning (197, 198) and attention (42) has been pointed out as possible endophenotypes of BD. Functional imaging research indicates that attending to both visual and auditory stimuli requires a recruitment of the frontal lobe (199). This means that the task involves besides attentional also executive processes. Deficits in these two domains are both frequently associated with BD (200). As part of executive function as well as attention, therefore, divided attention can be considered as a sensitive marker in mood disorders.

In the current study, we hypothesized that DA performance will be variable over time within patients, depending partly on the current fluctuating mood states, with increases of manic and depressive symptoms being associated with a decline in cognitive performance. Since low levels of manic symptoms could be associated with better performance, we also assessed potential non-linear relationships between level of manic symptoms and cognitive performance.

5.2 Methods

5.2.1 Study design

This is a 2-year prospective follow-up study among 189 bipolar outpatients with a diagnosis of BD I or BD II (also including BD not otherwise specified and cyclothymia) according DSM-IV-TR diagnostic criteria. All participants were older than 18 years. They were all treated in the Program for Mood Disorders at PsyQ in The Hague, The Netherlands. Exclusion criteria in this study were schizo-affective disorder, neurological disease and

substance abuse disorders. All participants gave full informed consent and this study was approved by the Medical Ethical Committee (METTIG) in Utrecht, The Netherlands, and was carried out in accordance with the declaration of Helsinki.

Diagnoses of BD and psychiatric co-morbidities were based on DSM-IV criteria and were assessed with a standardized diagnostic interview developed by Sheenan et al. (119) using the Dutch version of the MINI International Neuropsychiatric Interview Plus (version 5.00-R; MINI-PLUS) (120). The Questionnaire for Bipolar Illness, Dutch translation (23, 121) was used to specify subtypes of BD, its course over time and detailed information about age of onset of first symptoms regarding hypomanic, manic, and depressive episodes.

Of the total sample 90.2% of the patients (N=156) completed at least 1 year follow-up, eventually a cumulative number of 62 (32.8%) patients dropped out before the end of the study. The most common reasons for patients to quit prematurely were: being too unstable, being hospitalized, deeming the research too burdensome, discontinuing treatment at our outpatient clinic, and not showing up at an appointment more than 2 times. Patients missing more than one measurement were excluded from the current study. Figure 5.1 shows the number of patients who dropped out at the different time points. Between the group that participated until the end of the study (n=127) and the group that dropped out during the study (n=62) no significant differences in the demographic and clinical characteristics were found.

5.2.2 Assessment

After completing the baseline assessment, patients had face-to-face contacts with trained research assistants at 3-, 6-, 9-, 12-, 15-, 18-, 21-, and 24- months follow-up. During these contacts, mood based functional impairment (Life Chart), medication use and social support were assessed (see Figure 5.1). The study protocol was approved by the local Ethical Committee, and was carried out in accordance with the Declaration of Helsinki.

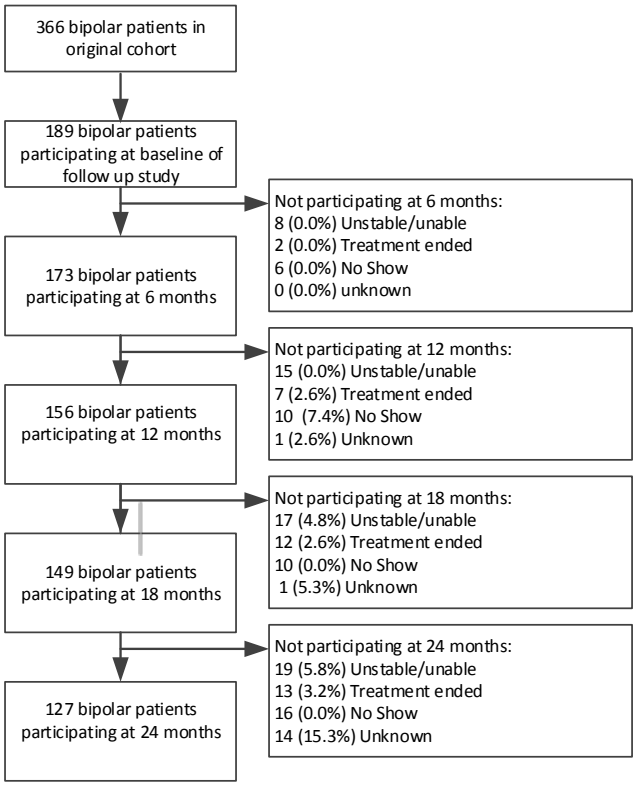

Figure 5.1 | Flow chart of cohort of bipolar patients during the study.

Divided attention test

Divided attention performance in this study was assessed by means of the TAP (Test for Attentional Performance, version 2.1) (201). The TAP is a widely used computer-based standardized test battery and easy to use in clinical practice (192, 202, 203). At baseline a total of 8 subtests of the TAP were assessed, including the divided attention (DA) subtest. During the follow-up only the DA test of the TAP was repeatedly assessed, and this test will be the focus of this study. The divided attention TAP subtest is a crossmodal task, with both visual and auditory input. During the task a visual and an auditory task must be processed in parallel. Four different visual stimuli are separately presented on the screen of which 2 are the target stimuli to which

the patient has to react by pressing a key. At the same time the patient hears high and low pitched tones alternately. When the high or low pitched tones emitted twice in succession the patient has to respond by pressing the key. Errors and omissions are the most important indicators for performance. To create a score for total performance, both errors and omissions are combined in one score. First, both variables were log-transformed because of their right-skewness. The log-transformed omission and error scores were then standardized as z-scores. Subsequently, the mean of those two z-scores was calculated, representing the overall performance on the divided attention test. This procedure resulted in one z-index-score for divided performance for every of the up to 5 waves, with a higher score indicating better performance

Assessment of mood states, clinical characteristics and medication use

All 189 patients who participated in the neurocognitive assessment at the baseline, were invited every 6 months for follow-up assessment during 24 months, at which divided attention was assessed, resulting in up to 5 time points. In those 6-monthly assessments, the current mood states were assessed using the self-report list: the Quick Inventory of Depressive Symptomatology - Self Report (QIDS-SR) (http://www.ids-qids.org) and the observer based Young Mania Rating Scale (YMRS) (60). Mean QIDS scores can be interpreted as follows: no (0-5) or mild (6-10) depressive symptoms; QIDS scores >16 indicate severe or very severe (>20) depressive symptoms. For YMRS scores no formal classification of severity have been published, but could be interpretation as follows: scores <8 indicate no clinically significant symptoms; light symptoms of mania scores between 8-14; moderate and severe scores are respectively 14-24 and >24 (204, 205). Medication use over time was also monitored. Detailed information on current use of psychotropic medication was assessed at every 6-month wave, and coded according to the Anatomical Therapeutic Chemical Classification System (http://www.whocc.no/). Medication use was further dichotomized (1 = any use of the particular psychotropic medication; 0 = non-user) for lithium (ATC code: N05AN01), other mood stabilizers (i.e., anti-epileptics, ATC code: N03AF01, N03AG01, N03AX09), antipsychotic medication (ATC code:

N05Ax with exclusion of N05AN01), benzodiazepines (ATC codes: N05BA, N05CD, N03AE01, N05CF), and antidepressants (N06A). As lithium was regarded as drug of first choice, it was coded separately. At baseline sociodemographic and illness related data, like age, sex, illness subtype, substance use, age at onset and level of education, were collected with the Mini International Neuropsychiatric Interview (MINI, Dutch translation) (206) and the Questionnaire for Bipolar Illness (QBP) (207, 208).

5.2.3 Statistical analysis

Sociodemographic and baseline characteristics were summarized as means (standard deviation [SD]) for continuous variable and as numbers (proportions) for categorical variables. To estimate the potential variability of DA performance within patients over the two-year period, we used intra-class correlation analyses (ICC) for absolute agreement with a two way random effect model for single measures. These analyses were performed on unstructured DA data, that is, for errors and omission data separately.

Because the up to 5 waves (i.e. baseline through 24 months) were dependent (repeated measurements within an individual) and missings occurred because of dropouts, multilevel regression analysis (i.e. linear mixed models) with a compound symmetry covariance matrix was used to investigate the cross-sectional associations of mood states with TAP results. Associations were first assessed in a crude model. Subsequently, we repeated the multilevel regression analyses adjusting first for age, sex, and level of education (Model 1). In Model 2, we additionally adjusted for variables that previously have been associated with cognitive disturbances: substance abuse (209) (smoking, alcohol use, drug abuse), BD diagnosis (210) , and medication use (192, 211, 212) (using 5 dichotomous groups).

A history of psychosis in BD patients is associated with worse cognitive performance (213), and in the current study data on history of psychosis was collected as well. However, since psychosis didn't appeared to be associated with DA performance during follow up (beta=.06, P=.496) this covariate was not included in the multivariate model.

Next, to test whether the association had the shape of a curve instead of

a straight line, a quadratic term of the QIDS and YMRS scales was added as predictor variable. Data are presented as standardized beta coefficients. All tests were two-tailed with $p<0.05$ denoting statistically significance. The software used was SPSS version 17.0 (SPSS Inc., Chicago, Ill).

5.3 Results

Table 5.1 shows the socio-demographic and health characteristics of the 189 participants with complete data for the main outcome variables on at least one time point. In total there were 687 data points with complete data during 24 months of follow-up. The included subjects had a mean age of 49.4 years and were predominantly female (61%). Most participants (79%) had at least secondary education.

Smoking was current for 43%, alcohol use for 64% (with 10% 3 or more units per day) and drug abuse for 7% of all patients. A bipolar I disorder was diagnosed in 73%. Over all 5 time points, mean QIDS scores fluctuated between 6.7 (SD=4.6) to 7.1 (SD=4.8), indicating on average mild depressive symptoms, with 52.7% (n=362) reporting mild to moderate depressive symptoms (QIDS 6-16) and 7.4% (n=51) reporting severe depressive symptoms (QIDS > 16). Mean scores on the YMRS during follow up fluctuated between 1.1 (SD=2.6) to 1.5 (SD=3.9), indicating only mild overall subclinical manic symptoms. During follow up 10.9% (n=75) reported subclinical manic symptoms (YMRS 4-7), 5.8% (n=40) reported mild manic symptoms (YMRS 8-14) and at 2.6% of the time points (n=18) severe manic symptoms (YMRS > 15) were reported; indicating that the majority of the sample having no clinically significant manic symptoms during follow-up (YMRS < 8).

At baseline 108 (57%) patients used 2 or more different psychotropics. Of all patients, 72% of the patients used lithium, during follow-up this percentage varied between 70% and 77%. At baseline 22% used anti-epileptics, in the next 24 months this varied between 12% and 21%. At baseline 35% used antidepressants, 25% used antipsychotics and 25% used benzodiazepines. During follow-up these percentages ranged respectively between 30% and 42% (antidepressants) with a remarkable decrease in the last 6 months; 24%-38% (antipsychotics) with an increasing pattern over 24 months; and 16%-25%

Variable name	N or mean
Male sex – n (%)	74 (39.2%)
Age – mean ± SD (yr)	49.4 ± 11.3
Age – range (yr)	19 – 81
Level of education: – n (%)	
- primary	40 (21.2%)
- secondary	59 (31.2%)
- higher	90 (47.6%)
Current smoker – n (%)	81 (42.9%)
Alcohol use: – n (%)	
- none	69 (36.5%)
- 1-2 units/day	101 (53.4%)
- ≥3 units/day	19 (10.1%)
Drugs abuse – n (%)	13 (6.9%)
Primary diagnosis: – n (%)	
- bipolar I disorder	138 (73.0%)
- bipolar II disorder or NAO	51 (27.0%)
Age of onset – mean ± SD (yr)	26.8 ± 9.8
Medication use: - n(%)	
- lithium	132 (71.7%)
- other mood stabilizer	39 (21.2%)
- antidepressant	64 (34.8%)
- antipsychotic	45 (24.5%)
- benzodiazepine	45 (24.5%)
QIDS – mean (SD)	7.7 ± 5.1
YMRS – mean (SD)	1.8 ± 3.1

Table 5.1 | Baseline sociodemographic characteristics in 189 participants with bipolar disorder.

(benzodiazepines) with a decreasing pattern over 24 months.

Table 5.2 shows the stability of for either errors and omissions of the DA over time for the unstructured data. ICCs between different time points varied between 0.20 and 0.75 indicating low to moderate stability over time. There was no clear pattern that consistency increased in case of shorter time intervals between DA measurements. The overall mean ICC of 0.58 for errors and 0.46 for omissions indicated that there was considerable variability in DA performance within patients over time.

Table 5.3 and Figure 5.2 present the results of the multilevel analyses on the association between mood states and divided attention performance. The results showed no significant association between depressive symptoms and divided attention performance, neither when linear nor when quadratic (non-linear) associations were tested. Yet, visual inspection of the figure seemed to indicate that a threshold existed for depressive symptoms above which divided attention performance was adversely affected.

	6 months		**12 months**		**18 months**		**24 months**	
	ICC (CI)	P-value (N)	ICC (CI)	P-value (N)	ICC (CI)	P-value (N)	ICC (CI)	P-value (N)
DA errors								
Baseline	.20 (0.04-0.35)	.009 146	.44 (0.29-.57)	<0.001 129	.75 (0.66-.82)	<0.001 123	.75 (0.65-0.83)	<0.001 103
6 months			.46 (0.30-0.59)	<0.001 122	.33 (0.16-0.49)	<0.001 113	.43 (0.26-0.58)	<0.001 100
12 months					.34 (0.17-0.50)	<0.001 115	.54 (0.38-0.67)	<0.001 96
18 months							.54 (0.38-.67)	<0.001 93
DA omissions								
Baseline	.43 (0.29-0.55)	<0.001 146	.52 (0.38-0.63)	<0.001 129	.39 (0.22-0.53)	<0.001 123	.36 (0.18-.52)	<0.001 103
6 months			.61 (.48-.71)	<0.001 121	.41 (0.25-0.56)	<0.001 113	.56 (0.41-0.68)	<0.001 100
12 months					.50 (0.35-0.62)	<0.001 115	.50 (0.33-0.64)	<0.001 96
18 months							.49 (0.31-0.63)	<0.001 93

Data (unstructured errors and omission) are intraclass correlation coefficient (ICC) with a two way random effect model for single measures (with 95% confidence intervals between brackets) and p-values. When using all time points for 72 patients with no missing data on any time point, the ICC for errors was 0.58 (95% CI: 0.47-0.68; P<0.001) and the ICC for omissions was 0.46 (95% CI: 0.35-0.58; P<0.001).

Table 5.2 | Stability of divided attention in bipolar patients over up to two years of follow up.

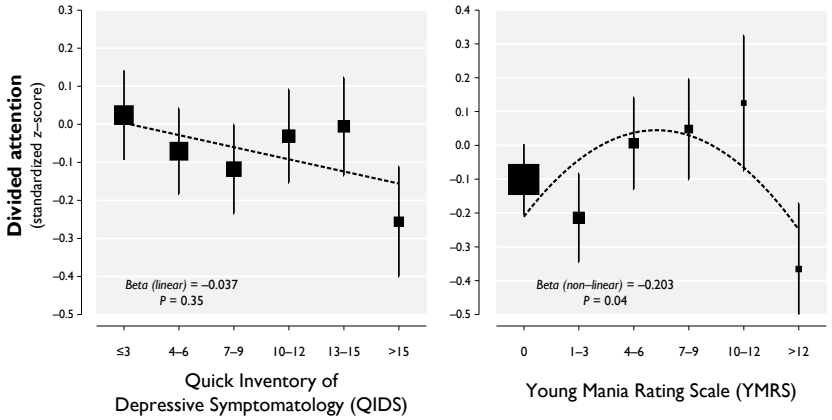

Figure 5.2 | Plots of the association between disease severity scores on the QIDS and YMRS and the standardized score of the divided attention. Categorized QIDS and YMRS scores are depicted on the x-axis to aid interpretability.These values were treated as continuous variables in all statistical analyses. The size of each square is proportional to the number of participants. Vertical lines indicate standard errors. Scores are adjusted for time, sociodemographic factors (gender, age, education), smoking, alcohol use, drug abuse, BD diagnosis, and medication use (5 dichotomous groups) in multilevel regression (i.e., mixed) models.

When dichotomizing patients according to their score on the QIDS, those patients with scores over 15, representing severe depression, had a lower mean divided attention score than those patients with scores of 15 or lower, representing mild or light depression, that approached significance (-0.26 SE 0.14 vs. -0.05 SE 0.10; P=0.07).

Manic symptoms were not linearly associated with divided performance, however a non-significant trend was found, with more manic symptoms leading to better performance on the divided attentions test (Table 5.3). However, the non-linear association appears to be significant, indicating this to be a more suitable model than the linear model (Table 5.3 and Figure 5.2). The non-linear model shows that in the range of YMRS scores between 4-12, reflecting mild manic symptoms, the scores on the DAT were increasing, however, with scores above 12, scores on the DAT were dramatically lower.

Scale	Term	Beta	p-value
QIDS linear:			
Crude	Linear	–0.050	0.21
Model 1	Linear	–0.041	0.29
Model 2	Linear	–0.037	0.35
YMRS linear:			
Crude	Linear	0.008	0.83
Model 1	Linear	0.010	0.78
Model 2	Linear	–0.005	0.90
QIDS nonlinear:			
Crude	Linear	–0.107	0.39
	Quadratic	0.059	0.63
Model 1	Linear	–0.083	0.49
	Quadratic	0.044	0.71
Model 2	Linear	–0.033	0.78
	Quadratic	0.004	0.97
YMRS nonlinear:			
Crude	Linear	0.171	0.047
	Quadratic	–0.213	0.037
Model 1	Linear	0.162	0.056
	Quadratic	–0.199	0.048
Model 2	Linear	0.151	0.077
	Quadratic	–0.203	0.044

Data are beta-coefficients (p value).
Crude: adjusted for time in multilevel regression (i.e., mixed) models.
Model 1: additionally adjusted for sociodemographic factors (gender, age, education).
Model 2: additionally adjusted for smoking, alcohol use, drug abuse, BD diagnosis, and medication use (5 dichotomous groups).

Table 5.3 | Linear and nonlinear associations between disease severity scores and the divided attention (standardized z-scores) in 189 participants with bipolar disorder.

5.4 Discussion

In this study we aimed to elucidate the influence of the current mood state on cognition. In this prospective longitudinal study data were available from a total of 189 patients with bipolar disorder with a total of 687 data points collected every 6 months during 24 months. All results were adjusted for the use of psychotropic medication use. First, we found that divided attention performance was rather variable over time within patients. Our results suggested that fluctuations in current mood state affected divided attention. The most apparent finding was that mild manic scores (between 4-12 on the

YMRS) predicted a better score on the divided attention task, while more severe mania led to significantly poorer divided attention scores. With respect to the association between depressive mood and DA performance, the findings only approached statistical significance levels.

Our study results indicated that very mild manic symptoms may have a positive effect on the cognition function of divided attention, while more severe symptoms may be impairing. This association only became visible when the data were analyzed using non-linear models, which is in line with the findings by Kravariti et al. (43). The existence of this specific association may at least partly explain the failure to find an association between mania and cognition in previous longitudinal studies (41, 42). These findings underline the importance of a non-linear approach of manic symptoms, implicating the need of using different statistic methods. Furthermore, analyzing mood as a continuous or categorized variable, rather than as a dichotomous variable (e.g. depressed/not depressed, manic/not manic), may help to uncover information about the diverging effects of subclinical mood symptoms on cognition.

Second, in our cohort the number of patients scoring >14 on the YMRS was limited. The scores below 14 however, could reflect a non-pathological "hyperthymic mood state" with clinical phenomena like cheerfulness, being overoptimistic, self-assured, eloquent, having high energy levels, highly explorative and low harm avoidance as proposed by Akiskal and Akiskal (214). The authors hypothesized in their review that this temperament could represent the most common phenotypic group with the genetic loading, vulnerability, for bipolar disorder. The development towards a pathological state, bipolar disorder itself, could be the aberrant end of the spectrum (214). In line with this "spectrum" approach, is the recently introduced bipolar spectrum disorder as separate diagnosis (205). Clinically it is relevant to realize that this "hyperthymic mood state" may be an asset in daily functioning for the patient and partner. 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). Besides, slight improvement in cognitive functioning may be an important indicator for the patient to be at risk of becoming (hypo-) manic. Poor divided attention is known to be associated

with diminished performance in more complex daily life tasks, for instance driving a car, which may have serious safety consequences for patients (217, 218) and as a consequence, with respect to medication use a complex trade off exists.

5.4.1 Depressive episodes and divided attention

In our sample, mean QIDS scores were between 6 and 8 during 2 years, indicating no or mild depressive symptoms. Our findings show that in the overall model there was no significant association between depression symptoms and DA performance. However, a borderline significant trend was found with patients with a severe depression (QIDS > 15) performing worse on the DA test compared to patients with a mild depression (QIDS < 15). The non-significant findings are likely due to the relatively low number of patients with higher QIDS scores who participated at any one time point. Our findings are contradictory to previous research, in which depressed mood was consistently associated with cognitive impairments. However, in the recent study by Arts et al. (42) impairments in sustained attention were found to be stable over time, irrespective of mood symptoms.

5.4.2 Strengths and limitations

A strength of this study is the prospective design over a 24 months period with a large cohort of 189 patients in a real life outpatient setting, making it possible to include 687 data points and hence increase the reliability of our findings. Second, we adjusted for psychotropic medication use to take the potential confounding effects into account. Third, we used a different statistical approach to investigate the association between mania and cognitive performance. However, several limitations have to be noted. First, the results can only be applied to relatively stable bipolar outpatients, as the number of time points of severely depressed as well as severely manic patients was low. Dropout may have selectively occurred in the more severe cases leading to withdrawal from the study or admissions, resulting in some selection bias. Second the rating of severity of mania was assessed with the YMRS, of which no strict classification of severity is provided for interpret-

ing the scores. Moreover, interpretation of YMRS scores is further hampered by cultural differences, as scores differ in study locations (219) and interviewers nationality (220). Third, we tested only one cognitive domain. Although divided attention is known as a combination between attention and executive functioning more elaborate cognitive batteries such as the more recently developed cognitive battery of the International Society of Bipolar Disorder (ISBD) (221) may be more appropriate. Fourth, since we did not compare cognitive performance over time with a healthy control group, it is unclear whether divided attention was on average already reduced in euthymic BD patients.

5.4.3 Conclusive remarks

Bipolar disorder is known as a severe mood disorder, characterized by manic or hypomanic as well as depressive episodes. Hypomanic symptoms can put patients at risk for developing severe mood episodes (12). However, hypomanic or hyperthymic states can also include increased creativity driven by executive function, speed of thought and higher alertness. Therefore, increased performance on an executive function task like divided attention has to be seen as subclinical state, indicating the two sides of the disease: severely ill, as well as the possibility of being in a "supranormal" or "hyperthymic" mood state with regard to some of the cognitive abilities. Therefore, in future research both sides of the hypomanic mood state should be taken into account when studying its relation to cognition.

CHAPTER 6

A network approach to bipolar symptomatology in patients with different course types

Koenders MA, de Kleijn R, Giltay EJ, Elzinga BM, Spinhoven P, Spijker AT. A network approach to bipolar symptomatology in patients with different course types. PLoS ONE, 10(10): e0141420.

Abstract

The longitudinal mood course is highly variable among patients with bipolar disorder (BD). One of the strongest predictors of the future disease course is the past disease course, implying that the vulnerability for developing a specific pattern of symptoms is rather consistent over time. We therefore investigated whether BD patients with different longitudinal course types have symptom correlation networks with typical characteristics. To this end we used network analysis, a rather novel approach in the field of psychiatry.

Based on two-year monthly life charts, 125 patients with complete 2 year data were categorized into three groups: i.e., a minimally impaired (n=47), a predominantly depressed (n=42) and a cycling course (n=36). Associations between symptoms were defined as the group-wise Spearman's rank correlation coefficient between each pair of items of the Young Mania Rating Scale (YMRS) and the Quick Inventory of Depressive Symptomatology (QIDS). Weighted symptom networks and centrality measures were compared among the three groups.

The weighted networks significantly differed among the three groups, with manic and depressed symptoms being most strongly interconnected in the cycling group. The symptoms with top centrality that were most interconnected also differed among the course group; central symptoms in the stable group were elevated mood and increased speech, in the depressed group loss of self-esteem and psychomotor slowness, and in the cycling group concentration loss and suicidality.

Symptom networks based on the time points with most severe symptoms of bipolar patients with different longitudinal course types are significantly different. The clinical interpretation of this finding and its implications are discussed.

6.1 Introduction

Bipolar disorder (BD) is a chronic and highly disabling disorder that is characterized by constant risk of recurrence, despite receiving treatment according to contemporary practice guidelines (12, 14). Course patterns seem to differ strongly between BD patients. From the few studies that specifically tried to identify different course types in patient groups receiving treatment, it appears that roughly three course types can be distinguished: 1) predominantly depressed, 2) episodic or cycling pattern, and 3) minimally impaired (28, 67, 222, 223). The current classification of BD into type I and II does not reflect these delicate distinctions in course patterns in sufficient detail (26, 28, 224). The three course types have clinical face validity, and have been associated with specific clinical and prognostic characteristics. For instance, patients with cycling pattern were shown to have more life-time and family history of substance abuse, a worse long term course, and more severe disability (3, 4, 9). A predominant depressive course was associated with more psychiatric comorbidity and a worse treatment response (10-12), whereas the relative stable BD patients were more often those who responded well to (pharmacological) treatment, who suffered less from comorbid disorders, and more often had a history of a 'classic bipolar pattern' of mania followed by depression (13, 14).

However, the prediction of future course patterns remains challenging. Still, the strongest and most consistent predictor for future polarity and severity of the disease course is the previous polarity and severity (12, 29, 56, 57). It is evident that symptomatology, cycling pattern, severity and polarity of episodes strongly differ between BD patients (28, 67), whereas recurrent episodes within a patient may show a highly similar pattern (12, 56, 57). This implies that the vulnerability for developing a specific pattern of symptoms is rather consistent over time. In clinical practice the clinician, patient and his or her loved ones may recognize such warning symptoms already in an early phase, as the symptoms and their patterns are typical for that individual patient. However, it is difficult to get a systematic and statistical grasp of such observations using conventional epidemiological and statistical methods. In a recently developed network approach for psychopathology, emphasis is

put on clusters and patterns of symptoms rather than on overall symptom severity. Some researchers have even suggested that psychiatric disorders can be defined as systems of causally connected symptoms (51, 225). The basic assumption of this theory is that an underlying common (genetic or neurobiological) cause or generic latent variable has not been identified for psychiatric disorders such as BD (226). Within the network approach, the collection of symptoms should be considered to be the disorder itself. This is opposed to most medical conditions in which symptoms are the expression of an underlying disease, such as a tumor or an inflammation in which the medical condition (e.g. the tumor) are directly responsible for its symptoms (e.g., headache, nausea etc.). Following this proposition, Borsboom and colleagues (51) suggested that studying symptom patterns and their complex intercorrelations will lead to more insight and understanding of psychiatric disorders.

Furthermore, using such an approach it is possible to identify those symptoms that are centrally positioned in the network and are more often and more strongly connected to other symptoms. An example of a simple network approach might be found in a BD patient with one night of shortened sleep duration, which results in increased energy and restlessness in patient A, but is strongly connected to loss of energy and feelings of sadness in patient B. Using a network approach within different bipolar course groups, such clinically important differences can be taken into account. The potential value of this approach has already been shown in previous studies. In a study by Cramer et al. (227) different networks were compared based on these network characteristics and it was shown that symptom networks behaved differently in subjects that experienced distinct stressful life events.

In a recent study by Goekoop et al. (52) the authors showed that within an unselected group of psychiatric patients, symptoms of a wide variety of disorders are closely interconnected, with particular groups of symptoms clustering together into 6 distinct psychiatric syndromes: depression, mania, anxiety, psychosis, retardation and behavioral organization. In line with these approaches, the purpose of the current study is to investigate whether BD patients with different longitudinal course patterns display differences in their symptoms networks. We hypothesize that specific symptoms play a

central role in the network and therefore are more strongly connected to other symptoms in the network. These 'central' symptoms function as a 'bridge' between other more peripheral symptoms in the network and might differ across the three different course groups. Insight into these different symptom structures may lead to a deeper understanding of mood states and shifts in BD, and ultimately symptom patterns may serve as predictors of the future disease course.

6.2 Method

6.2.1 Ethical statement

All patients participating in this study provided both written and verbal informed consent.

The study protocol was approved by the Medical Ethical Committee Mental Health Care Organisations Rotterdam (number: 7220) and the Central Committee Human Studies (number: NL18286.097.07) and was carried out in accordance with the Declaration of Helsinki.

6.2.2 Participants

The data for this study consisted of a subset of patients from a 2-year prospective follow-up study among 173 bipolar outpatients, treated for BD by the Outpatient Clinic for Mood Disorders in The Hague (The Netherlands), with a diagnosis of BD I or BD II according to DSM-IV-TR diagnostic criteria.

All BD patients at the outpatient clinic were invited to participate in the study. After written informed consent was obtained, 173 patients were willing to participate in the follow-up study. Participants were older than 18 years and exclusion criteria in this study were schizo-affective disorder, neurological disease and substance abuse disorders.

Diagnoses of BD were based on DSM-IV criteria and were assessed with a standardized diagnostic interview (119) using the Dutch version of the MINI International Neuropsychiatric Interview Plus (version 5.00-R; MINI-PLUS), which has good interrater (kappa > .75) and test-retest reliability (kappa >

.75) (119, 120). The Questionnaire for Bipolar Illness, Dutch translation (23, 121) was used to specify subtypes of BD. After completing the baseline assessment, patients had face-to-face contacts with the research assistant at 3-, 6-, 9-, 12-, 15-, 18-, 21-, and 24- months follow-up.

Of the 173 patients participating in the follow-up study, 125 patients completed all 8 assessments and were selected for the current study. There were no significant differences in baseline demographic and clinical characteristics between the group who participated until the end of the study and the group that dropped out during the study and no differences in the longitudinal disease course were found.

6.2.3 Procedure

Monitoring the longitudinal mood course

The NIMH monthly retrospective life chart method (LCM-r) (21, 124) was used at all 8 assessment sessions, to measure monthly functional impairment arising from manic or depressed symptoms during the previous 3 months. The LCM-r distinguishes four levels of severity for both mania and depression: (1) mild, (2) moderately low, (3) moderately high, and (4) severe. For every patient the 24 month life chart data were sorted for their overall course pattern based on proportion of time in a certain mood state and severity criteria. Proportion of time in depressive or manic mood state was calculated by counting the number of months with depressive or manic impairment divided by the total 24 months, which is a frequently used method (228). In case of mixed mood states we followed the LCM Manual (85), which states that in case of mixed mood states both the rated mania and depression score are included in the calculation of specific course variables. Based on earlier studies (28, 67) we distinguished three different course groups. Figure 6.1 shows examples of life charts of patients in the different course groups. All patients fall within the scope of one of the three categories:

1. *Mildly impaired:* stable mood for more than 90% of the time, or reporting mild depressive/manic impairment ≤ 1/3 of the time or mild up to moderate depressive/manic impairment ≤ 1/4 of the time.

2. *Predominantly depressed:* depression related impairment on the LCM for more than 1/3 of the time with mild to mild moderate depressive symptoms, or depression related impairment at least 1/4 of the time with at least one month exceeding high moderate severity. Manic impairment should not be more than 1/4 of the time without exceeding mild severity.

3. *Cycling:* > 1/4 of the time manic impairment and > 1/4 of the time depression impairment with at least one month with mild moderate impairment (depression and mania) or with at least 1/8 of the time manic and 1/8 depressed impairment with at least one month with severity levels exceeding high moderate. Patients with predominantly manic or mixed symptoms (≥ 1/3 of the time with manic/mixed symptoms and < 1/4 of the time depressed symptoms) were also included in this group.

Manic and depressed symptoms

For the assessment of manic and depressed symptoms the Quick Inventory of Depressive Symptomatology - Self Report (QIDS-SR) (123), and the observer-based Young Mania Rating Scale (YMRS) (60) were administered. Both the QIDS and the YMRS have good (interrater) reliability and validity (60, 123). Since the data used for the current study are part of a longitudinal study, both the QIDS and YMRS were assessed at 5 different time-points (at baseline and subsequently every 6 months). At study entry, most patients were euthymic, so very low QIDS and YMRS scores were obtained at baseline, making this time point less suitable (because of small variance) for the current analyses. Since we aimed to investigate how symptoms are connected when these are actually present in BD patients, for every patient we selected the time point at which they were most symptomatic. Selecting the most symptomatic time point has largely to do with the fact that bipolar patients appear to be non-symptomatic for an ample proportion of the time: patients are 50% of the time symptom free (euthymic), 35% of the time in a depressed state and 10% of the time in manic state(64). This means that when mood is measured at a random time point, a large proportion of the patients will

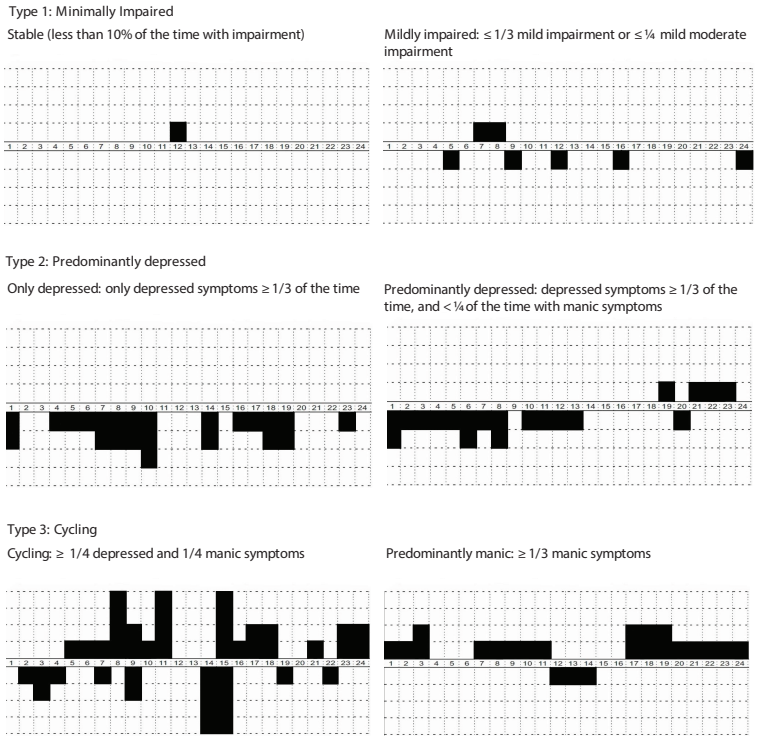

Figure 6.1 | Examples of course groups based on the LCM data.

report no or very slight symptoms only. This is also observed in the current study; on every time point a proportion of 35% to 40% of the patients appears to be euthymic. However, in order to ensure that networks are rather stable we will additionally perform sensitivity analyses over the average symptom scores on the 5 time-points and report on this in the results section. To this end, for all 3 course groups we will calculate edge weights between symptoms on all 5-timepoints separately and average these edge weights to construct 3 symptom networks that represent the average correlation network over the full 2-year period. Subsequently we will compare these 'full-data' networks with the networks containing only the most severe symptom scores.

To determine the time point with most severe symptoms, YMRS and QIDS total scores were standardized and summed, and for every patient the time-

point with the highest total score was selected. For network analyses the raw item scores on the QIDS and YMRS of that specific time-point were used.

In total the QIDS and YMRS consist of 27 items. Response scales on the QIDS and YMRS consist respectively of four and five categories. Some of the items assessed by the QIDS form separate domains (e.g. sleep) and several items of the QIDS and YMRS are overlapping. The items to which this applies were recoded if necessary and summed up in order to create symptom variables for the network analyses. Table 6.4 shows what overlapping items were used to compose these new variables. The overlapping YMRS and QIDS item scores were standardized and the highest score was selected to represent the combined item. For the network analyses standardized scores were transformed back into raw scores. Further, on three items (libido, lack of insight and appearance) of the YMRS a majority (≥ 94% of the participants) responded negatively (zero), leading to an unsuitable distribution for correlation analyses, therefore these items were not included in the analyses. The above mentioned adjustments resulted in a final total of 14 items that were included in the network analysis: irritability, increased speech, elevated mood, appetite/weight, restlessness, suicidality, concentration, self-esteem, interest, depressed mood, sleep duration, slowness, energy decrease, and sleep quality.

6.2.4 Statistical procedure

For comparison of baseline and clinical characteristics between the different course groups ANOVAs or Chi-square analyses were used. These analyses were performed using IBM SPSS for Windows (version 21.0; SPSS, Inc. Armonk, NY). Network analyses were performed using R 3.1.1 (229) with the igraph 0.7.1 package (230).

Network metrics

We constructed complete, weighted[1] graphs (or networks) for each of the three course groups, with the 14 items functioning as nodes, and edge weights

[1] In an unweighted graph, connections between two nodes are either present or absent. In weighted graphs, these connections are assigned a weight, representing the strength of the connection.

defined as the groupwise Spearman's rank correlation coefficient between the relevant items. The reason for using Spearman's rank correlation coefficient instead of the polychoric correlation coefficient is the assumption of the normally distributed, continuous nature of the latent variables underlying the data in the latter case. We believe that this assumption is not met due to the wording of the questionnaire items on which the networks are based, as well as the non-normal distribution of the data.

Node metrics

There are several metrics that are informative about the properties of a network. It is important to mention that the output of network analyses is mainly discussed in a descriptive fashion, also in previous studies (227). This means that the below mentioned metrics describe differences among the three course groups in terms of 'stronger-weaker' or 'higher-lower'. The following three metrics are discussed in a descriptive fashion in the results section.

1. *Network density.* This reflects how interconnected a network is. For fully connected networks (like those in the current study) where the edge weights are based on a correlation matrix, this measure is equivalent to the arithmetic mean of the correlation coefficients. In other words, it is a measure of the connectivity of a network's symptoms.

2. *Degree of centrality.* This reflects network characteristics on the node or symptom level. The degree of centrality is often referred to as node strength. With this measure, symptoms that have high degree centrality (e.g. symptoms that are most strongly connected to all other symptoms in the network) can be identified. Clinically this means that when a patient develops symptoms with high centrality, it will become more likely that other symptoms will emerge as well, since the central symptom is so strongly connected to other symptoms in the network (51).

3. *Random-walk betweenness.* An alternative way to look at the importance of a symptom is to look at route length or time it will take infor-

mation (or symptomatology) to spread from a given node to others in the network, which is known as betweenness centrality. To this end, one could calculate the shortest path between two symptoms. However, as noted by Newman (2005), this assumes that information is purposefully directed towards the shortest route. In real-world situations, information wanders around more randomly. To account for this, Newman suggested an alternative measure of betweenness based on random walks. This random-walk betweenness of a node is defined as the number of times that a node is encountered on a random walk between two other nodes. This will give insight in how often a specific symptom lies on the path between two other symptoms and therefore might be seen as a bridge symptom that is likely to be 'passed' to reach other symptoms.

To be able to compare network density and centrality measures (degree centrality and betweenness) of the different networks we bootstrapped 95% confidence intervals (CI) using 10,000 iterations.

6.3 Results

6.3.1 Baseline characteristics

Basic demographic and clinical characteristics of both the total sample and the separate course groups are summarized in Table 6.1. The mildly impaired, depressed and cycling group consisted of respectively 47 (37.6%), 42 (33.6%) and 36 (28.8%) patients. Mean age was 50.6 (SD=11.2) years and patients were predominantly female (60.0%). Mean YMRS and QIDS scores used for network analyses were 3.1 (SD 5.3) and 10.2 (SD 5.0), respectively, indicating overall light mania scores and mild depressive symptoms at the most symptomatic time-point.

There were some significant differences among the 3 course groups. First, the cycling group was significantly younger than the two other groups (F=5.1, p=.008). Furthermore, as expected (since the groups are classified based on the LCM mood data), the groups significantly differed on number of months in manic and depressed mood state. The depressed group had significantly

	Total (N=125)	Mildly impaired (N=47)	Depressed (N=42)	Cycling (N=36)	P-value
Male sex; n(%)	50 (40.0)	20 (42.6)	17 (40.5)	13 (36.1)	.836
Mean age (SD)	50.6 (11.2)	53.1 (10.8)	51.9 (11.7)	45.8 (10.0)	.008
Level of education, N (%)					
- primary	25 (20.0)	8 (17.0)	9 (21.4)	8 (22.2)	.837
- secondary	40 (32.0)	18 (38.3)	15 (35.7)	7 (19.4)	.140
- higher	59 (47.2)	20 (42.6)	18 (42.9)	21 (58.3)	.308
Clinical characteristics					
BD I; N (%)	90 (72.0)	31 (66.6)	32 (73.2)	27 (75.0)	.502
Age of onset first (hypo-) mania; mean (SD)	30.5 (10.2)	32.5 (10.9)	29.9 (10.5)	28.8 (8.9)	.284
Age of onset first depression: mean (SD)	27.3 (9.9)	28.6 (10.6)	27.6 (10.3)	25.1 (8.0)	.323
Medication use baseline; N (%)					
Lithium	91 (72.8)	37 (78.8)	30 (71.4)	24 (66.7)	.459
Anti-epileptics	28 (22.4)	9 (19.1)	10 (23.8)	9 (25.0)	.789
Anti-psychotics	39 (31.2)	12 (25.5)	13 (31.0)	14 (38.9)	.462
Benzodiazepines	32 (25.6)	8 (17.0)	14 (33.3)	10 (27.8)	.199
Antidepressant	42 (33.6)	13 (27.7)	17 (40.5)	12 (33.3)	.442
Mood/impairment during follow up					
QIDS (highest score for network)	10.2 (5.0)	7.1 (3.6)	12.9 (4.2)	11.1 (5.4)	<.001
YMRS (highest score for network)	3.1 (5.3)	3.3 (5.4)	1.8 (3.4)	4.4 (6.7)	.108
Number of months depressive impairment LCM	7.6 (5.5)	2.7 (2.1)	12.2 (4.5)	7.7 (5.5)	<.001
Number of months manic impairment LCM	3.3 (4.7)	1.4 (1.9)	1.3 (2.0)	3.3 (4.5)	<.001

Table 6.1 | Baseline and clinical characteristics of the total sample and separate course groups.

more depressed months than the other two and the cycling group had significantly more manic months on the LCM.

Furthermore, the minimally impaired group displayed significantly lower mean QIDS score than the depression and cycling groups. We also compared (ANOVA) mean scores on all 14 symptom items (Table 6.4). Symptoms that were more severely prevalent in the cycling and depressed group compared to the minimally impaired group were 'depressed mood', 'self-esteem', 'loss of interest' ,'lack of energy' and 'slowness'. On none of the symptoms significant differences in severity were found between the between the cycling and depressed groups.

6.3.2 Network density, structure and differences

Figure 6.2 shows the pruned correlation networks (only moderate to strong connections ($\rho > 0.2$) between symptoms are shown) of the 3 course groups. The minimally impaired, depressed, and cycling groups had weighted network densities and 95% confidence intervals (CI) of respectively .186 (95% CI: .166 – .185), .171 (95% CI: .131 – .166), .250 (95% CI: .198 – .269). These results implicate that symptoms were most strongly connected in the cycling group and least densely connected in the depressed group. Since the CIs of the three groups do not overlap it appears that the 3 groups differ significantly with respect to the overall connectivity of the symptoms.

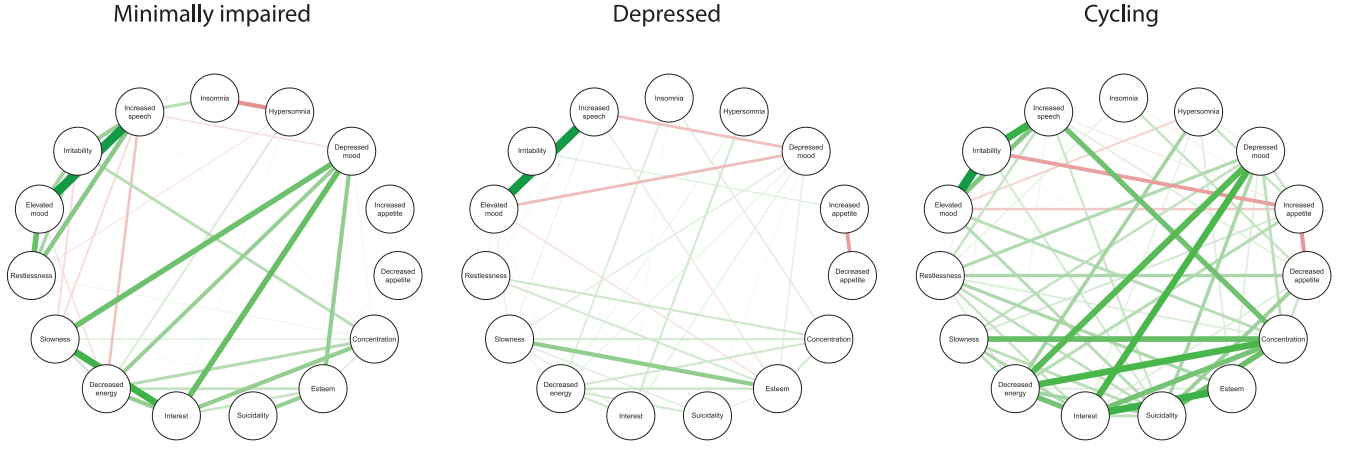

Figure 6.2 | Weighted networks with manic and depressive mood symptoms for the three bipolar disease course groups. Each symptom reflects a node in the network. Connections between the nodes are Spearman's rank correlation coefficients (green: positive correlation coefficient, red: negative correlation coefficient) based on the time point with most severe symptoms. Correlation coefficients lower than $\rho = .2$ are not shown.

6.3.3 Degree centrality of bipolar symptoms

As mentioned before, how strongly specific symptoms are connected to other symptoms can be measured by their weighted degree centrality. In Figure 6.3 the weighted degree centrality and the CI of the symptoms in the different networks is depicted. Table 6.2 shows the 5 items with the highest centrality within every group.

Mildly impaired	**Depressed**	**Cycling**
Item	*Item*	*Item*
Increased speech	Loss of energy	Concentration
Loss of interest	Elevated mood	Loss of interest
Depressed mood	Decr. self-esteem	Loss of energy
Loss of energy	Increased speech	Suicidality
Elevated mood	Slowness	Restlessness

Table 6.2 | Five items with highest weighted degree centrality in the different course groups.

First, based on centrality, the minimally impaired and depressed groups seemed to have most in common, and centrality strength of several symptoms seemed to overlap.When overlap of CI errorbars is about less than 50% (based on visual inspection) these can be considered significantly different (231). This means that within the cycling group especially the symptoms 'restlessness' and 'suicidality' had high centrality compared to the other two groups. In the minimally impaired group 'increased speech' and 'loss of interest' were the most central symptoms compared to the other groups, although overlap for these two symptoms was more than 50% with at least one of the other groups. Symptoms 'decreased self-esteem' and 'slowness' were distinct central symptoms for the depressed group. In all three groups 'loss of energy' was a highly central symptom.

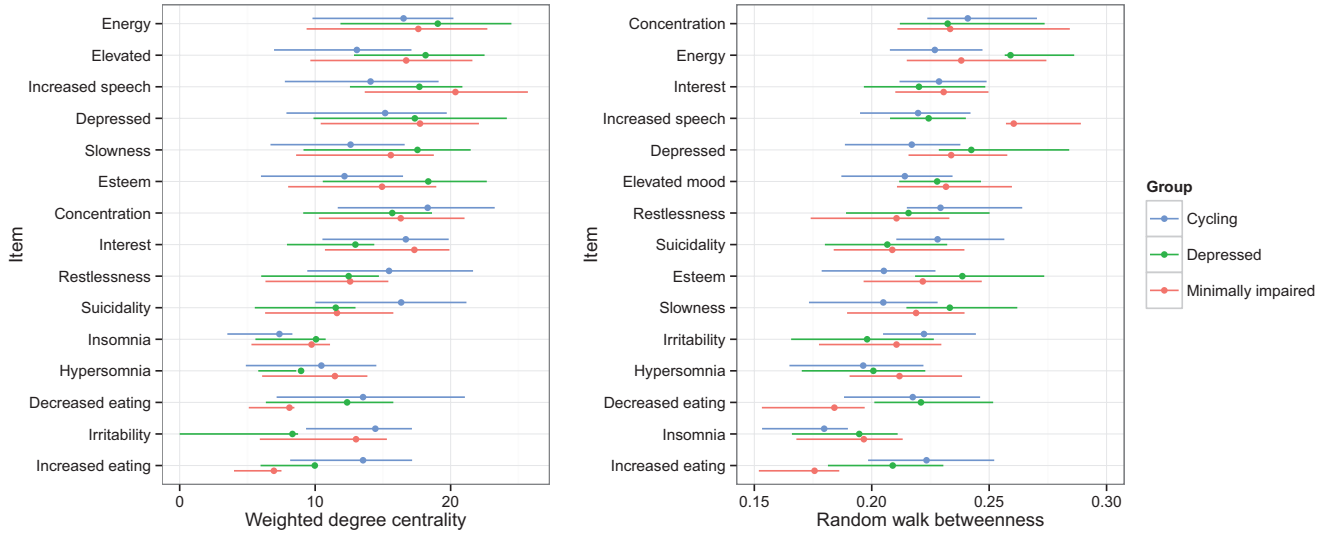

Figure 6.3 | Differences in centrality and betweenness in the 3 course groups: minimally impaired compared to depressed and cycling group.

6.3.4 Random walk betweenness

In Figure 6.3 the random-walk betweenness and the CI's of the symptoms in the different networks is depicted, and Table 6.3 shows the 5 items with the highest random-walk betweenness per group. The symptoms with high random-walk betweenness were rather comparable to the symptoms with high degree centrality, especially in the depressed and cycling group.

Mildly impaired	**Depressed**	**Cycling**
Item	*Item*	*Item*
Increased speech	Loss of energy	Concentration
Concentration	Decr. self-esteem	Loss of energy
Elevated mood	Concentration	Suicidality
Loss of interest	Slowness	Depressed mood
Loss of energy	Loss of interest	Loss of interest

Table 6.3 | Five items with highest random walk-betweenness in the different course groups.

6.3.5 Sensitivity analyses

For reasons described in the method section we chose to select the time point with most severe symptoms to compose our networks from. However, it is important to test whether the networks are not biased because of this specific selection of the time point. Therefore we performed sensitivity analyses based on all 5 time points. For all three groups symptoms correlations were calculated on every time point and the average edge weights were were used to construct the new networks. Figure 6.4 shows these new networks. The minimally impaired, depressed, and cycling groups had weighted network densities and 95% confidence intervals (CI) of respectively .159 (95% CI: .114 – .1911), .141 (95% CI: .113 – .164), .227 (95% CI: .185 – .263). These results show that network densities of the networks based on all time points are comparable to the 'severe score networks', since again the cycling network is most dense and symptoms in the depressed network are least densely connected. Further, the network figures indicate that the average symptom scores lead

to rather comparable network structures, although some additional associations appear.

6.4 Discussion

In the current study we approached the challenge of identifying mechanisms for the development of different bipolar course types from a novel methodological angle. With the use of a new approach in psychiatry, differences in symptom networks were studied within a large longitudinal cohort of BD patients with different course types. Our main finding was that symptom networks significantly differed between BD patients that were either minimally impaired, predominantly depressed or cycling over a two-year period. Descriptive comparison of the networks also indicated that symptoms that play a central role in the network differ across the groups. These findings and their clinical interpretation will be discussed in more detail in the following sections.

6.4.1 Differences in symptom networks between the course groups

The symptoms networks of the three groups differed most on overall connectivity of the network. Manic and depressed symptoms in the cycling group were most strongly interconnected compared to the depressed and minimally impaired group. This might imply that when any of the symptoms in the cycling group emerges, this will more likely lead to activation of other symptoms compared to the depressed or minimally impaired group. This stronger interconnection between manic and depressed symptoms might also explain the fact that the cycling patients are more prone to switch from one mood state to the opposite mood state. The depressed group on the other hand, shows the least connected network, even though they do suffer from rather severe symptoms (especially compared to the stable group). The weaker connection between symptoms might indicate that symptom states are less dynamic in this group. Clinically, the 'depression-prone' bipolar patients indeed seem to be a less dynamic group in terms that they often display long-lasting or even chronic depressed states with less alternation between manic or euthymic states (67, 27, 64).

In addition, in the three course groups symptoms also differed in terms of centrality (degree centrality and random walk betweenness). These central symptoms are concentration loss and suicidality for the cycling group, loss of self-esteem and psychomotor slowness for the depressed group, and increased speech and elevated mood for the minimally impaired group. This means that these symptoms are most strongly connected to the other symptoms in the network. When these symptoms emerge it is highly probable that other symptoms will develop as well. Inversely, since all symptoms are strongly connected to central symptoms, the development of more peripherally positioned symptoms will also likely lead to the development of the central symptoms. This last line of reasoning might also imply that central symptoms might be more prevalent, since they are easily activated when other symptoms emerge. In the current sample central symptoms were not more prevalent in the specific course groups. However, in previous studies some of these symptoms have been more frequently associated with specific course patterns.

For instance, both central symptoms in the cycling group have been associated with adverse course patterns before. Several studies found higher prevalence of suicidality among patients with more previous episodes, rapid cycling patterns (232) and mixed episodes (233). Patients that have more chronic and recurrent symptom patterns also show more cognitive impairment (including attentional/concentration problems) (234, 235).

In the depressed group, loss of self-esteem played a central role in the network. Self-esteem has been previously described as an important predictor of change in bipolar depression, suggesting that decreases in self-esteem are tightly linked to increases in other depressive symptoms (168), as was also displayed in the current analyses.

Finally, in the minimally impaired group the typically manic symptoms of increased speech and elevated mood are most consistently identified as central symptoms in the network. This finding is more difficult to interpret in light of previous literature. In this group it is likely that specific symptom patterns are more difficult to detect, since these patients simply display less severe manic and depressed symptomatology. However, one possible explanation for these specific symptoms patterns, might be that if these minimally

impaired patients develop symptoms, this will more likely lead to the activation of the central hypomanic symptoms which are by definition associated with less functional impairment. However, since the minimally impaired group reported significantly less severe symptoms on many items, any differences with the other two groups should be interpreted with caution and may be due to differences in prevalence of manic and depressed symptoms.

6.4.2 Similarities between the course groups

Although there are several important differences in symptom centrality between groups, decrease in energy level seems to be a highly central symptom in all three course groups. Thus, changes in energy levels are strongly associated with changes in other symptoms in all networks. In the light of the recent changes in diagnostic criteria of BD in the DSM-5 this is an interesting finding. The diagnostic A criterion for a (hypo-) manic episode (elation/euphoric or irritable mood in the DSM-IV) is now extended with the criterion that 'the mood change must be accompanied by persistently increased activity or energy levels'. Because of the lack of empirical evidence, the validity of this additional criterion has been disputed (236, 237). The current findings do show that changes in energy levels might be highly central symptoms in BD, but no direct evidence for a central role of energy increase is found here, since the currently found central energy decrease only reflects the energy decrease as a symptom of depression, and not mania. The symptoms 'restlessness' and 'elevated mood' reflect increases in (motor) energy but these symptoms are not identified as a central symptom in any of the networks.

Another important similarity between the networks is the fact that, across networks, symptoms do not form isolated 'manic' and 'depressed' symptom clusters, but symptoms of both poles are interconnected. This is in line with previous findings, showing that bipolar depression and mania do not occur as categorical as they are presented in diagnostic handbooks, but a substantial number of patients seems to experience episodes with manic and depressive admixtures (up to 65%) (238-240). This more dimensional representation is now acknowledged in the DSM-5 with the option to apply a 'with mixed features' specifier to depressed or manic mood states. Moreover,

these findings are also in line with previous studies using the network approach which challenged the current categorical approach of psychopathology by showing the interconnection between symptoms of different psychiatric disorders (52, 241). The fact that manic and depressed symptoms are interconnected, overlap and often occur simultaneously implicates that mania and depression are not at all total opposite and distinct mood states, but lie on the same spectrum and presumably overlap with regards to their structure and connectivity strengths of the symptom networks. From such a network perspective one could hypothesize that stronger interconnection and overlap between manic and depressed symptoms (especially in the cycling group) explains a cycling pattern rather than a stable state of either deep depression or mania. The latter would have been expected in case of non-overlapping attractors. In BD decreased sleep, psychomotor agitation and irritability are symptoms associated both with mania and depression (240) and therefore possibly connecting both ends of the mood spectrum. For instance, decreased sleep could lead to increased energy levels and (hypo-) manic mood states, however after some time energy levels might eventually drop leading to a more depressed state. A transition from mania to depression might for instance be due to insomnia within a manic mood state due to feelings of grandeur. This overlapping insomnia symptom may activate depressive symptoms such as loss of energy, restlessness, and concentration problems, subsequently leading to a depressed state. However this interpretation is rather tentative and underlines the need for confirmation in other BD populations as well as longitudinal monitoring of symptoms and their temporal development.

6.4.3 Strengths and limitations

This is the first attempt to explain differences in bipolar mood course by investigating symptom associations through a network approach. This could be a first step in explaining the variety of course patterns that are clinically displayed by BD patients by investigating how bipolar symptoms interact and reinforce each other. Further, the current study is also novel to the extent that manic and depressed symptoms are not treated as separate constructs, but fitted into the same model.

However, some important limitations should be taken into account. First, patients were divided into three groups based on their longitudinal course patterns. Although these three specific course groups have been previously described in the literature and roughly reflect what is observed in clinical practice, one could argue for the existence of many more different course groups (28). Second, course data were assessed through monthly ratings on the LCM which provides a global impression of the disease course, but lacks detailed information about more subtle mood changes and every minor episode. Third, in the current outpatient sample severe mood states (especially manic symptoms) were rare, which also led to the exclusion of some symptom items because of low variance. This implicates that the current findings can only be translated to BD patients with relatively mild symptom severity. Fourth, we used the time point with most severe symptomatology to construct the symptom networks, which requires careful interpretation to prevent the trap of circular argumentation. As the minimally impaired group by definition had low symptom severity this may partly explain some of the differences, although the other two groups showed important distinctions in their networks, but not in symptom severity. Fifth, the use of Spearman's rank correlation shows the global structure of the interconnections of symptoms, however different correlation techniques such as polychoric correlations, partial-correlation analyses or the Lasso procedure are valuable to use in future studies since they allow for a more refined exploration of the network structure.

Last, although a clinical sample of 125 patients is relatively large, for the analyses of 14 different variables within three groups of (on average) 40 patients, sample sizes are small. Due to low statistical power, the current results should be interpreted with caution and replication in larger samples is needed.

6.5 Conclusion and future directions

The current approach might be a first step in investigating the mechanisms behind the development of different bipolar course patterns by looking at bipolar symptoms themselves. The current network structures are based on

Spearman's rank correlations and only show the global structure of the interconnections of symptoms, however different correlation techniques such as partial-correlation analyses or the Lasso procedure are valuable to use in future studies since they allow for a more refined exploration of the network structure (242). Further, longitudinal studies are needed to show whether symptom networks have truly predictive and clinical value. Within these studies follow-up measurement should be very frequent to allow for the detection of (directed) relations between bipolar symptoms. In the current study follow-up measurements for the QIDS and YMRS were 6 months apart, making studying of the development of symptoms over time impossible, hence the cross-sectional symptom networks. Novel approaches such as the Experience Sampling Method (243, 244) might be highly suitable for the measurement of moment-to-moment development of symptoms and by that gain insight in the causal chain in which symptoms interact in BD. A recent publication (245) already showed the value of ESM data in detecting temporal mechanisms in depressive symptom patterns and identifying so called 'tipping points' that indicate a downfall into a full mood episode. Identifying these patterns in bipolar patients might have great clinical value in predicting future mood course and ultimately the prevention of new mood episodes.

Course Groups	Minimally impaired (1) Mean (SD)	Depressed (2) Mean (SD)	Cycling (3) Mean (SD)	P-value	Post hoc (Bonferroni)
Mood Symptoms					
Elevated mood (Y)	.36 (.82)	.24 (.58)	.44 (.77)	.455	-
Speech (Y)	.60 (1.4)	.44 (1.10)	.83 (1.68)	.433	-
Depressed (Q)	.40 (.54)	1.51 (.78)	1.22 (1.05)	<.001	1<2, 1<3
Esteem (Q)	.43 (.80)	1.63 (1.2)	1.11 (1.04)	<.001	1<2, 1<3
Suicidality (Q)	.32 (.63)	.68 (.85)	.53 (.74)	.086	-
Loss of interest (Q)	.43 (.58)	1.20 (.87)	1.00 (.89)	<.001	1<2, 1<3
Loss of energy (Q)	.81 (.92)	1.49 (.68)	1.33 (8.6)	<.001	1<2, 1<3
Slowness (Q)	.37 (.74)	1.10 (.97)	.86 (.93)	<.001	1<2, 1<3
Hypersomnia (Q)	.72 (.90)	.61 (.74)	.89 (.95)	.329	-
Insomnia	2.09 (.90)	2.26 (.60)	1.86 (.93)	.143	-
Waking up too early (Q)	.60 (.99)	.98 (1.11)	.44 (.65)		
Falling asleep (Q)	.74 (1.10)	.95 (1.18)	1.06 (1.12)		
Sleep decrease (Y)	.36 (.92)	.17 (.54)	.33 (.83)		
Restlessness				.076	-
Feeling restless (Q)	.36 (.74)	.76 (.89)	1.03 (1.00)		
Increased motor activity (Y)	.38 (.82)	.22 (48)	.36 (.72)		
Concentration	.98 (.79)	1.40 (.79)	1.28 (.94)	.053	-
Concentration (Q)	.79 (.69)	1.27 (.78)	1.11 (.89)		
Thought disorder (Y)					
Decreased weight/appetite	.79 (1.02)	.79 (.95)	.81 (.92)	.995	-
Decreased appetite(Q)	.19 (.45)	.29 (.51)	.47 (.61)		
Decreased weight (Q)	.70 (1.02)	.63 (.94)	.61 (.93)		
Increased weight/appetite	.40 (.89)	.64 (.93)	.67 (1.0)	.360	-
Increased appetite (Q)	.15 (.51)	.32 (.52)	.47 (.94)		
Increased weight (Q)	.30 (.78)	.46 (.93)	.39 (.73)		
Aggression/irritability	.72 (1.2)	.29 (.84)	.89 (1.3)	.051	-
Irritability (Y)	.60 (1.4)	.29 (.84)	.83 (1.3)		
Aggressive behavior (Y)	.21 (.62)	.05 (.31)	.22 (.64)		
Not included					
Libido (Y)	.11 (.43)	.02 (.16)	.11 (.32)		
Lack of inside (Y)	.06 (.32)	.00 (.00)	.06 (.33)		
Appearances (Y)	.04 (.20)	.00 (.00)	.11 (.32)		

Bold symptoms represent variables included in the network analyses. The variables 'sleep duration', motor activity', 'concentration', 'weight/appetite', 'aggression/irritability' are composed of the italicized symptoms depicted below these variables. Whether symptoms reflect items from the YMRS (Y) or QIDS (Q) is displayed between brackets.

Table 6.4 | Mean scores on symptom items and differences between the 3 course groups.

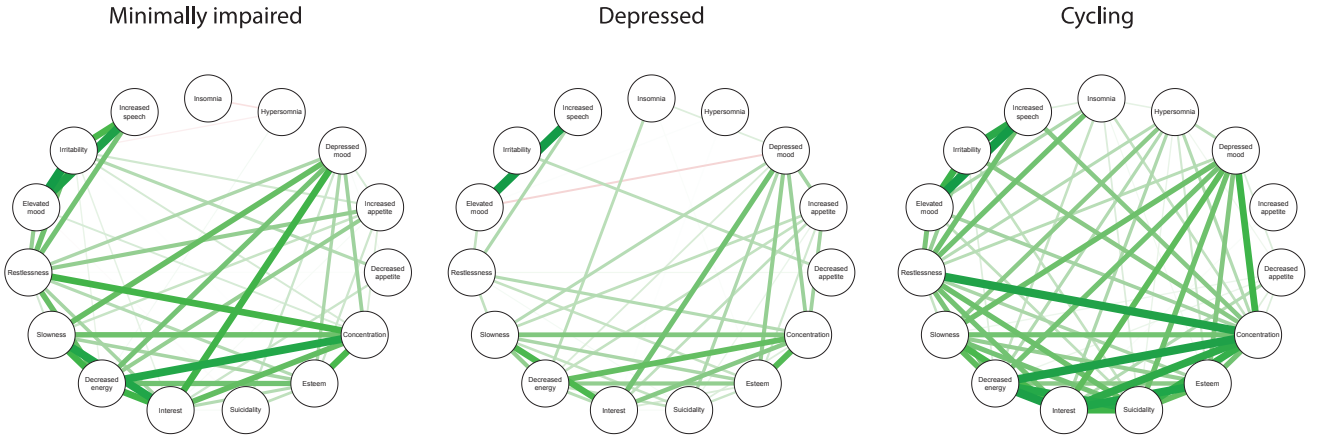

Figure 6.4 | Weighted networks with manic and depressive mood symptoms for the three bipolar disease course groups. Each symptom reflects a node in the network. Connections between the nodes are Spearman's rank correlation coefficients (green: positive correlation coefficient, red: negative correlation coefficient) based on the average edge weights between symptoms of all 5 separate time points. Correlation coefficients lower than $\rho = .2$ are not shown.

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 an 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, sinc 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.

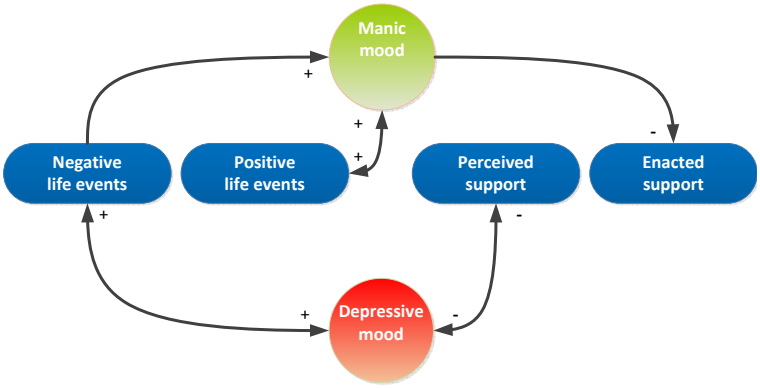

Figure 7.1 | Bidirectional associations between bipolar mood and psychosocial variables.

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 Falrets 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 samples 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.

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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 has 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.

Nederlandse samenvatting

Achtergrond

De bipolaire stoornis is een stemmingsstoornis die zich kenmerkt door periodes waarin een patiënt een stabiele stemming heeft en goed functioneert en andere periodes waarin er sprake is van depressie of juist een erg uitgelaten stemming die hypomanie of manie wordt genoemd. Tijdens depressies hebben patiënten last van verminderde energie, sombere stemming, gevoelens van lusteloosheid, verminderde interesse, veranderingen in het slaappatroon en negatieve gedachten. Tijdens een hypomanie of manie zien we juist een tegenovergestelde stemming, waarbij er juist sprake is van veel energie, een eufore stemming, toegenomen zelfvertrouwen, weinig behoefte aan slaap en snelle gedachten. Tijdens de hypomanie zijn deze symptomen in milde mate aanwezig en kunnen ze zelfs leiden tot beter functioneren dan normaal, omdat men zich in een hypomanie onder andere goed kan focussen, creatief is en gemakkelijk contact legt. Echter als de symptomen ernstiger worden spreken we van een manie. Er is dan in toenemende mate sprake van het ontbreken van een 'rem', waardoor patiënten bijvoorbeeld zeer grote hoeveelheden geld gaan uitgeven, ruzie maken met hun naasten, of gevaarlijke situaties opzoeken. Een manie kan zo ernstig worden dat patiënten psychotisch kunnen worden of opgenomen moeten worden in een psychiatrisch ziekenhuis.

De bipolaire stoornis komt ongeveer bij 2% van de bevolking voor en heeft vaak ernstige gevolgen voor het functioneren van de patiënt. Cijfers van de Wereld Gezondheidsorganisatie laten zien dat mensen met een bipolaire stoornis meer beperkingen ondervinden gedurende hun leven dan mensen met kanker of ernstige neurologische aandoeningen zoals Alzheimer dementie. De enorme impact die de ziekte heeft op het dagelijks leven hangt voor

een groot deel samen met het feit dat de ziekte al op jonge leeftijd aanvangt (gemiddeld rond de 25 jaar) en dat patiënten vaak hun hele leven kampen met terugkerende stemmingsepisodes. Echter zelfs als patiënten symptoomvrij zijn, blijft er in veel gevallen sprake van verminderd dagelijks functioneren. Dit hangt mogelijk samen met de cognitieve klachten die patiënten rapporteren. Het is echter nog niet bekend in hoeverre deze cognitieve achteruitgang samenhangt met de stemmingsklachten of dat deze ook aanwezig blijft tijdens stabiele periodes.

Omdat er gedurende het hele leven een grote kans is op terugval, is het belangrijk om mogelijke voorspellers van deze steeds terugkerende stemmingsepisodes te identificeren, met als doel om vervolgens interventies te ontwikkelen die zich richten op deze ongunstige factoren. Voorheen was zowel onderzoek als behandeling voor een belangrijk deel gericht op de biologische aspecten van de bipolaire stoornis. De laatste tijd is er ook meer aandacht voor de psychologische en psychosociale factoren die samenhangen met de ziekte. Zo is inmiddels bekend dat psychosociale factoren, zoals gebrek aan sociale steun en stressvolle levensgebeurtenissen, samenhangen met een meer ernstig ziektebeloop. Echter, oorzaak en gevolg van deze relatie is nog niet goed onderzocht. Zo kunnen psychosociale omstandigheden nieuwe ziekte episoden veroorzaken, maar het is evenwel mogelijk dat de ziekte zelf er voor zorgt dat patiënten uiteindelijk meer stressvolle situaties creëren en minder steun vanuit hun omgeving ontvangen.

Verder blijkt uit longitudinale studies dat het ziektebeloop vaak een constant patroon over de tijd laat zien. Dit betekent dat patiënten met overwegend depressieve episodes in het verleden, deze zeer waarschijnlijk ook in de toekomst zullen hebben, en dat patiënten met een meer fluctuerend beloop van manische en depressieve episodes in het verleden dit patroon waarschijnlijk ook in de toekomst weer zullen laten zien. Dit geeft aan dat het karakter of de uitingsvorm van de ziekte redelijk stabiel is over de tijd, maar het is onduidelijk waar dit aan ligt.

Het belangrijkste doel van dit proefschrift is om een meer verfijnd model te ontwikkelen voor de complexe relaties tussen het bipolaire ziektebeloop en verschillende (omgevings-) factoren in de loop van de tijd. Dit is gebaseerd op de veronderstelling dat cross-sectionele en unidirectionele benaderingen

niet geschikt zijn om de complexiteit van deze chronische stoornis goed in beeld te krijgen.

De studies in dit proefschrift zijn gebaseerd op data die zijn verzameld binnen de 'Bipolar Stress Study'. Binnen deze longitudinale studie zijn 173 bipolair patiënten twee jaar lang gevolgd. De stemming werd over de volledige periode geregistreerd en patiënten kwamen iedere drie maanden langs voor metingen waarbij levensgebeurtenissen en de hoeveelheid sociale steun gedurende de afgelopen periode in kaart werd gebracht. Daarnaast werden er herhaaldelijk aandachtstaken afgenomen om te kunnen bestuderen wat de relatie tussen stemming en aandacht is.

In onderstaande paragrafen zullen de resultaten van de studies worden samengevat, gevolgd door een korte discussie.

Resultaten

Het meten van het ziektebeloop van bipolaire patiënten over langere periodes is complex, en er bestaan verschillende methoden voor. Voor ons onderzoek hebben wij de life chart methode (LCM) gebruikt, en als eerste stap in het onderzoek beschrijven wij in **hoofdstuk 2** een literatuurstudie naar het gebruik en de interpretatie van de LCM in wetenschappelijke studies. De LCM wordt veel gebruikt in klinische en in onderzoekssituaties om over langere periodes het ziektebeloop in kaart te brengen, met als resultaat dat er zeer veel data per patiënt worden verzameld. Het verwerken, analyseren en interpreteren van deze grote hoeveelheid data wordt vaak gedaan door allerlei afgeleide variabelen te berekenen (zoals stemmingsepisodes, gemiddelde ernst, percentage van de tijd ziek, en aantal stemmingsomslagen). Echter na literatuurstudie blijkt dat deze variabelen niet op eenduidige wijze gedefinieerd en berekend worden door verschillende onderzoekers. Vooral voor het berekenen van de hoeveel stemmingsepisodes over de tijd en de hoeveelheid stemmingswisselingen over de tijd worden uiteenlopende criteria gebruikt. In dit hoofdstuk geven wij richtlijnen voor welke variabelen en definities het meest geschikt zijn, afhankelijk van de vraagstelling van de onderzoeker. Daarnaast laten we zien dat het dagelijks monitoren van de stemming belastend is voor patiënten en mogelijk tot hoge uitval in onderzoek leidt.

Vervolgens hebben we in **hoofdstuk 3 en 4** onderzocht in hoeverre psychosociale omstandigheden samenhangen met het ziektebeloop. Zoals eerder gezegd is voorheen alleen onderzocht of deze factoren nieuwe ziekte episodes voorspellen, maar wij hebben ook onderzocht of de relatie ook de andere kant op kan werken, namelijk dat de ziekte ook meer negatieve omstandigheden veroorzaakt.

In **hoofdstuk 3** is onderzocht wat de relatie is tussen stemmingssymptomen en negatieve en positieve levensgebeurtenissen over een periode van twee jaar. De resultaten laten zien dat negatieve levensgebeurtenissen in de afgelopen drie maanden samenhangen met meer depressieve en manische symptomen in de daarop volgende maanden. Positieve levensgebeurtenissen hangen alleen samen met meer manische symptomen in de daarop volgende maanden. Opvallend is dat voornoemde associaties alleen bleken te bestaan in de groep van bipolaire I patiënten en niet in de groep van bipolaire II patiënten. Dit lijkt erop te wijzen dat levensgebeurtenissen alleen effect hebben op de stemming in bipolaire I patiënten, maar niet in bipolaire II patiënten.

Daarnaast hebben we ook de omgekeerde relatie onderzocht. Hieruit blijkt dat manische symptomen zijn geassocieerd met meer positieve levensgebeurtenissen in de daarop volgende maanden, en depressieve symptomen juist met meer negatieve gebeurtenissen in de daarop volgende maanden. Dit betekent dat de relatie tussen manische en depressieve symptomen en levensgebeurtenissen wederkerig is. Dit impliceert dat er een vicieuze cirkel bestaat waarin levensgebeurtenissen tot meer symptomen leiden en symptomen vervolgens meer levensgebeurtenissen induceren.

Vergelijkbare wederkerige relaties werden gevonden in de studie die is beschreven in **hoofdstuk 4**. In dit hoofdstuk is de relatie tussen de stemming over een tweejarige periode en de hoeveelheid gerapporteerde sociale steun bekeken. Er wordt onderscheid gemaakt tussen daadwerkelijk ontvangen of objectieve sociale steun (hoe regelmatig iemand daadwerkelijk steun ontvangt uit de omgeving) en subjectieve sociale steun (het idee dat steun beschikbaar is en voldoende aanwezig). Dit onderscheid is gemaakt, omdat eerdere studies in niet-bipolaire groepen laten zien dat de perceptie van de persoon over het al dan niet ontvangen van voldoende sociale steun meer van belang is voor het welbevinden dan de hoeveelheid daadwerkelijk ont-

vangen steun. Dus iemand die weinig steun ontvangt, maar het idee heeft dat het genoeg is heeft een beter lichamelijk en geestelijk welzijn, dan iemand die veel steun ontvangt maar de kwaliteit of hoeveelheid ervan onvoldoende vindt.

In onze studie laten we zien dat dit ook voor bipolaire patiënten geldt: minder subjectief ervaren steun is geassocieerd met meer depressieve symptomen in de daarop opvolgende maanden. De daadwerkelijk ontvangen steun blijkt niet samen te hangen met stemming in de daarop volgende maanden. Ook in deze studie vonden we wederom dat er sprake is van een omgekeerd verband. Namelijk dat depressieve symptomen samenhangen met verminderd subjectief ervaren sociale steun in de daarop opvolgende maanden. Manische symptomen zijn juist gerelateerd aan minder daadwerkelijk ontvangen sociale steun in de daarop opvolgende maanden. Ook hier lijkt er dus een circulair verband te bestaan.

In **hoofdstuk 5** is onderzocht wat de relatie is tussen de ernst van depressieve en manische symptomen en de prestatie op een aandachtstaak. In eerdere studies heeft men laten zien dat vooral depressieve symptomen negatief samen te hangen met cognitief functioneren, maar er worden nauwelijks effecten gevonden van manische stemming op het cognitief functioneren. In onze studie hebben we daarom onderzocht of het verband tussen manische symptomen en aandacht wellicht non-lineair is. De aandachtstaak bestond er uit dat patiënten hun aandacht moesten verdelen over tekens die ze op het beeldscherm zagen en piepjes die ze hoorden. Ze kregen vervolgens de instructie om op bepaalde tekens en opeenvolgende piepjes te reageren. Uit onze studie blijkt inderdaad dat er een non-lineair verband is tussen de hypomane stemming en de prestatie op de taak. Dat betekent dat lichte manische symptomen geassocieerd zijn met verbeterd functioneren en pas als de symptomen ernstiger worden dat er een vermindering in het cognitief functioneren zichtbaar is (een relatie die op een omgekeerde U lijkt). In tegenstelling tot eerdere studies vonden wij geen relatie tussen depressieve symptomen en de prestatie op de VA taak.

Zoals eerder genoemd is het patroon van het longitudinale beloop van de bipolaire stoornis doorgaans consistent over de tijd. In hoofdstuk 6 hebben we onderzocht of specifieke beloopstypes samenhangen met symptoompa-

tronen. Hiervoor hebben we gebruik gemaakt van een nieuwe statistische benadering binnen psychiatrisch onderzoek, namelijk de netwerk benadering. Binnen deze benadering ligt de focus op de manier waarop symptomen met elkaar samenhangen en elkaar onderling versterken. Wij hebben onderzocht of patiënten met een verschillend longitudinaal beloop (overwegend stabiel, overwegend depressief, cyclisch beloop) verschillende symptoomnetwerken hebben. Het blijkt dat de symptoomnetwerken van deze drie groepen van beloopstypen significant van elkaar verschillen. Symptomen van de patiënten met een cyclisch beloop zijn bijvoorbeeld veel sterker met elkaar verbonden, wat mogelijk een verklaring is voor het patroon waarin manische en depressieve episodes elkaar regelmatig afwisselen. Verder bleken in de drie netwerken ook verschillende symptomen een centrale rol te spelen. Tot slot is een interessante bevinding dat depressieve en manische symptomen geen losstaande clusters vormen, maar sterk met elkaar verbonden zijn. Deze bevindingen laten mogelijk zien dat verschillende beloopstypen het resultaat zouden kunnen zijn van verschillende onderliggende symptoomstructuren.

Conclusie en discussie

Een van de belangrijkste bevindingen van dit proefschrift is het feit dat psychosociale factoren zoals negatieve levensgebeurtenissen en weinig sociale steun niet alleen een trigger zijn voor nieuwe stemmingsepisodes, maar dat deze ook als gevolg van stemmingsepisoden kunnen ontstaan. De studies in dit proefschrift hebben bijgedragen aan het verkrijgen van meer inzicht in het longitudinale beloop van de bipolaire stoornis door het gebruik van nieuwe onderzoeksbenaderingen die het mogelijk maken om complexe longitudinale associaties te analyseren en te interpreteren. De resultaten impliceren dat het lastig is, en wellicht ook niet erg zinvol, om oorzaak en gevolg te bepalen wanneer patiënten al langer durende klachten hebben en ziekte en psychosociale factoren elkaar wederzijds beïnvloeden. Modellen waarin monocausale richtingen worden losgelaten lijken derhalve een betere benadering te geven van de werkelijkheid van deze complexe stoornis. De netwerk benadering die in het laatste hoofdstuk is toegepast zou mogelijk een goede benadering zijn om dergelijke complexe data te analyseren en te be-

grijpen.

De huidige resultaten zijn ook van belang voor de klinische praktijk. Het feit dat ongunstige psychosociale omstandigheden zowel oorzaak als gevolg van stemmingepisoden kunnen zijn betekent dat hier rekening mee moet worden gehouden in het kader van psychosociale interventies binnen de behandeling. Hierbij kan gedacht worden aan het betrekken van naasten bij de behandeling. Verder is het registreren van de stemming een goede methode om meer inzicht te krijgen in factoren die effect hebben op de stemming en vice versa. Registratie kan ook inzicht geven in hoe verschillende symptomen invloed op elkaar kunnen uitoefenen.

Ook cognitieve interventies zijn mogelijk geschikt, aangezien vooral negatieve percepties samenhangen met een ongunstig stemmingsverloop. Het feit dat lichte hypomane symptomen samenhangen met een verbeterd functioneren op een cognitieve taak kan ook leiden tot negatieve percepties. Wanneer patiënten een stabiele stemming bereiken wordt dit supranormale niveau van functioneren niet meer bereikt, vanwege de afwezigheid van de hypomanie. Dit kan leiden tot gevoelens van falen, teleurstelling en verlies en zou mogelijk kunnen zorgen voor behandelontrouw en een instabielere stemming. Ook deze thema's kunnen onderdeel zijn van de psychologische behandeling.

Tot slot is het belangrijk om te noemen, dat alhoewel we in dit proefschrift hebben laten zien dat psychosociale factoren een rol spelen in het beloop van de bipolaire stoornis, de mate waarin ze dit beloop bepalen niet groot is. Dit betekent dat een multifactorieel model met verschillende factoren nodig is, waaronder omgevings-, klinische en biologische factoren, om het beloop van de stoornis beter te begrijpen en te voorspellen.

Curriculum vitae

Manja Koenders is geboren in de gemeente Haarlemmermeer op 16 april 1985. Na het afronden van het Gymnasium in 2003 volgde zij de studie Criminologie aan de Universiteit Leiden. In 2008 rondde zij haar master Forensische Criminologie af. Aansluitend volgde zij de studie Psychologie, waarvan zij in 2010 de master Klinische Neuropsychologie afrondde. Haar scriptieonderzoek vond plaats op de afdeling stemmingsstoornissen van PsyQ Den Haag, alwaar zij na haar afstuderen aan het werk is gegaan als psycholoog en onderzoeker. Vanuit deze positie kon zij haar promotieonderzoek starten, waarvan dit proefschrift het resultaat is.

Op dit moment werkt Manja als docent en post-doctoraal onderzoeker aan de Universiteit Leiden, waar zij de onderzoekcoördinatie op zich heeft genomen van een nieuwe studie naar de bipolaire stoornis (BINCO studie). Daarnaast werkt zij als psycholoog op de polikliniek bipolaire stoornissen bij PsyQ Rotterdam, en is zij werkzaam voor het specialisme stemmingsstoornissen van de Parnassia Groep. Tevens verzorgt zij onderwijs in het kader van de postdoctorale GZ-opleiding en heeft zij zitting in de werkgroep van de Zorgstandaard Bipolaire Stoornissen van het Trimbos.

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